

# “I Have Often Walked Down This Street Before”: fMRI Studies on the Hippocampus and Other Structures During Mental Navigation of an Old Environment

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**ABSTRACT:** The role of the hippocampus in recent spatial memory has been well documented in patients with damage to this structure, but there is now evidence that the hippocampus may not be needed for the storage and recovery of a spatial layout that was experienced long before injury. Such preservation may rely, instead, on a network of dissociable, extra-hippocampal regions implicated in topographical orientation. Using functional magnetic resonance imaging (fMRI), we investigated this hypothesis in healthy individuals with extensive experience navigating in a large-scale urban environment (downtown Toronto). Participants were scanned as they performed mental navigation tasks that emphasized different types of spatial representations. Tasks included proximity judgments, distance judgments, landmark sequencing, and blocked-route problem-solving. The following regions were engaged to varying degrees depending on the processing demands of each task: retrosplenial cortex, believed to be involved in assigning directional significance to locales within a relatively allocentric framework; medial and posterior parietal cortex, concerned with processing space within egocentric coordinates during imagined movement; and regions of prefrontal cortex, present in tasks heavily dependent on working memory. In a second, event-related experiment, a distinct area of inferotemporal cortex was revealed during identification of familiar landmarks relative to unknown buildings in addition to activation of many of those regions identified in the navigation tasks. This result suggests that familiar landmarks are strongly integrated with the spatial context in which they were experienced. Importantly, right medial temporal lobe activity was observed, its magnitude equivalent across all tasks, though the core of the activated region was in the parahippocampal gyrus, barely touching the hippocampus proper. © 2004 Wiley-Liss, Inc.

**KEY WORDS:** retrograde memory; spatial memory; functional neuroimaging; medial temporal lobe; neocortex

## INTRODUCTION

The ease with which humans and animals, alike, conjure up representations of an environment to reach an unseen destination belies the complex perceptual, mnemonic, motor, and executive computations necessary for navigation. Despite this complexity, until recently, researchers, particularly

those concerned with animals, focused their attention on the hippocampus and on adjacent regions as the structures vital to spatial memory and navigation to the relative neglect of other parts of the brain.

Evidence that the hippocampus is needed for the formation and storage of allocentric representations of recently encountered spatial layouts is widespread, the earliest and arguably most powerful support deriving from single-cell recording and lesion studies in animals (e.g., O'Keefe and Nadel, 1978; Morris et al., 1982; O'Keefe, 1999). That the hippocampus is limited to this form of memory, however, is under considerable debate, particularly with respect to humans (see Cohen and Eichenbaum, 1993). Moreover, the literature in humans suggests that the neighboring parahippocampal gyrus (PHG) is at least as good a candidate as the hippocampus as a structure crucial for memory for spatial relations. Patients with right hippocampal lesions, but an intact PHG, have been shown to retain over a delay the location of a hidden sensor solely by means of allocentric environmental cues, whereas those with right PHG lesions were unable to do so (Bohbot et al., 1998; for a recent demonstration in nonhuman primates, see Málková and Mishkin, 2003). Moreover, the peak coordinate of activity revealed in neuroimaging studies on spatial memory is often better characterized as within PHG, at most bordering the hippocampus, rather than in the body of the hippocampus itself (e.g., Aguirre et al., 1996; Maguire et al., 1998; Shelton and Gabrieli, 2002).

Insofar as it has been tested, this pattern is also true of memory for spatial layouts learned in the remote past (Maguire et al., 1997; Niki and Luo, 2002). In fact, detailed investigations in amnesic patients indicate that the hippocampus is not needed for remote spatial memory (Teng and Squire, 1999; Rosenbaum et al., 2000), defined in the present study as involving the maintenance and recovery of large-scale spatial representations, including allocentric cognitive maps, that had been acquired and used extensively since long before injury, and in some cases continue to be used (Rosenbaum et al., 2000). Although it is possible that the small amount of hippocampal tissue that might have survived injury in the patients is adequate to support remotely formed spatial memories, a more likely interpretation is that these memories depend on a distributed network of extra-hip-

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pocampal structures implicated in spatial representations and spared in amnesic patients. Structures outside the medial temporal lobe (MTL) include, but are not limited to, retrosplenial cortex, which enables access to directional information from recognizable landmarks within an allocentric or survey framework; medial parietal cortex or precuneus, assigned to spatial imagery; posterior parietal cortex, involved in egocentric, route-based processing of landmarks in relation to the navigator; and a region of inferior temporal cortex believed to be unique to landmark perception (for comprehensive reviews, see Barrash, 1998; Aguirre and D'Esposito, 1999). A number of studies have shown differential recruitment of these brain structures to be dictated by the perspective in which a novel environment is first encoded (Mellet et al., 2000; Shelton and Gabrieli, 2002), but it remains unknown whether the precise nature of an already well-established spatial representation would differ if retrieval depends more on a survey or route perspective.

By exploring different aspects of remote spatial memories, the present study addresses two related questions: Are the hippocampus and related MTL structures, which are needed for supporting spatial memories formed more recently, also implicated in the retrieval and manipulation of those formed long ago? Are extra-hippocampal structures activated selectively for different aspects of remote spatial memory as they have been shown to be activated on tests of recent memory? To answer these questions, brain activity was examined with functional magnetic resonance imaging (fMRI) in healthy young adults as they relied on their knowledge of an extensively experienced, downtown environment to make a variety of spatial judgments. Mental navigation tasks were selected that have a number of overlapping features but that differ in some fundamental way from one another. These include proximity and distance judgment tasks, which rely most on a map-like, survey representation of landmarks in relation to each other, and sequencing and detour tasks, which rely more on egocentric representations of landmarks during imagined movement along routes. The mental navigation experiment was followed by a second experiment, which used an event-related design to explore the neural basis of landmark identification as distinct from seeing a building for the first time. This additional ventral-stream aspect of topographical knowledge (Aguirre and D'Esposito, 1999) necessarily requires visual perception at test to enable examination of the brain regions involved in distinguishing known landmarks from unknown buildings.

## MATERIALS AND METHODS

### Participants

Ten healthy, right-handed male adults (mean age, 26.4 years) participated in the experiment in return for monetary compensation. All reported on a detailed questionnaire that they had intensive experience navigating in downtown Toronto from 5–10 years ago to the time of scanning. None had a history of neurological or psychiatric illness or <20/20 vision uncorrected without access to



**FIGURE 1.** Map of the region of downtown Toronto on which all tasks were based. Participants did not see the map but instead were asked to make decisions about the routes and landmarks from their mental representation of the environment.

correctable contact lenses. Informed written consent was obtained from all participants in accordance with the Baycrest Centre for Geriatric Care and Sunnybrook and Women's College Health Science Centre ethical guidelines.

### Stimuli and Tasks

Based on a screening questionnaire administered 1 month prior to scanning, we included in the stimulus set only those landmarks selected as familiar by all participants. Prior to scanning, participants were given instructions and a practice trial for each task. Stimuli were presented with MEL v2.01 software (Psychology Software Tools, Pittsburgh, PA) on a back-projection screen using an LCD projector (model 6000, Boxlight, Poulsbo, WA) external to the magnet room, and line-of-site was achieved using angled mirrors mounted on the head coil. Responses were collected with fMRI-compatible keypads (Lightwave Technologies, Surrey, BC, Canada).

### Mental Navigation

With names of landmarks as cues, participants were required to perform various mental navigation tasks (see below). Each trial consisted of a novel pairing of words denoting well-known landmarks in downtown Toronto (Fig. 1). Landmark names were presented side by side in the center of the screen, and participants were

required to make right and left button presses according to task instructions presented prior to scanning and indicated by a written cue presented centrally on the screen at the beginning of each block. Each scanning run consisted of five blocks, with each block representing one of five tasks and lasting 30 s. Each block alternated with 30 s of a visuomotor control condition (passive viewing of strings of x's in place of words while pressing both buttons) for a total of 5 min per run. Tasks were presented five times and consisted of three trials, with each trial lasting 10 s as determined by a pilot study with nonparticipating young adults. To allow for direct comparisons across tasks, a block of each task was presented once within each of five scanning runs in a counterbalanced order; stimulus display and motor response were identical, with only task instructions distinguishing between experimental conditions as follows:

- *Task 1: Proximity judgments.* Participants indicated which of two landmarks was closest in distance to a reference landmark (specified in the instructions) with a button press corresponding to the side of the screen (left or right) on which the name of the correct landmark appeared.
- *Task 2: Distance judgments.* Participants judged whether the distance between each pair of landmarks was less than or greater than 2.5 km with respective left and right button presses (prior to scanning, participants were informed that the distance between the specified northern and southern limits of downtown Toronto is ~5 km).
- *Task 3: Landmark sequencing.* Participants determined whether each pair of landmarks was in the true order that would be passed if walking from the western to eastern limit of downtown Toronto as specified by street names presented in the instructions. A left button press referred to a "yes" response and a right button press to a "no" response (opposite for half of the participants).
- *Task 4: Blocked-route navigation.* Participants were told that a specified major street in downtown Toronto was blocked and asked to imagine walking along the most efficient route between each pair of landmarks, avoiding the blocked street. Participants were to respond "yes" if a second street specified in the instructions would be passed along the generated detour and "no" if not (right button press referred to a "yes" response for half of the participants).
- *Task 5: Perceptual baseline.* Participants selected which of two landmarks had more vowels in its name by pressing the button corresponding to the side of the screen in which the choice landmark appeared.

After the landmark identification experiment (described next), participants were provided with detailed descriptions of map-like, survey-based, and ground-level, route-based representations of environments. Participants were then asked to perform three additional trials of each spatial task and to comment on their relative use of a survey perspective, route perspective, or both when solving each trial with a "yes/no" response. The results of this formal test corresponded to the participants' own informal comments about the strategies they used.

## Landmark Identification

Twenty-one color photographs of downtown Toronto landmarks indicated by all participants as familiar were included. A second set of 21 photographs of landmarks that are structurally similar to those located in Toronto, but never encountered by the participants, served as distracters. All photographs were taken from an unobstructed view and were digitally scanned and adjusted for luminance and contrast. Twenty-one unrecognizable scrambled photographs of equivalent visual complexity to the targets and distracters were included as a control condition. Using an event-related design, stimuli from each of the three conditions (i.e., target landmarks, distracter landmarks, scrambled) were presented singly for 5 s in random order. An average stimulus onset asynchrony of 5 s was randomly varied between 4 and 6 s to ensure that event onsets were evenly distributed in time across image slices (see Josephs and Henson, 1999; Miezen et al., 1999). Participants were instructed to press the right button if the stimulus was located in downtown Toronto, the left button if not (opposite for half of the participants), and both buttons simultaneously if the stimulus was a scrambled photograph. During the inactive period between stimulus presentations, participants were asked to maintain visual fixation on a small, centrally located cross presented on an otherwise blank screen. Accuracy and response latency to the button press were recorded.

## Image Acquisition

Participants were scanned with a Signa 1.5-tesla (T) magnet with a standard coil (CV/i hardware, LX8.3 software; General Electric Medical Systems, Waukesha, WI). A standard high-resolution, 3D T1-weighted fast spoiled gradient echo image (TR = 12.4 ms; TE = 5.4 ms; flip angle = 35°; acquisition matrix = 256 × 192; FOV = 22 × 16.5; 124 axial slices; slice thickness = 1.4 mm) was first obtained to register functional maps against brain anatomy. Functional imaging was performed to measure brain activation by means of the blood oxygenation level-dependent (BOLD) effect (Ogawa et al., 1990) with optimal contrast. Functional scans were acquired with a single-shot T2\*-weighted pulse sequence with spiral readout (TR = 2,000 ms; TE = 40 ms; flip angle = 80°; effective acquisition matrix = 90 × 90; FOV = 22 cm; 26 slices; slice thickness = 5.0 mm), including off-line gridding and reconstruction of the raw data (Glover and Lai, 1998).

## Data Analysis

Accuracy (percentage correct) and reaction time were analyzed with repeated-measures analysis of variance (ANOVA). Image processing and analysis were performed using the Analysis of Functional Neuroimages (AFNI, version 2.25) software package (Cox, 1996; Cox and Hyde, 1997). The initial 10 images, in which transient signal changes occur as brain magnetization reaches a steady state, were obtained prior to task presentation and excluded from all analyses. Time series data were spatially co-registered to correct for head motion using a 3D Fourier transform interpolation (the peak range of head motion was <1 mm for all partici-

TABLE 1.

*Areas of Activation Associated with the Mental Navigation Task Versus Baseline Comparisons ( $P < 10^{-8}$ ; cluster size  $> 150$ )\**

Area of activation	Proximity (coord/ <i>t</i> -score)	Distance (coord/ <i>t</i> -score)	Sequencing (coord/ <i>t</i> -score)	Blocked routes (coord/ <i>t</i> -score)
R superior frontal gyrus (BA 6)	18, 15, 49/9.3			18, 14, 49/11.02
L middle frontal gyrus (BA 6)	-36, 5, 58/10.52			-35, 3, 50/11.52
R parahippocampal gyrus (BA 36) <sup>a</sup>	25, -35, -10/13.59	24, -35, -10/11.87	24, -35, -10/11.84	25, -35, -10/14.06
L parahippocampal gyrus (BA 36)				-19, -42, -8/9.92
L retrosplenial cortex (BA 29/30)	-7, -49, 9/20.46	-19, -59, 17/17.29	-19, -58, 17/16.63	-19, -58, 18/19.98
R superior occipital gyrus (BA 19)	39, -79, 27/14.27	40, -79, 27/9.58	40, -78, 26/11.12	44, -70, 25/12.82
L superior occipital gyrus (BA 19)	-31, -83, 31/12.19		-33, -85, 31/12.13	-32, -84, 30/12.79

BA, Brodmann's area; L, left; R, right.

\*The Talairach coordinates are based on the peak voxel in *t*-value. Brodmann's area according to the atlas of Talairach and Tournoux (1988).

<sup>a</sup>Talairach coordinates reported by Maguire et al. (1997) as right hippocampus were 16, -38, 0; those reported by Shelton and Gabrieli (2002) as parahippocampus-posterior hippocampus were 21, -41, -3 on the right and -18, -41, -6 on the left.

pants). The five scanning runs were then concatenated and activation maps of the BOLD signal for each subject were calculated for each condition with respect to the perceptual baseline (analysis of each experimental task was also performed against the visuomotor control task, the results of which were similar to the perceptual baseline comparisons and thus not described). The resulting individual activation images representing each task contrast of interest were transformed into Talairach coordinates and smoothed with a Gaussian filter of 6-mm full-width-at-half-maximum (FWHM) to increase the signal-to-noise ratio. This was done to permit subsequent group analysis, consisting of a voxel-wise, mixed model, two-factor ANOVA with participants as a random factor and task as a fixed factor.

The event-related experiment was analyzed by deconvolution of the fMRI time-series data. Based on a subject's fMRI signal data and the input stimulus function, AFNI estimates the impulse response function and performs a multiple linear regression analysis of the time series data. The impulse response function is then convolved with a stimulus time series to provide the estimated response. Group analysis was done on the regression parameters with repeated-measures ANOVAs, and only those trials on which the subject made a correct response were included in the analyses.

Statistically significant brain activity was established using a voxel-cluster threshold technique for a whole brain corrected level of significance of  $< 0.001$  for the baseline comparisons (voxel  $P < 10^{-8}$ ; minimum cluster size,  $150 \text{ mm}^3$ ) and 0.05 for the direct task comparisons (voxel  $P < 0.001$ ; minimum cluster size,  $540 \text{ mm}^3$  for mental navigation; voxel  $P < 0.01$ ; minimum cluster size,  $900 \text{ mm}^3$  for landmark recognition). The coordinates of clusters were determined by the location corresponding to the peak *t*-value. Finally, the extent of the hippocampus was defined through visual inspection of structural MRI data guided by published anatomical procedures (Shenton et al., 1992) and the atlas of Talairach and Tournoux (1988) to permit individual-subject analysis of activation within this region for each task.

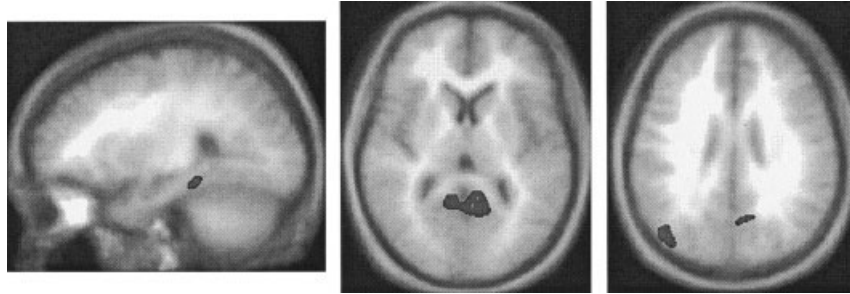
## RESULTS

### Mental Navigation

Accuracy was significantly worse for the proximity judgment task (mean, 69%; SD, 5.4) relative to the landmark sequencing task (mean, 87%; SD, 8.3),  $t_9 = 1.8$ ;  $P < 0.01$ , and perceptual baseline task (mean, 87%; SD, 4.9),  $t_9 = 3.25$ ;  $P < 0.01$ , but not the distance judgment task (mean, 82%; SD, 14.3),  $t_9 = 1.1$ ;  $P < 0.09$ , or blocked route task (mean, 75%; SD, 10.9),  $t_9 = 0.59$ ;  $P = 0.99$ . There were no other significant differences in accuracy. In contrast, response latency did not differ significantly across tasks. In post-scan interviews, participants reported a greater contribution of world-centered, allocentric processing to solving proximity and distance judgment tasks (on average, 2.6 of the 3 trials were reported as survey-based for both tasks) and of body-centered, egocentric processing to solving the remaining landmark sequencing and blocked route tasks (on average, 2.5 and 2.4 of the 3 trials were reported as route-based, respectively).

### Task Versus Baseline Comparisons

Mean percentage increase in BOLD signal intensity from the perceptual baseline condition was first calculated for each task to reveal areas of shared and unique activity (Table 1; Fig. 2). Significant increases in activity common to all tasks were found in right PHG (BA 36) extending into the posterior edge of the hippocampus only at a lower threshold ( $P < 0.001$  uncorrected), left retrosplenial cortex (BA 29/30; 30/31) incorporating left precuneus (BA 7), and right superior occipital gyrus (BA 19), but the extent of activity of each region varied across tasks. Likewise, a number of brain regions responded selectively to some tasks and not others. Significantly greater activation was observed in right superior and left middle frontal gyrus (BA 6) only in response to the proximity and blocked-route tasks and in left superior occipital gyrus (BA 19) in response to all but the distance task. Task-specific activity was also found in the left PHG (BA 36) for the blocked-route task.



**FIGURE 2.** Brain regions activated in the comparison of all remote spatial memory tasks with the perceptual baseline task. Areas of common activity included right parahippocampal gyrus, left retrosplenial cortex, and right superior occipital cortex. The functional

maps are overlaid on the averaged anatomical scans from all participants in relevant sagittal and axial views. The right hemisphere is shown on the left side of the images. Images were thresholded at  $P < 0.001$ , corrected. Coordinates and  $t$ -values are listed in Table 1.

There were no areas of activity exclusive to the perceptual baseline condition, nor was activation of the hippocampus found in response to any task in individual-subject analysis.

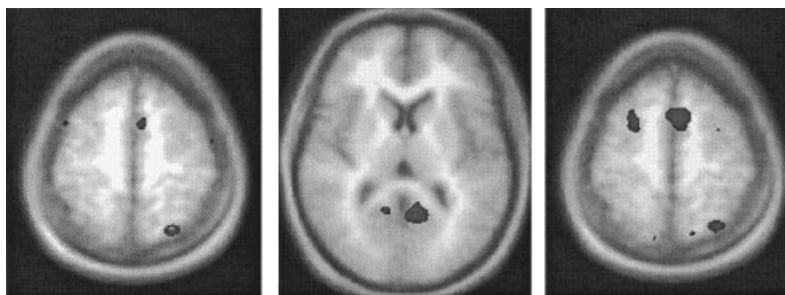
### Comparisons Among Tasks

Direct comparisons among tasks suggested that at least some areas of shared activity revealed in the baseline comparisons were, in fact, recruited to a different extent in each task, even when demands on mental navigation and imagery were equated (Fig. 3). The main effect of processing strategy was first analyzed based on the participants' assignment of tasks into allocentric and egocentric categories in post-scan interviews. This analysis revealed a region of medial-superior parietal cortex (peak voxel:  $-23, -64, 55$ ) to be more active for the egocentric tasks compared to the allocentric tasks (landmark sequencing,  $t = 10.39$ ; blocked route,  $t = 11.57$ ). Additional post-hoc comparisons of tasks with each other showed left retrosplenial cortex to be significantly more active during the proximity judgment task (peak voxel:  $-5, -52, 10$ ;  $t = 17.72$ ) when compared directly to each of the landmark sequencing and blocked-route tasks but not when compared to the distance judgment task. Finally, significantly greater activity was observed in the right middle frontal gyrus (peak voxel:  $38, 6, 47$ ;  $t = 8.37$ ) and the left superior frontal gyrus (peak voxel:  $-10, 20, 59$ ;  $t = 4.24$ )

during the route task when compared directly to the distance task. Activity in PHG and superior occipital gyrus was not found to differ significantly across tasks.

### Landmark Identification

Areas showing increased response to the known Toronto landmarks and unknown distracter buildings when compared to baseline and directly to each other are presented in Table 2. Common areas of activity included left inferior and middle occipital gyrus (BA 18/19) and right PHG (BA 36). The Toronto landmarks, but not distracters, activated right lingual gyrus (BA 17), as well as other regions previously implicated in topographical orientation, including PHG (BA 36) and retrosplenial cortex (BA 30) in the left hemisphere and superior occipital gyrus (BA 19) and cerebellum in the right. When contrasted directly with the unknown buildings, significant activation was found for the known landmarks in right PHG/lingual gyrus (BA 19), just posterior to the shared PHG activation (see Fig. 4). There was no evidence of any region of significant activity unique to the distracter condition. Again, participants did not show hippocampal activity in group or individual-subject analyses.



**FIGURE 3.** Regions in which activity increased significantly in response to direct task comparisons. Images show activity in left medial-superior parietal cortex associated with the main effect of egocentric vs. allocentric processing (left), in right retrosplenial cortex unique to the proximity judgment task (middle), and in right middle

and left superior frontal gyrus unique to the blocked route task (right). The functional maps are overlaid on the averaged anatomical scans from all participants in axial views. The right hemisphere is shown on the left side of the images. Images were thresholded at  $P < 0.05$ , corrected. Coordinates and  $t$ -values are listed in Table 1.

TABLE 2.

Areas of Activation Associated With the Toronto Landmarks and Distracter Buildings Revealed by Baseline ( $P < 10^{-8}$ ; Cluster Size  $> 150$ ) and Direct ( $P < 0.01$ ; Cluster Size  $> 900$ )\* Comparisons\*

Area of activation	Landmark > baseline (coord/ <i>t</i> -score)	Distracter > baseline (coord/ <i>t</i> -score)	Landmark > distracter (coord/ <i>t</i> -score)
R parahippocampal gyrus (BA 36) <sup>a</sup>	22, -41, -9/17.64	22, -41, -9/13.64	
R parahippocampal/lingual gyrus (BA 19)			17, -45, -3/8.42
L parahippocampal gyrus (BA 36)	-22, -43, -7/13.27		
L retrosplenial cortex (BA 29/30)	-11, -55, 9/10.51		
R superior occipital gyrus (BA 19)	36, -83, 25/13.31		
L middle occipital gyrus (BA 18/19)	-34, -92, 5/12.34	-35, -90, 6/11.14	
L inferior occipital gyrus (BA 18)	-30, -89, -6/10.61	-34, -83, -6/10.82	
R lingual gyrus (BA 17)	12, -91, -5/12.12		
R cerebellum	34, -48, -19/14.55		

BA, Brodmann’s area according to the atlas of Talairach and Tournoux (1988); L, left; R, right; PPA, parahippocampal place area.

\*The Talairach coordinates are based on the peak voxel in *t*-value.

<sup>a</sup>The Talairach coordinates reported by Epstein et al. (1999) as corresponding to the PPA were 20, -39, -5 on the right and -28, -39, -6 on the left.

## DISCUSSION

fMRI was used to examine the status of the hippocampus and other brain structures in different aspects of real-world topographical memories formed many years ago using a wider range of tests than used previously. The results of this investigation cast doubt on the long-held view that the hippocampus is fundamental to supporting and operating on spatial representations, particularly those established in the remote past. Instead, a predominantly temporoparietal network was found to be engaged during memory retrieval of an environment that was extensively experienced many years before scanning, with differences in task demands reflected in neural activity in some regions but not others. These two main findings are discussed in turn.

### Is There a Place for the Hippocampus in Remote Memory for Places?

The MTL was engaged to the same degree in all tests of mental navigation of an environment learned long ago. As in earlier neu-

roimaging studies of spatial memory (e.g., Maguire et al., 1997; Shelton and Gabrieli, 2002), its peak activity was well within the PHG, reaching the base of the hippocampus only at lower thresholds. The absence of a functionally separate voxel of activity within the hippocampus itself, even in individual participants, is consistent with recent observations of relatively preserved spatial memory for a neighborhood familiar from childhood in patients with extensive hippocampal damage bilaterally. For example, patients E.P. (Teng and Squire, 1999) and K.C. (Rosenbaum et al., 2000) were able to create detours between landmarks when faced with unusable routes, and more extensive examination of K.C. revealed normal performance on other remote neighborhood tests, including those used in the present study. It is still possible, however, that the hippocampus is needed for memory of more detailed features of a spatial representation as suggested by K.C.’s inability to recognize houses that he had visited often in the past, a deficit that resembles his profound episodic memory failure for details of personally relevant information. Nonetheless, we now have corroborating evidence from neuroimaging and from patients with large hippocampal lesions to show that at least some kinds of well-

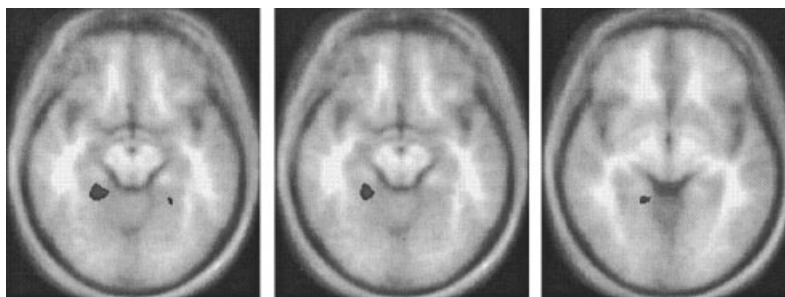


FIGURE 4. Inferior temporal cortex activity associated with both Toronto landmarks (left) and distracter buildings (middle) when compared with the perceptual baseline and with Toronto landmarks (right) when contrasted directly with distracter buildings. The func-

tional maps are overlaid on the averaged anatomical scans from all participants in axial views. The right hemisphere is shown on the left side of the images. Images were thresholded at  $P < 0.05$ , corrected. Coordinates and *t*-values are listed in Table 2.

learned spatial memories that have existed for years can be represented outside of the hippocampus. The absence of hippocampal activation for tests of remote spatial memory contrasts with our finding of hippocampal involvement in remote autobiographical retrieval using similar stimuli, equipment, and analytic procedures (Gilboa et al., in press; see also Maguire and Mummery, 1999; Ryan et al., 2001). Together, these results are consistent with the observation that detailed memory for remote autobiographical events is impaired following hippocampus lesions (e.g., Nadel and Moscovitch, 1997; Cipolotti et al., 2001; but see Bayley and Squire, 2003) but remote spatial memory is spared (Teng and Squire, 1999; Rosenbaum et al., 2000). Thus, we find parallel correspondence between activation and lesion studies for remote spatial memory and for autobiographical memory.

The precise nature of these spatial representations has yet to be determined. Rosenbaum et al. (2000, 2001) proposed that these memories might be schematic cognitive maps that retain the gist of the environment without rich contextual details that allow one to re-experience it. In this sense, they are spatial analogues of semantic memory. An alternative interpretation is that navigation through highly familiar and well-rehearsed environments no longer depends on allocentric cognitive maps but relies more on route knowledge (Hartley et al., 2003). Either way, the hippocampus should not be implicated, as indeed we found to be the case. Of the two alternatives, we prefer the former because performance on proximity judgments, which was tested in this study, and vector mapping, which was tested in a separate experiment (Rosenbaum et al., 2004), are not likely to rely on route knowledge. Moreover, participants in this study reported using allocentric cognitive maps to make these judgments.

### Parahippocampal Contributions to Spatial Memory

Using a more extensive series of tests of mental navigation and memory than had been used previously, we confirmed suggestions from previous neuroimaging and lesion studies that the PHG, and not the hippocampus, is the region that is consistently responsive during all tests of spatial memory. The PHG has been implicated in studies using virtual-reality (Aguirre et al., 1996; Shelton and Gabrieli, 2002) and videotaped real-world environments (Maguire et al., 1996) that have been learned recently as well as in mental simulation of routes learned by physical navigation in a small-scale environment a few days before scanning (Ghaem et al., 1997; Mellet et al., 2000) and within a large city many years before (Maguire et al., 1997). Detailed testing of patients with compromised PHG function is also consistent with a role for this structure in mental representations of space, at least with respect to acquisition. Such patients are disoriented in environments experienced for the first time post-injury (Ross, 1980; Habib and Sirigu, 1987; Maguire et al., 1996; Barrash et al., 2000; Epstein et al., 2001) and are unable to retain unfamiliar scene-like displays over filled delays despite intact perception of the same stimuli (Epstein et al., 2001). In contrast, there is some suggestion that remotely learned environmental representations are available to these patients, but this has been based on very limited testing via sketch maps, verbal

reports, and landmark recognition, and not on a large battery of tasks, such as the ones we used. Moreover, intact performance on more detailed tests of remote spatial memory in patients E.P. and K.C. might reflect bilateral PHG sparing, which was reported in both E.P. (Teng and Squire, 1999; Bayley and Squire, 2002) and K.C. (Rosenbaum et al., 2000).

With this in mind, our results may be interpreted in several ways. The most straightforward explanation would be that the equivalent contribution of the PHG across tasks reflects its role as a permanent repository for many types of spatial information that are or have become independent of hippocampal function (Eichenbaum et al., 1999; Nadel et al., 2003). This would include visual imagery of landmarks and their locations (see next section and Epstein and Kanwisher, 1998). If, on the other hand, it is discovered that navigation in premorbidly familiar places can be accomplished without the PHG, it is still conceivable that the PHG is implicated in updating or re-encoding the retrieved topographical information in normal people. In either case, our finding of additional left-sided PHG activity only during the blocked-route task is consistent with the highly temporal nature of mentally traveling from one destination to another, analogous to the sequential quality of an episode (Burgess et al., 2001).

### Beyond the Medial-Temporal Lobe

We identified extra-MTL areas that were engaged in all tasks but, unlike the PHG, the extent of their contribution depended on task requirements. This is in agreement with reports of patients with selective navigational disturbance within environments that were familiar prior to lesion onset, pointing to dissociable regions outside of the MTL that together might be responsible for supporting cognitive maps old enough to be impervious to hippocampal dysfunction (e.g., Barrash, 1998; Aguirre and D'Esposito, 1999). For example, though recognizable, landmarks lose meaning with respect to allocentric direction in patients with retrosplenial lesions (Cammalleri et al., 1996; Takahashi et al., 1997) and with respect to egocentric location in patients with posterior parietal lesions (Levine et al., 1985; Stark et al., 1996). In contrast, patients with lesions to inferotemporal cortex lose the ability to identify previously familiar landmarks visually, yet retain allocentric and egocentric spatial relations when given landmark names (Whiteley and Warrington, 1978; Hécaen et al., 1980; Landis et al., 1986; Rosenbaum et al., 2003). Impaired navigation following lesions to retrosplenial cortex often resolves within months (Maguire, 2001), indicating that compensation for the loss of function associated with this structure is possible. Our results and the lesion data, however, indicate that under normal circumstances, this structure plays a crucial role in navigation.

The functional behavior of distinct cortical sites in the present study conforms to the neural taxonomy based on such patient findings (Aguirre and D'Esposito, 1999). In addition, the allocentric-egocentric distinction made by participants in post-scan interviews was honored, as indicated by differences when tasks were directly compared with one another to control for the mental navigation and imagery common across tasks. Specifically, consistent with its known role in allocentric processing of landmarks in

relation to each other (see also Vann and Aggleton, 2002), retrosplenial cortex was found to be engaged preferentially during the proximity judgment task for which participants reported a survey perspective, a strategy that is well-suited to the maintenance of Euclidean relations (O'Keefe and Nadel, 1978; Thorndyke and Hayes-Roth, 1982). By contrast, medial-superior parietal cortex, specialized in egocentric processing, was found to be most active in the sequencing and blocked-route tasks in which participants reported an egocentric perspective, imagining their body position with respect to an invariant sequence of reference points when generating the most efficient route between landmarks in the presence of a detour.

To our knowledge, this study is the first to relate differences in brain activation to retrieval of survey and ground-level representations of very familiar, real-world environments acquired long ago. It is, nonetheless, informative to contrast our study with others in the literature that have distinguished between these two perspectives of newly encountered environments. Mellet et al. (2000) also investigated retrieval of a real-world environment, but one that was learned recently. This difference between retrieval of recent and of remote spatial memory likely accounts for the presence of hippocampal activity for both survey and route imagery in their study but its absence in ours, consistent with the neurological literature. Together, our study and the study by Mellet et al. differ from Shelton and Gabrieli's (2002) investigation of encoding of novel environments from route and survey perspectives. The route-encoding task involved on-line navigation in an immersive virtual reality environment. Despite this difference, encoding of routes was found to engage the PHG region of the MTL, as in Mellet et al., which may reflect the experiential aspect of ground-level navigation of a new environment as compared to the more detached survey task. In the survey task, participants had an aerial view of the region, as in a map, and navigated from one location to another. It is unclear, however, whether the survey or map-like representation formed by participants in Shelton and Gabrieli's study is the same as that derived from real-world experience navigating in an environment and, instead, may have been treated more like a complex object, which may account for recruitment of inferotemporal cortex during this task.

Returning to our study, the presence of activity within superior occipital cortex common to all tasks possibly reflects the requirement to hold in mind visual information related to the spatial needs of the tasks for the duration of each trial (e.g., Postle and D'Esposito, 1999). The added recruitment of superior and middle frontal gyri in the behaviorally more complex proximity and blocked-route tasks attest to the further monitoring and manipulation of these space-based contents of short-term memory demanded by the tasks, whether allocentric or egocentric in nature (e.g., Courtney et al., 1998). Similar dorsal extrastriate-prefrontal circuitry figures prominently in studies of mental exploration performed on a temporarily reactivated visual image (Mellet et al., 1996), consistent with the mental operations required to refer back and forth between the locations of two landmarks to make relative nearness judgments and to construct an alternate route during mental navigation.

As with visual imagery, perceptual processing of place location yields dorsal-stream activity that is perhaps more robust than its mentally generated counterpart and that is distinct from the ventral-stream activity that is manifest when processing place appearance (Aguirre et al., 1996). Indeed, we found known landmarks and unknown buildings to engage both lower-level occipital regions and the higher-order "parahippocampal place area" (PPA), a ventral inferotemporal region that has been found to respond selectively to passive viewing of static enclosed spaces, independent of familiarity (Epstein and Kanwisher, 1998; Epstein et al., 1999; Gorno-Tempini and Price, 2001). This region corresponds to that identified in our mental navigation tasks, consistent with the possibility that this region also is involved in visual imagery of landmarks (O'Craven and Kanwisher, 2000). The present study, nonetheless, represents the first direct comparison of frequently visited landmarks with buildings viewed for the first time using a whole-brain group analysis. As such, landmarks correctly recognized as familiar recruited an additional PHG site immediately posterior to the region identified in perceptual tasks and bordering anterior lingual gyrus that was not activated by unknown buildings. Although it remains unclear whether this region is functionally and anatomically separate from the PPA, it corresponds roughly to that found by Aguirre and D'Esposito (1997) to respond to buildings that have gained landmark status over the course of only a few days. Somewhat unexpectedly, this landmark recognition structure was active within the context of a subset of regions identified in the mental navigation tasks, particularly the left PHG and retrosplenial cortex and right superior occipital gyrus, suggesting an obligatory union of a landmark with the spatial richness of its stored locale.

Taken together, we have identified for the first time a network of structures that supports a range of mental representations of an environment experienced many years ago, including: (1) a temporoparietal, mental navigation pathway coursing between anatomically connected yet functionally specialized medial-superior parietal, retrosplenial, and parahippocampal cortices; (2) a dorsal extrastriate-prefrontal short-term memory circuit; and (3) posterior parahippocampal/anterior lingual portions of ventral inferotemporal cortex unique to landmark perception and identification. These very same structures are concerned with memory for comparable aspects of more recently encountered environments (Aguirre and D'Esposito, 1999; Shelton and Gabrieli, 2002).

In view of such correspondence, we propose the following model of spatial navigation. Retrosplenial and posterior parietal regions are complementary components of a spatial processing system, providing allocentric heading direction and egocentric imagery information, respectively. These regions operate on the contents of spatial short-term memory guided either by the nature of the environment to be encoded or the retrieval demands of a particular task, which may be determined by prefrontal cortex. In both cases, the PHG serves to collate input from these sites with information about imageable landmarks when made available by adjacent inferotemporal cortex. During initial encounters with a spatial layout, the PHG feeds its product to the hippocampus for binding, to facilitate the extraction of schematic spatial information (spatial "gist") from multiple topographical representations of the layout.

With time, this schematic, cortically based representation is completed, and the hippocampus is no longer needed to gain access to it. In this way, the integrity of remotely formed spatial representations is secure within a strongly linked matrix of extra-hippocampus specialized neocortical sites, each having been responsible for representing certain aspects of the environment from the time that it was first experienced. It remains for future research to determine whether the same can be said for the finer spatial detail contained within these schematic "cognitive maps" as would be predicted by standard consolidation theory (Squire, 1992) or if, according to Multiple Trace Theory (Nadel and Moscovitch, 1997), the hippocampus is always involved in representing details much as it is for episodic memory.

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