

# Allocentric Spatial Memory Activation of the Hippocampal Formation Measured With fMRI

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Hippocampal activation was investigated, comparing allocentric and egocentric spatial memory. Healthy participants were immersed in a virtual reality circular arena, with pattern-rendered walls. In a viewpoint-independent task, they moved toward a pole, which was then removed. They were relocated to another position and had to move to the prior location of the pole. For viewpoint-dependent memory, the participants were not moved to a new starting point, but the patterns were rotated to prevent them from indicating the final position. Hippocampal and parahippocampal activation were found in the viewpoint-independent memory encoding phase. Viewpoint-dependent memory did not result in such activation. These results suggest differential activation of the hippocampal formation during allocentric encoding, in partial support of the spatial mapping hypothesis as applied to humans.

There is substantial evidence for the involvement of the hippocampus and related medial temporal lobe structures in spatial memory function, as demonstrated in a range of species, including rodents (R. G. M. Morris, Garrud, Rawlins, & O'Keefe, 1982), nonhuman primates (Feigenbaum & Rolls, 1991), and humans (R. G. Morris, Nunn, Abrahams, Feigenbaum, & Recce, 1999). As a mechanism for supporting spatial memory, O'Keefe and Nadel (1978; Burgess, Maguire, & O'Keefe, 2002; Nadel, 1991; O'Keefe, 1991) have proposed that there is a "locale" system for map-based navigation. This theory has been largely supported by animal experimentation, including studies exploring the firing properties of hippocampal place cells (O'Keefe & Speakman, 1987) and deficits caused by hippocampal lesions on spatial memory tasks, such as the Morris Water Maze (Fenton, Arolfo, Nerad,

& Bures, 1994; R. G. M. Morris et al., 1982) and the Olton 8-Arm Maze Task (Brown, 1992; Olton & Samuelson, 1976).

In humans, notions of hippocampal involvement in spatial memory have been modified to take into account the finding that only damage to the right hippocampal formation appears to produce specific spatial memory impairment. This includes early studies by Smith and Milner (1981, 1989), which found impairments in remembering the location of objects in a spatial array only in patients with unilateral right temporal lobectomies (RTLs), which are also related to the degree of hippocampal removal. This finding has been replicated by Nunn and colleagues (Nunn, Graydon, Polkey, & Morris, 1999; Nunn, Polkey, & Morris, 1998) using both objects and cards with abstract drawings, showing that if item recognition memory is equated across patients with left temporal lobectomies (LTLs) and RTLs by titrating the delay interval between study and test, there remains a robust spatial memory deficit in the RTL group only. Similar findings of right temporal lesions associated with spatial memory impairment have been reported for locating objects in scenes (Baxendale, Thompson, & Van Paesschen, 1998; Pigott & Milner, 1993).

In comparing spatial memory between species, one aspect typically differentiates the types of studies used. In the human studies, such as those by Smith and Milner (1981, 1989) and Nunn et al. (1998, 1999), the spatial locations are presented in a fixed position in relation to the participant; in other words they are viewpoint dependent. In contrast, most of the animal experimental techniques, such as the Morris Water Maze or Olton Maze, place the animal immersively in a visual domain and require navigational abilities. To bridge the gap between animal and human experiments and, hence, investigate analogous functioning, several investigators have developed viewpoint-independent spatial memory tasks for use with humans. This includes a series of studies of patients with unilateral temporal lesions from our own laboratory

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(R. G. Morris & Parslow, 2004). For example, Feigenbaum, Polkey, and Morris (1996) developed a *rotate* task in which the participant had to search for a specific location presented on a turntable that was depicted graphically on a computer, with rotations of the spatial array between searches. Abrahams, Pickering, Polkey, and Morris (1997; Abrahams et al., 1999) had participants inspect a circular array of bins and then walk around the array, identifying which bins had been tagged previously by having items hidden in them. Additionally, R. G. Morris, Parslow, and Recce (2000) designed an immersive virtual reality room in which the participants had to walk around a virtual table inspecting upturned shells to search for blue cubes. Each search followed the Olton Maze principle of having to avoid returning to a previously successful location. These studies all showed a specific impairment in patients with RTL lesions, with the Abrahams et al. (1999) study revealing that the extent of focal hippocampal damage correlated with allocentric spatial memory loss. Similarly, in more naturalistic settings, simulating large, real-world environments using virtual reality, patients with RTLs have been found to be significantly less accurate when performing spatial navigation tasks (Spiers et al., 2001).

Allocentric spatial memory loss has also been observed in patients with bilateral lesions. Holdstock, Mayes, Cezayirli, Aggleton, and Roberts (1999) investigated spatial memory in 2 patients (R.S. and N.M.) with bilateral hippocampal damage, requiring them to inspect and remember LED-lit locations on a display board from different angles. They found that only 1 patient was impaired when the task was a viewpoint-dependent task and that both patients were impaired when it was viewpoint independent. Holdstock et al. (2000) reported similar results on the viewpoint-independent task with an additional patient (Y.R.) who also had specific bilateral hippocampal damage. Finally, King, Burgess, Hartley, Vargha-Khadem, and O'Keefe (2002) compared same-view and shifted-view spatial memory in a virtual reality walled town square, with participants moving round the surrounding ramparts. A bilateral hippocampal lesion patient, "Jon," had differential impairment on the viewpoint-independent aspect of this task.

A number of neuroimaging studies have also explored the brain structures implicated in spatial memory function. One of the first studies was conducted by Aguirre, Detre, Alsop, and D'Esposito (1996) using functional magnetic resonance imaging (fMRI). They designed a virtual reality maze with landmark objects placed at the end of cul-de-sacs to aid orientation. Neural activity was measured during an orientation phase and then during a retrieval task, showing bilateral hippocampal activation during both phases. Maguire, Frith, Burgess, Donnett, and O'Keefe (1998) used positron emission tomography (PET) combined with a virtual reality maze to investigate encoding of topographical information with and without salient objects. They found increased activation in the right hippocampal region during exploration of large-scale space with salient objects present. Another study by Maguire, Burgess, et al. (1998) in which a computer game was adapted to create a large-scale spatial environment compared activation on successful versus unsuccessful navigation compared with following arrows, showing right posterior parahippocampal activation extending into the hippocampus. Successful navigation produced more bilateral hippocampal activation than unsuccessful

navigation. Additional spatial memory studies have also found parahippocampal or hippocampal activation, including those using imaginary or filmed navigation (Ghaem et al., 1997; Maguire, Frackowiak, & Frith, 1996, 1997). More recently, the findings of the neuroimaging studies using representations of large-scale environments have been supplemented by single-cell recording using intracranial electrodes in humans. Ekstrom et al. (2003) required their patients to navigate in a virtual town and found that cells that responded to spatial locations were primarily in the hippocampus, whereas those that responded to views of landmarks were in the parahippocampal region.

The studies reviewed above add strong support to the involvement of the hippocampus or parahippocampus in spatial memory, with some evidence of specificity in relation to allocentric memory. This is indicated largely by the studies of patients with bilateral hippocampal lesions (Holdstock et al., 1999, 2000; King et al., 2002). The principle aim of the current study was to see whether this holds also for neural activation, in this case measured using fMRI. To test this, a virtual reality human analogue of the Morris Water Maze (R. G. M. Morris et al., 1982), with a circular arena, was constructed with random patterns rendered onto the walls. The participant enters the arena from a particular direction. Instead of learning to locate a hidden platform, which would produce more variable responses in an fMRI experiment because of the unconstrained search times involved, the participants move to a shown location, a pole within the arena. The pole then disappears and, after a delay period, the participant has to move to where he or she thought the pole had been, but from a different starting direction. This task requires the participant to encode the location with respect to the frame of reference of the environment. In other words, the participant's egocentric location has been changed from encoding to test and is therefore not valid as a cue to location, and the task tests the ability to encode locations with respect to relative positions in the environment, hence, testing allocentric memory. In a viewpoint-dependent task, the participants are immersed in an arena with different patterns on the walls and again have to move to a pole; as before, the pole disappears and there is a delay period. The arena walls are then rotated in a random fashion so as not to provide the participant with cues to aid orientation. Finally, the task is to move to the pole location in relation to the initial starting point. In this scenario, the task requires the participant to recall the location with respect to an egocentric frame of reference, with the environmental cues changed from the encoding phase to the test phase so as to render them invalid.

On the basis of the neurophysiological findings, which implicate the hippocampus and neighboring structures in viewer-independent representation of location (Ekstrom et al., 2003; R. G. M. Morris et al., 1982; O'Keefe & Nadel, 1978; Rolls, Robertson, & Georges-Francois, 1997), and the human lesion and neuroimaging studies reviewed above, we predicted that the viewpoint-independent spatial task would be associated with hippocampal activation, but the viewpoint dependent task would not. Whether bilateral activation would be seen was not clearly predicted because of the finding of either bilateral, unilateral hippocampal, or parahippocampal activation in previous neuroimaging studies, with no studies to date reporting a direct comparison between left and right activation and showing a significant difference.

## Method

### Participants

There were 11 right-handed male participants ( $M$  age = 26.72, range = 19–45 years) who were free from significant physical illness and had no history of neurological impairment or psychiatric conditions. They were assessed for estimated general intelligence ( $M = 119$ , range = 114–123) using the National Adult Reading Test (2nd ed.; Nelson & Willison, 1991) and for mental rotation abilities ( $M = 30.45$ , range = 22–32) using the Ratcliff Mental Rotation Task (Ratcliffe, 1979). All participants gave informed consent for the study.

### Apparatus

*Virtual reality.* The procedures were programmed by Third Dimension (Dorset, United Kingdom) using Superscape Virtual Reality software (Superscape, Hampshire, United Kingdom). The procedures were presented on a 450-MHz microprocessor fitted with an 8-MB, three-dimensional graphics card. The image was displayed via a projector onto a Perspex screen at the foot of the scanning table. For moving around the virtual reality environment, the participant used an MR-compatible analogue joystick specifically designed for the experiment.

*MR scanner.* The scanner was a GE Signa 1.5T Neuro-optimized MR system (General Electric, Milwaukee, WI).

### Testing Room and Experimental Setup

The participants were placed in the magnet bore wearing noise-attenuating headphones, which also served to communicate instructions. In their right hand they held a joystick fixed in position by their side. The lights in the control room were extinguished, with only the test screen images visible.

### Overview of the Virtual Environment

A virtual arena was constructed, with a set of 16 abstract patterns rendered onto the walls in circular fashion. The patterns were also faded into each other to make a seamless larger pattern surrounding the arena. Both the floor of the arena and the outside background (i.e., sky) were gray. To enhance the perception of motion and perspective when moving around the arena, short markers were distributed on the arena floor in a random fashion. Different sets of patterns were used for the viewpoint-independent and -dependent phases of the experiment, thus preventing proactive interference. Within the arena in the encoding phases of each task (see Figure 1, Parts A, B, and C [viewer-independent task shown]), a pole was presented. At the base of this pole was a circular puck. Tilting of the joystick signaled movement around the environment: Pushing forward accelerated forward movement to fixed speed, and sideways tilt rotated direction either to the left or right.

### The Tasks

For each task (viewpoint independent and viewpoint dependent), there were a series of five trials. Each trial was split into six 30-s phases (or epochs), with fMRI activation measurements made for each of them.

The epochs were as follows:

1. *Encoding.* The participant started from the periphery of the arena, with the pole always in their field of view. If necessary, they were required to rotate round until the pole was in the center of the screen (e.g., see Figure 1A). They then had to move toward the pole until they had reached the puck, at which point the image on the monitor froze for the remainder of the 30-s epoch (e.g., Figure 1B). This image consisted of viewing the pole at close range (e.g., Figure 1C).

2. *Rest.* The monitor was blank throughout the epoch.

3. *Retrieval.* The arena was shown again without the pole (e.g., see Figure 1D) and, within 30 s, the participant had to move to where it had been located. The participant had to signal this by pressing a button on the joystick, at which point the image froze for the rest of the epoch (e.g., Figure 1E).

4. *Rest.* There was a further epoch in which the monitor was blank.

5. *Visual.* An amalgam of the patterns used on the walls of the arena was presented for 30 s (e.g., see Figure 1F).

6. *Rest.* This final epoch acted as an additional resting control condition and also provided a gap between the trials.

For the viewpoint-independent experiment retrieval epoch, the starting point was moved to a different location in the periphery of the arena. For the viewpoint-dependent task, this starting point was the same but with the arena walls rotated.

The two tasks were administered in the same scanning session, each taking 15 min. The order of the tasks was counterbalanced across participants.

### Instructions

For the viewpoint-independent task, the participants were instructed to move to the pole steadily using the patterns around the arena wall to remember the pole location. For the retrieval phase, they were instructed to go to where the pole had been using the arena wall patterns to guide their positioning. For the viewpoint-dependent task, the instructions were again to move the pole in the same fashion. This time participants were told that they had to recall the pole location in relation to their own body axis and not to use the background patterns to determine the remembered position. When inspecting the patterns for the visual epoch, participants were instructed to passively observe the image until the end of this phase.

### Start, Relocation, and Pole Positions

The starting and relocation positions were located on a hidden circle just within the arena walls. This circle was divided into 18 radians to define an equivalent number of possible positions. Pseudorandom selections of starting and relocation positions were used. For the pole position, an additional hidden circle, again with 18 radians, was used to define position. This circle was approximately one third of the diameter of the arena in from the periphery.

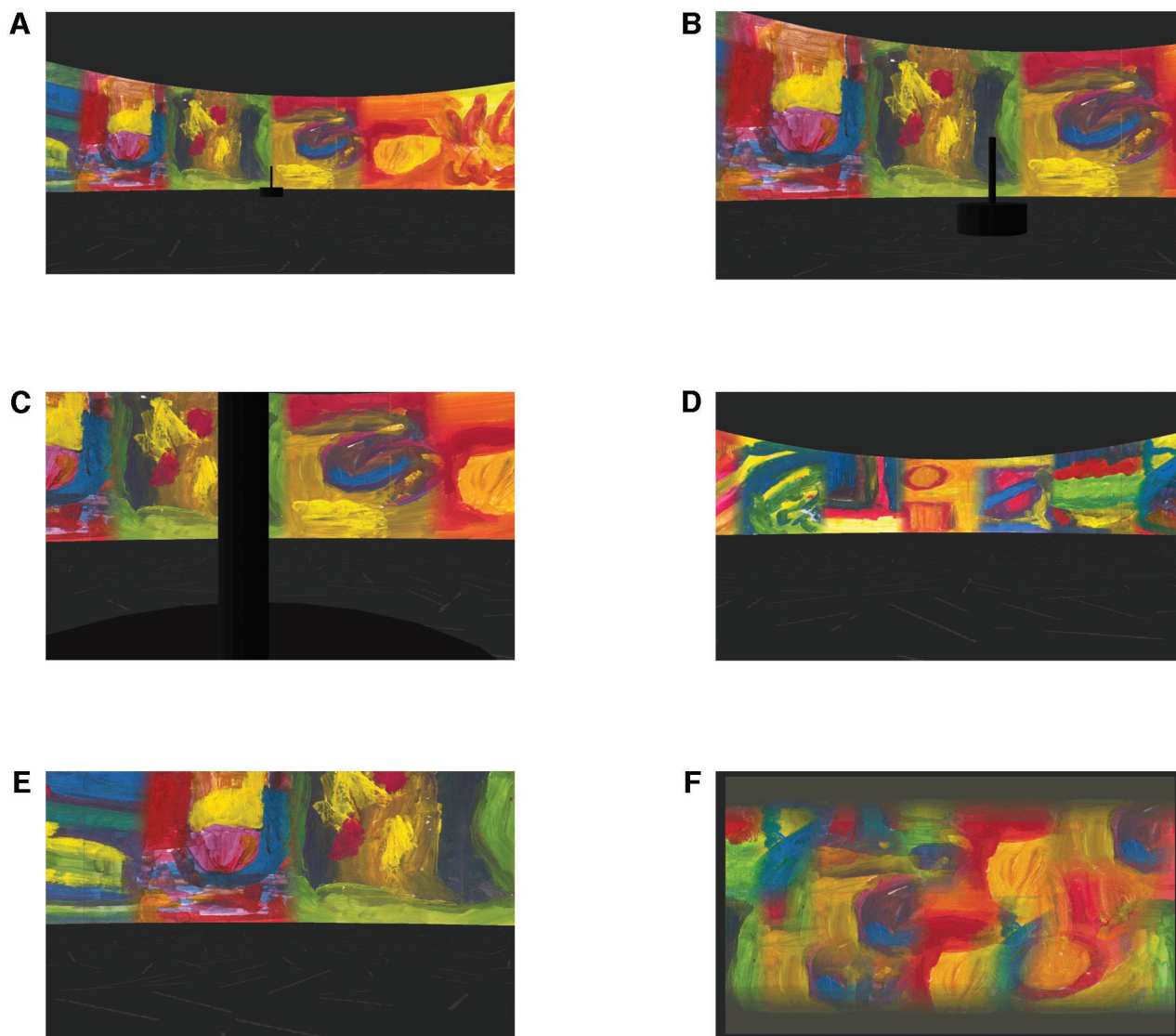
### Training

Twenty minutes prior to scanning, the participants were trained on the tasks in a testing room, where they sat at a desk and viewed the images on a standard computer monitor at a distance of approximately 30 cm, with the joystick on the desk to their right. They were trained on both tasks, in each case with an initial instruction trial taking them through the different phases without fixed time limits. An additional trial was administered in which participants could attempt the procedure but ask questions if unsure. The final two trials used the same time sequences as in the scanning procedure.

### Data Acquisition and Analysis

For each task, the MRI scanner acquired 300 T2\*-weighted images depicting Blood Oxygenation Level Dependent (BOLD) contrast (Ogawa, Lee, Kay, & Dank, 1990) at each of 16 noncontiguous near-axial planes (7-mm thick, 0.7-mm slice skip) parallel to the intercommissural anterior commissure–posterior commissure (AC–PC) line and covering the whole brain; echo time (TE) = 40 ms, repetition time (TR) = 3 s, flip angle = 90°, number of signal averages = 1.

Prior to time-series analysis, the data were processed to remove low-frequency signal changes and motion-related artifacts (Bullmore et al.,



*Figure 1.* Images from the virtual reality arena task designed to assess both viewer-independent and -dependent spatial memory (only viewer independent shown). A = encoding (the participant has rotated toward the pole); B = encoding, midway view; C = encoding, finish position; D = retrieval start position (participant moved to a new location); E = retrieval finish position; F = visual comparison condition.

1999). The responses at each voxel were then analyzed by regressing the corrected time-series data on a linear model produced by convolving each contrast vector to be studied with two Poisson functions parameterizing hemodynamic delays of 4 and 8 s (Bullmore, Fadili, Breakspear, Salvador, & Brammer, 2003). Following least squares fitting of this model, a goodness-of-fit statistic composed of the ratio of model to residual sum of squares was calculated (Edgington, 1995) for each contrast. The distribution of the same statistic under the null hypothesis of no experimental effect was then calculated by wavelet-based resampling of the time series at each voxel and refitting the models to the resampled data (Bullmore et al., 2003). Colored noise is a major problem for statistical inference in fMRI, because normal analysis using the general linear model assumes that the residuals (following fitting a model of the experimental response to the data) are independent and randomly distributed. If this is not the case, a common consequence may be an increase in the Type I error rate. This has been addressed at the Institute of Psychiatry (London, United Kingdom)

since 1996 (see Bullmore et al., 1996). We first proposed an autocorrelational model for the structure in the residuals following model fitting. This approach was later generalized and refined (Bullmore et al., 2003) by transforming the time series at each voxel into the wavelet domain and permuting the wavelet coefficients independently at each detail level. This is the wavelet analogue of frequency-dependent phase shifting in Fourier analysis, a technique commonly used in physics to produce surrogate data sets for statistical inference. We have used wavelets because they are naturally good at modeling the 1/f-type noise structures often found in fMRI (see Bullmore et al., 2003). The transformation is then reversed. This creates a time series in which the spectral characteristics of the noise are well preserved but the temporal link between the experiment and the response is destroyed (see Bullmore et al., 2003).

An experimentally derived null distribution of the goodness-of-fit statistic was then obtained by repeating this procedure 10 times at each intracerebral voxel and combining the resulting data. This method has been

shown to give excellent control of nominal Type I error rates in fMRI data from a variety of scanners. The number of expected positive pixels (epi) for the whole brain used during these analyses was 50. This value was chosen because Talairach (Talairach & Tournoux, 1988) transformation of the fMRI data gives approximately 25,000 voxels in standard space. There are 25 slices in the Talairach template, so an epi of 50 equals an average of 50/25 error voxels per slice of the standard template. This is considered a reasonably acceptable number for reducing Type II errors, producing an approximate  $p$  value of less than .002. Talairach transformation was carried out as described by Brammer (2001) onto a standard template constructed locally by transforming 10 normal brain structural (high-resolution Echo Planar Imaging; EPI) data sets using the Analysis of Functional NeuroImages package and anatomical landmark identification. The transformation for each individual in these experiments reported in the current study was performed as follows: A high-resolution EPI data set was obtained for each individual in the study, and the fMRI data for each participant were first normalized onto his or her EPI image using a rigid body transform (allowing brain movement but no deformation). The affine transform of the high-resolution EPI for each participant onto the Talairach template was then computed and used to transform the fMRI data into Talairach space.

### Task Accuracy Measurement

A displacement error distance was obtained during both tasks: the distance between the pole location during the encoding phase and the

judged position of the pole at the retrieval phase. This is measured using arbitrary units where the radius of the arena is 800,000 units.

## Results

### Analysis of the fMRI Data

*Viewer-independent and viewer-dependent tasks.* The first analyses of fMRI data were confined to the task versus the “rest” (blank screen) phases. Thus, both viewer-independent and viewer-dependent encoding and retrieval epochs were compared with the rest epochs. Where activation was detected in the hippocampal region, analysis was conducted on a voxel-by-voxel basis.

The viewer-independent condition analysis showed several regions to be active during both encoding and retrieval (see Table 1 and Figures 2, 3, and 4). These included regions in the frontal (medial frontal [Brodmann Area; BA 9]; anterior cingulate [BA 32], inferior frontal [BA 45], and precentral [BAs 4, 6, and 43]), temporal (hippocampal–parahippocampal [encoding only; BA 30], superior temporal [BA 22]), parietal (precuneus [BA 7], superior parietal [BA 7], inferior parietal [BA 40], and paracentral [BA 7]), occipital (medial occipital [BA 18], cuneus [BAs 17,19], lingual [BAs 17,19], and fusiform [BA 19]), cerebellum, and thalamus.

The same analysis for the viewer-dependent versus rest comparison showed a similar set of regions activated, the main differ-

Table 1  
*Viewer-Independent Encoding and Retrieval Versus Rest-Activated Brain Regions*

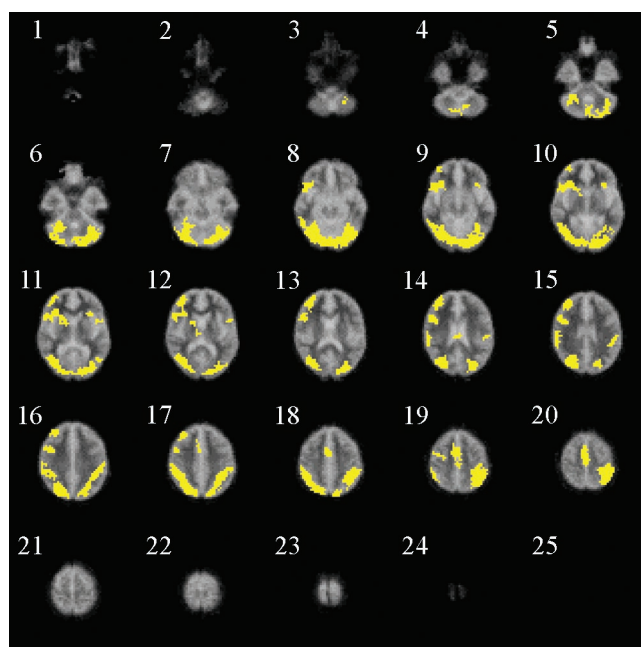
Brain region	Encoding			Retrieval		
	Location	No. of voxels	Brodmann	Location	No. of voxels	Brodmann
Frontal	38 26 9	17	45	7 -13 48	23	6
	42 23 26	11	9	17 40 -18	10	11
	-31 -34 59	7	2	46 -4 26	19	6
	46 -4 20	17	43	14 10 -24	7	6
	46 -7 37	14	6	38 -13 48	19	4
	5 -7 42	7	32	35 26 9	19	
Temporal	-22 -30 -2	22	66/35	52 -37 20	12	22
	18 -30 -2	14	66/35			
	22 -30 -7	14	66/35			
	-11 -26 -7	9	66/35			
	18 -30 -13	7	66/35			
	52 -34 20	8	22			
Parietal	11 -77 42	152	7	-4 -77 42	170	7
	-11 -70 48	70	7	-31 -60 48	54	7
	28 -56 48	20	7	4 -34 53	30	7
	52 -34 31	14	40	55 -40 26	21	40
	-46 -43 31	10	40			
Occipital	-7 -90 -13	179	17-19	-7 -90 -13	224	17-19
	-7 -86 9	37	17-19	4 -60 -2	18	17-19
	14 -80 31	124	17-19	14 -77 37	162	17-19
	-17 -83 20	26	18	-4 -83 31	140	17-19
				-24 -60 -7	9	19
				14 -83 20	62	18
Cerebellum	17 -83 -18	129	—	-14 -83 20	37	18
	-35 -80 -24	28	—	11 -86 -18	164	—
	-20 -34 4	27	—	-7 -77 -40	40	—
Thalamus	20 -30 4	17	—	14 -17 9	17	—

*Note.* Table 1 shows Talairach coordinates for the brain regions activated during the viewer-independent encoding and retrieval tasks. In the column labeled *location*, the numbers represent, respectively, the  $x$ ,  $y$ , and  $z$  Talairach coordinates. Each voxel size is 3 mm  $\times$  3 mm  $\times$  7 mm. See Garey (1999) for translation and full description of Brodmann areas.

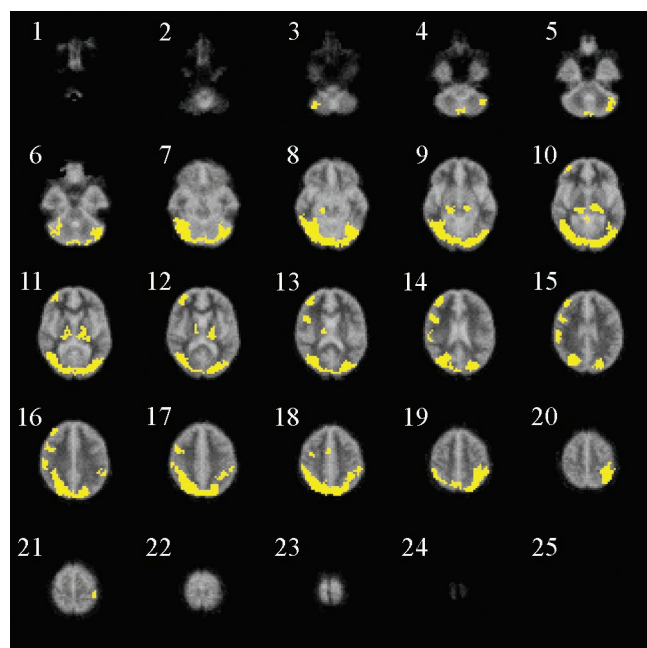
ence being no hippocampal or parahippocampal activation (see Table 2 and Figures 5 and 6). The activated regions included the frontal (medial frontal [BA 9], anterior cingulate [BA 32], precentral [BAs 6,4], and inferior frontal [BAs 45,47]), parietal (precuneus [BA 7], temporal [superior temporal; BA 22], superior parietal [BA 7], paracentral [BAs 2, 5/7], and inferior parietal [BA 40]), occipital (medial occipital [BAs 18,19], cuneus [BAs 18,19], and lingual [BA 17]), insula, cerebellum, and thalamus.

The encoding condition for the viewer-independent and viewer-dependent tasks were compared directly. This revealed no differences except for a right-sided cluster of activation from the inferior temporal gyrus ( $Z = -2$ ) through the medial temporal gyrus to the precuneus–inferior parietal lobe ( $Z = 42$ ), suggesting relatively greater activity in the viewer-dependent condition.

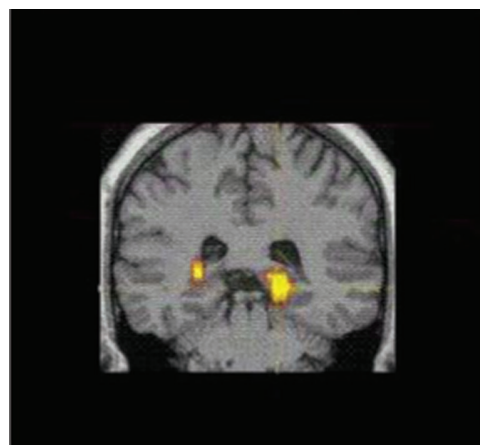
*Visual control analysis.* The viewer-independent and -dependent visual control versus rest analyses activated mostly visual cortical areas (data not shown). During the viewer-independent visual control task, two frontal regions (medial frontal [BA 6] and anterior cingulate [BA 32]), two parietal regions (postcentral [BA1/2/3] and inferior parietal [40]), two occipital regions (lingual



*Figure 3.* Viewer-independent retrieval versus rest activation. Slice 14 shows right lateral superior temporal gyrus activation. Large precuneus activation with its peak activation in the left hemisphere is bilateral (see Slice 18). Left superior parietal lobe activation is found in Slice 19. Right paracentral region is present on Slice 20, and right inferior parietal lobe activation in Slice 15. Right medial frontal and right precentral gyrus activations are present on Slice 19. A right medial frontal activation is also found on Slice 7. Right inferior frontal activations are found on Slices 10–14. Large bilateral lingual gyri activations are present on Slices 8–10. Several cuneus activations are also found on Slices 12, 13, 16, and 17. Left fusiform gyrus activation is shown on Slice 9, and bilateral medial occipital activations are found on Slice 14. Bilateral cerebellar activity is evident on Slices 3–7. Right thalamic activation is found on Slice 12. See the Method section for statistical threshold used. Right side of image represents left side of brain.



*Figure 2.* Viewer-independent encoding versus rest activation. Bilateral hippocampal–parahippocampal activations are shown on Slices 8, 9, and 10. Bilateral (and central) precuneus activations are observed on Slices 17–19. Inferior parietal regions of activation are present on Slices 15–16, and superior parietal lobe activation on Slice 19. Slices 20–21 show the left postcentral gyrus activation. Precentral gyrus activation is present on Slices 14–17. Inferior and medial frontal activations are found on Slices 11–16. The largest single regions of activations are the visual areas. Large left lingual gyrus activation is observed on Slices 8–11. Slices 9–16 present a series of occipital cortex activations. Bilateral cerebellar activations can be clearly seen on Slices 3–7. Strong posterior thalamic activation is present on Slices 11–13. Right anterior cingulate gyrus activation is present on Slice 18. See the Method section for statistical threshold used. Right side of image represents left side of brain.



*Figure 4.* Coronal image showing mainly right hippocampal activation. This slice ( $Z = -2$ ) represents most clearly the pattern of activation observed in the detailed analyses shown in Table 3. Right side of image represents right side of brain.

Table 2  
*Viewer-Dependent Encoding and Retrieval Versus Rest-Activated Brain Regions*

Brain region	Encoding		Retrieval			
	Location	No. of voxels	Brodmann	Location	No. of voxels	Brodmann
Frontal	46 17 26	22	9	42 20 20	25	45
	38 20 31	12	9	46 26 4	15	47
	-38 -7 31	10	6	38 37 -7	8	47
	46 0 15	41	4	42 20 26	22	9
	31 23 20	21	45	46 0 9	47	6
	-35 34 -2	6	47	28 -17 48	12	4
Temporal	11 -7 37	7	24	7 -10 42	16	24
	46 7 -7	17	22	42 4 -7	32	38
	52 4 4	9	22	-35 10 -7	6	22
	55 -37 20	11	42			
	11 -77 42	90	7	-20 -64 48	73	7
	-14 -67 48	71	7	17 -73 42	65	7
Parietal	35 -53 48	14	7	-24 -56 53	61	7
	55 -40 26	18	40	35 -53 48	13	7
	-42 -43 26	18	40	4 -26 53	34	5/7
	4 -30 48	28	2	52 -43 26	21	40
				-35 -40 26	15	40
Occipital	-7 -90 -13	184	17-19	-7 -90 -13	191	17-19
	20 -86 4	64	17-19	-14 -90 4	90	17-19
	14 -77 37	160	17-19	14 -77 37	84	17-19
	-4 -90 -2	151	17-19	28 -77 26	39	19
	20 -83 15	40	19	31 -77 20	34	19
	-17 -83 20	22	18	-42 -67 4	8	
Cerebellum	11 -86 -18	60	—	11 -86 -18	67	—
	-4 -83 -18	50	—	-7 -86 -18	76	—
Thalamus	17 -26 9	21	—	14 -7 9	7	—
	-17 -34 9	12	—			
Insula	35 10 -2	29	—	-28 10 -2	8	—
Basal ganglia				14 -4 -2	42	—
Clastrum				-38 -4 4	8	—

*Note.* Table 2 shows Talairach coordinates for the brain regions activated during the viewer-dependent encoding and retrieval tasks. In the column labeled *location*, the numbers represent, respectively, the *x*, *y*, and *z* Talairach coordinates. Each voxel size is 3 mm × 3 mm × 7 mm. See Garey (1999) for translation and full description of Brodmann areas.

gyrus [BA 17] and cuneus [BA 18]), and the cerebellum were activated. During the viewer-dependent visual control task, regions of activation were reported in two frontal regions (medial frontal [BA 8] and anterior cingulate [BA 32]), one temporal region (parahippocampal [BA 35]), one parietal region (precuneus [BA 7]), and several occipital regions (medial occipital [BA 18], superior occipital [BA 19], cuneus [BA 17], and lingual [BA 17]).

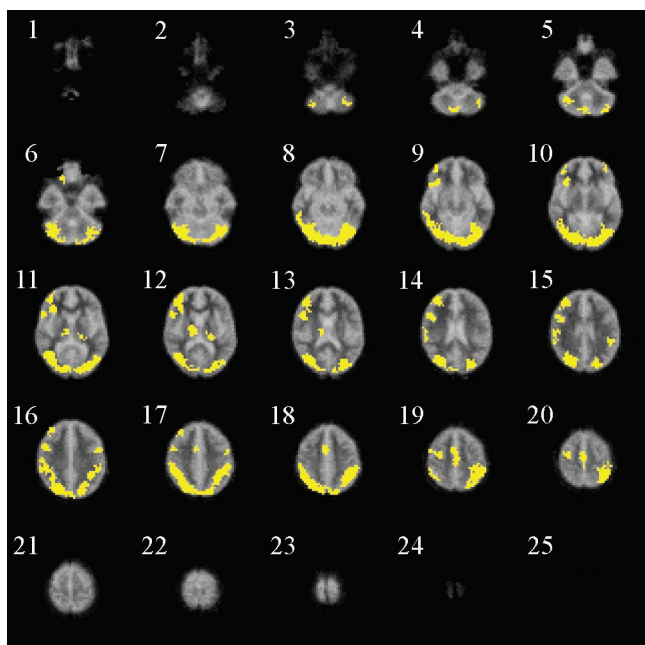
*Hippocampal-parahippocampal region analysis.* In line with the experimental prediction, there was activation during the viewer-independent task in the hippocampal-parahippocampal region, but this was observed in the encoding condition only. This activation was found in the task versus resting baseline condition, but with no difference in a direct comparison between the viewpoint-independent and viewpoint-dependent conditions. Nevertheless, the significant activation in the viewpoint-independent condition in a cluster of voxels in the predicted region of the hippocampus and parahippocampal gyri suggests that such activation was more robust in this condition (see again Figure 4). In this connection, these data were subjected to further detailed analysis in which the coordinates for each voxel within the activated brain regions were identified (see Table 3). Using the Talairach atlas, voxels were assigned as being either hippocampal or parahippocampal, if they

either overlapped with these regions or were within 5 mm of their boundaries (see Table 3 legend for details of the method used).

The analysis showed 9 voxels to be situated within the Talairach-defined hippocampus and 6 voxels within the Talairach-defined parahippocampal gyrus. Moreover, 7 additional voxels were shown to be within 5 mm of the hippocampus and another 12 within 5 mm of the parahippocampal gyrus. One voxel was found on the cusp of the hippocampus and parahippocampal gyri. The remaining voxels in each activation were found to be more than 5 mm from either the Talairach-defined hippocampus or parahippocampal gyrus and are therefore not considered.

In summary, using the method described above, 5 voxels were allocated to the left hippocampus and 11 to the right, and 11 voxels were allocated to the left parahippocampal gyrus and 7 to the right, with 1 voxel found on the cusp of the right hippocampus-parahippocampal gyri.

*Displacement error behavioral analysis.* The mean displacement values for the two tasks were as follows: viewer-independent  $M = 63,907.53$  units ( $SD = 20,881.72$ ), and viewer-dependent  $M = 41,669.64$  units ( $SD = 21,180.23$ ). This was confirmed using a one-way analysis of variance (ANOVA), which showed that performance on the viewer-independent task was significantly less



**Figure 5.** Viewer-dependent encoding versus rest activation. All activity shown on the images occurred during the egocentric encoding phase. No activity was found above threshold during the rest phase during these analyses. Slices 9–10 indicate the involvement of the right superior temporal gyrus, and Slice 14 the activation of the transverse temporal gyrus. Large bilateral superior parietal activations are observed on Slices 16–19. Paracentral lobule activation is found on Slice 19. Inferior parietal activations are present on Slice 15. Right-sided precentral gyrus activation is clearly seen on Slice 13, and left-sided activation in this region on Slice 17. Slices 15–16 present the right medial frontal activations, and the bilateral inferior frontal regions are shown on Slices 9–14. Lingual gyri activations are observed on Slices 8–11, and the additional occipital cortex activations on Slices 10–13. Bilateral medial occipital activations are present on Slices 13–14. Bilateral cerebellar activity is present on Slices 3–7. A large right posterior thalamic activation is observed on Slices 11–13, and a smaller left posterior thalamic activity on Slices 11–12. Right anterior (anterior–posterior delineated by the central sulcus) cingulate gyrus activation is shown on Slices 17–18. See the Method section for statistical threshold used. Right side of image represents left side of brain.

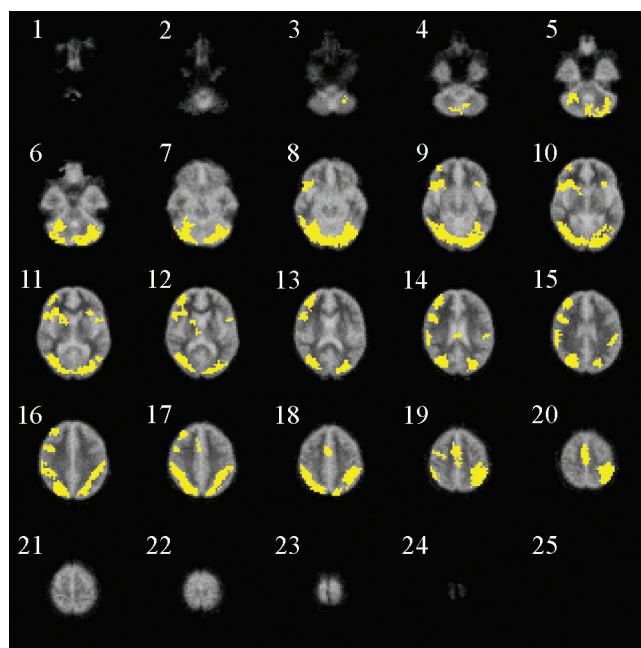
accurate,  $F(1, 10) = 6.41, p = .03$ . Displacement error scores were also correlated with mean activation values for each of the activations reported in the hypothesized region of interest (again, see Table 3). These analyses found no significant correlations among these measures:  $-22 -30 -2, r(11) = -.11, p = .73$ ;  $18 -30 -2, r(11) = -.34, p = .30$ ;  $22 -30 -2, r(11) = -.26, p = .43$ ;  $-11 -26 -7, r(11) = .22, p = .52$ ; and  $18 -29 -13, r(11) = .36, p = .27$ .

### Discussion

In summary, this study showed a network of activation associated with spatial memory function, including parietal, thalamic, and hippocampal–parahippocampal activation. Bilateral hippocampal–parahippocampal activation was only shown during the viewer-independent encoding phase, with the hippocampal activation mainly in the right brain. A region-of-interest analysis that

was based on individual voxel coordinates demonstrated, in further detail, the distribution of active voxels within the hippocampal region. There were no significant differences between left- and right-sided activation. Hence, the study set out to investigate whether the hippocampus was involved in processing of allocentric and not viewpoint-dependent processing. This is indicated by the data but only at the encoding phase of the experiment.

The hippocampal–parahippocampal activation was associated with viewer-independent spatial memory processing. This is in a scenario where the participant has to judge location in relation to the frame of reference of the environment, with egocentric location changed from encoding to test. The findings are consistent with those of Holdstock et al. (1999, 2000) and King et al. (2002), where bilateral hippocampal lesions specifically produced a deficit in this function. The type of memory tested in these studies may be the same, but there are procedural differences. For example, in the Holdstock et al. (1999, 2000) studies, the patient had to walk around the display and several locations were used. In the King et



**Figure 6.** Viewer-dependent retrieval versus rest activation. Slice 8 shows right superior temporal gyrus activation, and Slice 9 bilateral superior temporal activations. Bilateral parietal activations are evident on Slices 15–18. Inferior parietal lobe activations are present on Slices 15–16, and superior parietal on Slices 17–18. In addition, paracentral activations are found on Slice 20, and right precentral activations on Slices 12 and 19. Right inferior frontal activation is present on Slices 9–14. Slices 15–16 show the medial frontal gyri activations. Bilateral lingual gyrus activations are shown on Slices 8–10. Bilateral cuneus activations can be found on Slices 11–17. Bilateral medial occipital activations are present on Slices 11–14. Slices 3–7 show bilateral cerebellar activations. Thalamic activity can be clearly seen on Slice 13. The thalamus is also activated anteriorly on Slice 11 (with most of the activation in the inferior frontal lobe). Right basal ganglia structures are shown to be at the peak of an activation that mostly involved the right inferior frontal lobe (see Slice 10). Slice 18 shows an anterior cingulate activation. See the Method section for statistical threshold used. Right side of image represents left side of brain.

Table 3  
*Individual Voxel Coordinates With the Hippocampal–Parahippocampal Region*

Region coordinate	Voxel coordinate
-22 -30 -2 (Total: 22 voxels)	-22 -30 -2: Hipp
	-25 -29 -2: Hipp
	-14 -25 -2: PHG
	-18 -25 -2: PHG
	-21 -25 -2: PHG
	-25 -25 -2: PHG
	16 voxels > 5 mm from Hipp/PHG
18 -30 -2 (Total: 14 voxels)	25 -25 -2: Hipp
	21 -25 -2: Hipp
	18 -30 -2: PHG
	14 -29 -2: PHG
	11 -29 -2: PHG
	18 -25 -2: PHG
	14 -25 -2: PHG
	7 voxels > 5 mm from Hipp/PHG
22 -30 -7 (Total: 14 voxels)	22 -25 -7: Hipp
	26 -22 -7: Hipp
	22 -22 -7: Hipp
	26 -18 -7: Hipp
	22 -18 -7: Hipp
	18 -29 -7: PHG
	14 -29 -7: PHG
	18 -25 -7: PHG
	14 -25 -7: PHG
	11 -25 -7: PHG
	18 -22 -7: PHG
	14 -22 -7: PHG
	22 -30 -7: Cusp of Hipp/PHG
	1 voxel > 5 mm from Hipp/PHG
-11 -26 -7 (Total: 9 voxels)	-18 -22 -7: Hipp
	-11 -26 -7: PHG
	7 voxels > 5 mm from Hipp/PHG
18 -29 -13 (Total: 7 voxels)	18 -29 -13: Hipp
	14 -29 -13: Hipp
	21 -25 -13: Hipp
	18 -25 -13: Hipp
	14 -25 -13: Hipp
	18 -22 -13: Hipp
	14 -22 -13: Hipp

*Note.* Table 3 shows individual voxel coordinates within each hippocampal–parahippocampal activated brain region during the viewer-independent encoding task (see Figure 2, Slices 8, 9, and 10, and Figure 4). The table lists voxels within the Talairach-defined boundary of the hippocampal and parahippocampal regions. It also gives voxels within 5 mm of these boundaries (7-mm smoothing was used during the analyses and, therefore, only voxels within 5 mm from either the hippocampus or parahippocampal gyrus were considered). Hipp = hippocampus; PHG = parahippocampal gyrus.

al. study, virtual reality was used, so the patient had to navigate without the ideothetic self-motion cues associated with being immersed in an environment. These two studies incorporated a design in which the patients rotated around a central array; for the Holdstock et al. (1999, 2000) studies, LEDs were observed on a display board from the perimeter, and for King et al., object and pattern cues were associated with a spatial environment in which the patient was looking from the ramparts of a walled town square. Despite these differences, a similar result was obtained. Consistent with these paradigms, the current study also required the participant to move from the outer limits of the experimental environment. The difference with the current arena, however, was that the

navigational cues came from the periphery, rather than the configural cues of the spatial layout generated by multiple locations presented in the Holdstock et al. (1999, 2000) and King et al. experiments.

In the current study hippocampal–parahippocampal activation was found during the encoding but not retrieval phase of the viewpoint-independent task. Other studies of spatial memory have found activation during the retrieval phase (e.g., Ghaem et al., 1997; Maguire, Burgess, et al., 1998; Maguire, Frackowiak, & Frith, 1997). This result, however, may in part relate to the procedure used to test spatial memory. In the encoding phase the participant was presented with a familiar spatial environment, with the encoding aspect being the requirement to link the location of the pole with the layout of the arena. Hence, encoding may have involved retrieval of a cognitive map to remember the pole location. It is possible that the requirement to link the position of the pole to the arena cues sets up a more robust activation of the neuronal systems specifically involved in spatial mapping, whereas with retrieval of this information, the processes are more automatic and require less neural activation. Alternatively, the encoding phase may have been associated with longer encoding activity, throughout the 30-s epoch. In the retrieval phase the participant might have determined the location more rapidly. Similarly, it is possible that in the encoding phase the participant was continuously processing the pole location in relation to the frame of reference of the environment; in the retrieval phase, the location was immediately recoded into an egocentric frame of reference. Moreover, it should be noted that a greater number of trials would make the procedure more sensitive and result in measurable hippocampal–parahippocampal activation.

Many studies exploring spatial memory in patients with unilateral hippocampal formation lesions (see R. G. Morris, Nunn, Abrahams, Feigenbaum, & Recce, 1999) have shown right-sided deficits. In this study the activation pattern was bilateral but mainly in the right brain, approximately congruent with this finding. In other neuroimaging studies, there has been a mixed pattern of results. Some studies (e.g., Maguire, Burgess, et al., 1998) found greater right hippocampal activation while the participants navigated through a naturalistic environments, whereas other studies found bilateral or even left-sided activation (e.g., Aguirre & D'Esposito, 1997; Aguirre et al., 1996; Aguirre, Zarahn, & D'Esposito, 1998a, 1998b; Burgess, Maguire, Spiers, & O'Keefe, 2001; Maguire et al., 1996). Various explanations for bilateral activation can be considered. A straightforward explanation is based on the left hemisphere being responsible for verbal memory such as narratives (Frisk & Milner, 1990), with left activation associated with verbal recoding or visual or spatial information. Another notion is that the left hippocampus has a more general role in episodic memory, with the right more specifically involved in the geometric aspects of spatial navigation (Burgess, 2002; Maguire, Burgess, et al., 1998). In this case, spatial navigational tasks could activate the left hippocampus if they are making demands on the episodic aspect. As an elaboration of this theory, Burgess et al. (2001) have suggested that an evolutionary progression from a spatial to an episodic system in the left hippocampus may have taken place, and this occurred through the retrieval of context as a specific mechanism. A more simple explanation for bilateral involvement is that there may be a more even distribution of spatial representation across the hemispheres than implied by the unilat-

eral lesion studies. A possible way of reconciling the functional neuroimaging and lesion data would be to assume that the input to the system is predominantly from the right hemisphere, but the representation is bilateral. Lesioning a right-hemisphere neural mechanism could impair the input of spatial information and, hence, result in spatial memory impairment.

Activation was found in both hippocampal and parahippocampal regions. Previous studies have shown variability in the degree of involvement of the two structures. For example, some studies have shown activation involving the hippocampus (e.g., Ghaem et al., 1997; Maguire, Burgess, et al., 1998), and others have reported it within the parahippocampal region either alone or combined with the hippocampus; these findings are from studies using virtual reality (e.g., Aguirre et al., 1996; Aguirre & D'Esposito, 1997; Maguire, Frith, et al., 1998), imagined navigation (Ghaem et al., 1997; Maguire, Frackoviak, & Frith, 1997), and films of routes (Maguire, Frackoviak, & Frith, 1996). There are various possible explanations for these differences, including, for example, the differences in procedures, which may invoke different patterns of activation within the same system. In addition, the boundaries between the two structures can be difficult to differentiate within the spatial resolution of fMRI combined with Talairach mapping. In some cases, the technique is to take a peak activation within a particular activated region; although this may provide an indication of where the epicenter of the activation resides, the spread of activation may incorporate additional regions. In the individual voxel analysis above, activated voxels were found in both hippocampal and parahippocampal regions. This is in keeping with some studies that have suggested a role for the parahippocampal gyrus as a substrate for viewpoint-independent navigation (e.g., Aguirre et al., 1996). This finding may also be supported by the finding of spatial view and place-cell firing in the parahippocampal region in nonhuman primates (Nishijo, Ono, Eifuku, & Tamura, 1997; Rolls et al., 1989). Other studies have indicated parahippocampal involvement in the spatial elements of visual scene processing, also involving the fusiform cortices. These studies include work by Epstein and Kanwisher (1998) and Epstein, Harris, Stanley, and Kanwisher (1999), who allocated a part of the parahippocampal gyri to an area called the parahippocampal place area, which responded to static spatial scenes. This result even applied to scenes broken up into their component parts but still in a configuration that could be formed into a coherent spatial structure.

The current study found posterior hippocampal–parahippocampal activation. In meta-analyses of episodic PET memory studies, Lepage, Habib, and Tulving (1998) and Schacter and Wagner (1999) reported activations in the hippocampal region located primarily in the anterior area during encoding tasks and the posterior area during retrieval tasks. They referred to this general pattern as the hippocampal encoding/retrieval (HIPER) model. Schacter and Wagner similarly concentrated on the role of the medial temporal lobe activations during episodic encoding and retrieval in their meta-analysis of PET data. Although less sharply defined, Schacter and Wagner also found that encoding activations tended to occupy anterior sites and retrieval activations tended to occupy more posterior sites.

In our method, during the encoding phase, the participant is presented with a familiar spatial environment. Thus, during this phase the neural processing required by the participants may

involve retrieval of a cognitive map to lay down a memory trace of the pole location. Thus, in line with Lepage et al. (1998) and Schacter and Wagner (1999), perhaps it is this process that provides the posterior activation of the hippocampal–parahippocampal region during the encoding phase of our arena task.

An alternative explanation is that the posterior hippocampal formation tends to preferentially support spatial memory function. Partial support for this explanation lies in the fact that the posterior hippocampal region in humans corresponds to the dorsal hippocampus in rodents. In rodents, spatial learning impairment becomes worse with increased resection of the dorsal hippocampus but is hardly present after ventral (anterior) lesions (Moser, Moser, & Anderson, 1993). In addition, in studies of patients with unilateral hippocampal formation lesions, the extent of spatial memory impairment appears to increase significantly as the lesions encroach on the posterior region, as supported by studies of patients who have undergone unilateral temporal lobectomies (Graydon, Nunn, Polkey, & Morris, 2001; Nunn et al., 1998, 1999; Smith & Milner, 1981, 1989).

The nature of the spatial representations explored in this study is an important issue, and the investigation is based on the assumption that the viewer-independent condition in this test can be solved using cognitive mapping, whereas the viewer-dependent condition relies on a different form of representation. It should be acknowledged that different frameworks exist that can accommodate the same data, including the notion that all spatial memories are primarily egocentric (Diwadkar & McNamara, 1997; Shelton & McNamara, 1997; Wang, 1999). For example, it has been proposed recently that humans can solve so-called allocentric tasks by representing the egocentric positions of target objects and updating these representations while moving (Wang, 2003). According to this theory, place cells that appear to be coding position in a cognitive map may be involved in learning associative rules, consistent with finding that hippocampal lesions give rise to deficits in associative learning (Eichenbaum, Otto, & Cohen, 1992). In our study, the neural activity associated with the viewpoint-independent condition may be associated with the increased number of the representations rather than spatial mapping. Nevertheless, other theorists have challenged the notion that egocentric spatial representations are stored in long-term memory and suggested that there may be a more transient egocentric system and more permanent representation that is based on object-to-object relations (McNamara, 2003).

The study highlights several other regions that may be involved in spatial orientation, including the parietal lobes and thalamus. The results are broadly consistent with previous studies that have examined the network supporting spatial memory (Burgess, 2002; Burgess, Maguire, & O'Keefe, 2002). Posterior parietal lobe activation was observed, with the largest activation represented bilaterally in the precuneus (BA 7). The parietal lobes, in particular, have well-established involvement in spatial processing. For example, posterior parietal lobe cells in nonhuman primates respond to egocentrically encoded object location (Andersen, Essick, & Siegel, 1985). Computational models have been proposed that incorporate activity within the posterior parietal cortex (Pouget & Sejnowski, 1997; Zipser & Anderson, 1988). Burgess et al. (2001) have proposed that the posterior parietal region is involved in mapping between view-independent and body-centered (viewer-dependent) representations. If this is the case, then both the view-

point-independent and -dependent tasks are activating such functions. Bilateral thalamic activation was also apparent during both tasks. The existence of head-direction cells (e.g., Taube, 1995) in the thalamus supports a role in spatial orientation. Activation of this region in the current experiment may suggest recoding of spatial information into an egocentric framework. Although there are no proprioceptive or otolithic inputs that signal changes in head direction because the head is static throughout the tasks in the fMRI experiment, the visual input of changes in viewpoint may nevertheless indicate changes in head direction relative to the visual display and, therefore, provide activation in this region.

In conclusion, this study has shown that a network of regions are involved during encoding and retrieval of both viewer-independent and -dependent spatial memory. The study found, in line with experimental hypothesis, bilateral activation in the hippocampal region, mainly in the right brain, during viewer-independent spatial memory processing (although only during encoding). Additionally, more detailed analysis has shown voxels within these activations to be in both the hippocampus and parahippocampal gyri. No activation was observed in this region during performance in the viewer-dependent task. These data, therefore, provide further support for the hypothesis that the hippocampal region preferentially supports allocentric or viewpoint-independent spatial memory but with bilateral involvement.

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