

The Hippocampus Is Involved in Mental Navigation for a Recently Learned, but Not a Highly Familiar Environment: A Longitudinal fMRI Study

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ABSTRACT: Functional magnetic resonance imaging (MRI) was used to investigate the hypothesis that memory for a large-scale environment is initially dependent on the hippocampus but is later supported by extra-hippocampal structures (e.g., precuneus, posterior parahippocampal cortex, and lingual gyrus) once the environment is well-learned. Participants were scanned during mental navigation tasks initially when they were newly arrived to the city of Toronto, and later after having lived and navigated within the city for 1 yr. In the first session, activation was observed in the right hippocampus, left precuneus, and post-central gyrus. The second session revealed activation in the caudate and lateral temporal cortex, but not in the right hippocampus; additional activation was instead observed in the posterior parahippocampal cortex, lingual gyrus, and precuneus. These findings suggest that the right hippocampus is required for the acquisition of new spatial information but is not needed to represent this information when the environment is highly familiar. © 2011 Wiley Periodicals, Inc.

KEY WORDS: spatial memory; learning; medial temporal lobe; neocortex

INTRODUCTION

Navigating from one place to another along familiar routes, an essential part of everyday life, cannot be accomplished without an internal representation of the environment. It has been widely demonstrated that the hippocampus is required to learn the layout of a new environment and represent it as a cognitive map (O'Keefe and Nadel, 1978) in the service of navigation (Maguire et al., 1996b; Bohbot et al., 1998; Shelton and Gabrieli, 2002), but its role in the long-term storage and retrieval of such representations is disputed. Several neuroimaging studies have looked at brain regions involved in long-term spatial memory, but

many of these studies used virtual environments (Maguire et al., 1998; Parsalow et al., 2004; Spiers and Maguire, 2006; Newman et al., 2007) or small-scale environments that were learned within a day (Ghaem et al., 1997; Mellet et al., 2000). To date, no one has conducted a longitudinal study that tracks changes in brain activation that occur as participants become familiar, over time, with a large-scale city environment. Comparisons across studies of short-term and long-term spatial memory suggest that at least some types of spatial memory may become independent of the hippocampus with increased familiarity (see below). However, only a longitudinal study can demonstrate that spatial memories that are initially dependent on the hippocampus eventually can become independent of it. In this paper, we compare brain activation in normal adults performing mental navigation tasks in a large-scale environment, downtown Toronto, at two time-points: initially, when they are newly arrived to Toronto, and then, after about a year of living and navigating within the city. This allows us to look at changes in brain activation (hippocampus and elsewhere) as participants become familiar with an environment as a result of living and navigating within it. Such findings will have general implications for theories of hippocampal–neocortical interactions in memory formation and consolidation over time.

Early evidence that the hippocampus is required for the acquisition of allocentric spatial representations comes from single-unit recordings and lesion studies in animals (O'Keefe and Dostrovsky, 1971; Morris et al., 1982; O'Keefe, 1999). Human patients with hippocampal lesions are similarly impaired in learning the layout of new real-world (Milner et al., 1968; Teng and Squire, 1999; Holdstock et al., 2000; Rosenbaum et al., 2000) and virtual environments (Spiers et al., 2001; Bohbot et al., 2004). Neuroimaging studies provide converging evidence for the necessary role of the hippocampus during spatial learning (Maguire et al., 1996b; Shelton and Gabrieli, 2002; Bohbot et al., 2004).

There is less agreement as to whether the hippocampus is needed for the long-term retention and retrieval of spatial memories. A number of investigators have shown that retention is impaired in rodents with hippocampal lesions made as long as nine months after learning spatial locations (Becker et al., 1981;

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Abbreviations used: AFNI, analysis of functional neuroimages; ANOVA, analysis of variance; BOLD, blood oxygenation level-dependent; FWHM, full-width-at-half-maximum; MRI, magnetic resonance imaging; PHC, parahippocampal cortex; RT, reaction time; SD, standard deviation; TPPT, Toronto Public Places Test.

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Morris et al., 1982; Clarke et al., 2005; Winocur et al., 2005). However, recent studies have demonstrated that spatial memory can be preserved in rats with hippocampal lesions, following extensive preoperative training and experience in a complex environment, although the hippocampus is needed for acquisition (see Winocur et al., 2005, 2010 for a full review). These findings replicate reports that humans with extensive medial temporal lobe damage have preserved spatial memory and navigational abilities for environments learned prior to their brain damage (Teng and Squire, 1999; Rosenbaum et al., 2000; Corkin, 2002; Rosenbaum et al., 2005; Maguire et al., 2006), although they, too, have great difficulty learning a new environment (Barrash, 1998; Rosenbaum et al., 2000, 2005; but see Corkin, 2002). Together the above findings suggest that in healthy individuals, the hippocampus is implicated only in the acquisition and short-term retention and retrieval of spatial memories of a new environment, but not at longer intervals.

Although findings from functional neuroimaging studies strongly support a role for the hippocampus in the acquisition and initial storage of spatial memories (e.g., Maguire et al., 1996b), neuroimaging evidence in support of a hippocampal role in the retention and retrieval of such memories long after they were acquired remains equivocal. Some studies report hippocampal activation during mental navigation tasks in a well-learned environment (Maguire et al., 1997), but careful examination suggests that the reported activation is on the border between the hippocampus and parahippocampal cortex, not the hippocampus proper. More recent studies with long-time residents of London report hippocampal activation during mental navigation tasks (Kumaran and Maguire, 2005) and when participants planned routes prior to navigating in a virtual simulation of the city of London (Spiers and Maguire 2006). However, another study with long-time Toronto residents did not report any hippocampal activation during a variety of mental navigation tasks (Rosenbaum et al., 2004). Although activity was reported in the right medial temporal lobe, the core of this activation was in the parahippocampal cortex (PHC), not the hippocampus. Further, preserved remote spatial memory for a premonstrably familiar neighborhood in a hippocampal amnesic was found to be supported by the parahippocampal cortex, rather than residual hippocampal tissue (Rosenbaum et al., 2007). The latter findings are consistent with the lesion literature in humans that suggests that the PHC, but not the hippocampus, may be crucial for remote memory of spatial relations (Aguirre et al., 1996; Bohbot et al., 1998).

The wide range of methods (environments, participants) used to examine acquisition and long-term retention makes comparison across studies difficult. What is needed to determine whether the hippocampus, in healthy humans, is implicated in spatial memory at short and long retention intervals is a single study that uses an identical methodology at both time periods. By filling this need, the current study aims to determine whether spatial representations of large scale environments that are initially dependent on the hippocampus can become independent of it over time. A complementary goal of this study is to identify other brain regions such as the PHC

and posterior parietal cortex, which may support such representations at one or both time intervals (Aguirre et al., 1996; Aguirre and D'Esposito, 1999).

Thirteen participants who had moved very recently (within three months) to Toronto were scanned with fMRI while performing various mental navigation tasks involving newly encountered Toronto landmarks. Eight of these participants returned for a second fMRI session after living and navigating in the city for about 1 yr. Based on our own findings that the hippocampus is not necessary for retention of spatial memories acquired long ago (Rosenbaum et al., 2004), we expected to find a decrease in hippocampal activation from the first to the second session. This decreased hippocampal activity should be accompanied by a corresponding increase in activity in the PHC and posterior parietal cortex, reflecting the role of these regions in the long-term maintenance of spatial relations (Epstein, 2008). In addition to these predicted changes in activity in the medial temporal lobe, we expected the rest of the brain to show a relatively stable pattern of activation over time. Brain regions such as the medial prefrontal cortex and lateral temporal cortex are commonly implicated in studies of mental navigation (Ghaem et al., 1997; Maguire et al., 1998; Rosenbaum et al., 2004). Therefore such regions should be consistently activated both when participants are new to the city of Toronto, and after they have lived and navigated extensively in the city for 1 yr.

MATERIALS AND METHODS

Participants

Thirteen participants (five male; mean age 26.7 yr, standard deviation (SD) = 4.0; two left-handed) who had three or fewer months of experience with downtown Toronto participated in the first session. Eight of these participants (one male; mean age 27.0 yr, SD = 3.1; 1 left-handed) repeated the experiment after one year of living and navigating in downtown Toronto. The five remaining participants were no longer living in Toronto and were unavailable for a second scanning session. All participants were free of psychiatric and neurological disorders, current substance abuse, diabetes, and hypertension. All participants had 20/20 or corrected to normal vision. Informed consent was obtained from all participants in accordance with the Sunnybrook Health Sciences Centre and University of Toronto ethical guidelines. Participants received compensation upon completion of the study.

Prescan Interview

All participants completed a survey assessing their degree of familiarity with a list of 60 downtown Toronto landmarks on a scale of 1–5. This questionnaire was used to individualize the test for each participant, such that only those landmarks that were recognized by the participant were used as test stimuli. The same individualized set of landmarks was used for each

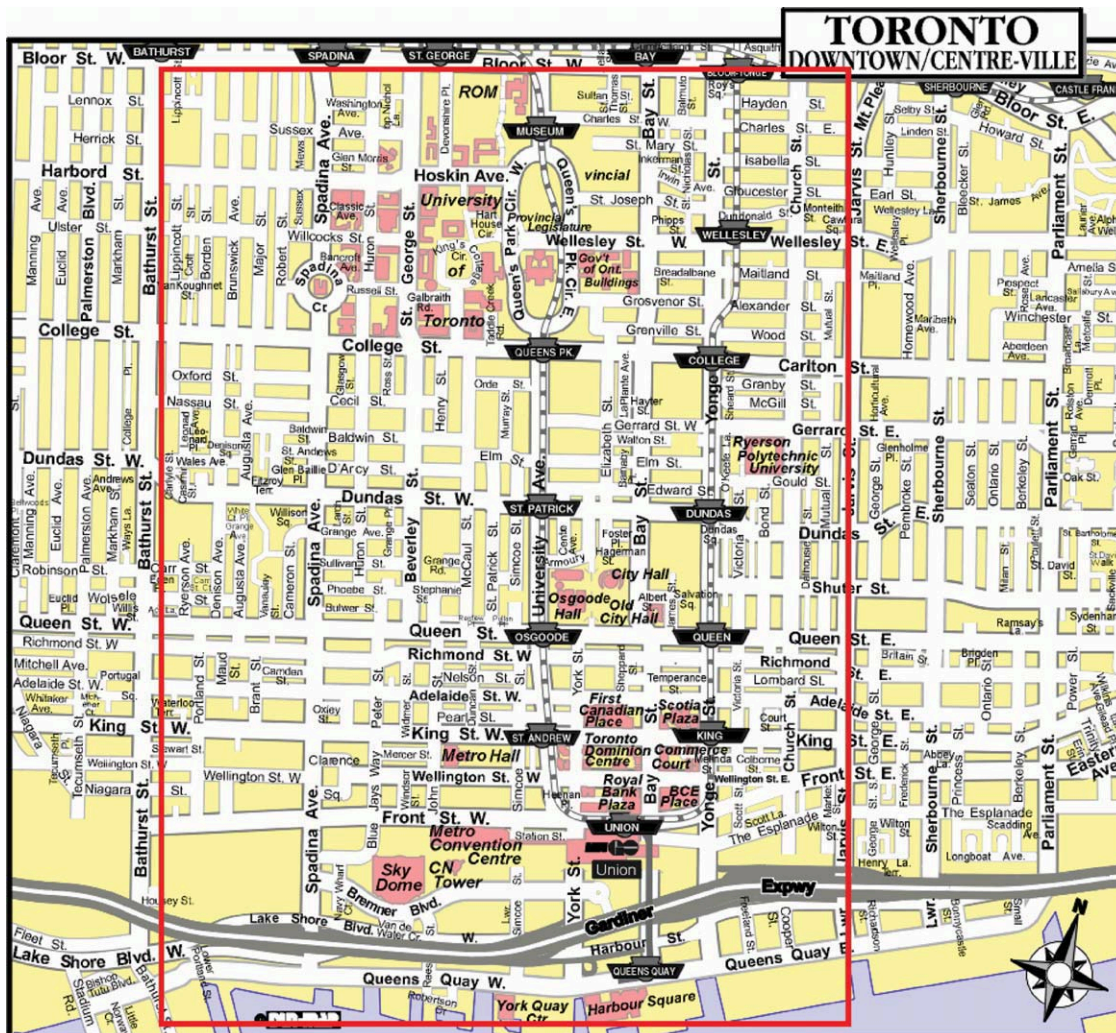


FIGURE 1. The region of downtown Toronto which contains the landmarks that were tested on the Toronto Public Places Test. Image taken from: <http://rehelv-acrd.tpsgc-pwgs.gc.ca/images/Toronto-DT-Final.gif>. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

participant in both the scanning sessions. Our goal was to minimize changes in accuracy across the two sessions so that any observed changes in brain activity over time could not be attributed to changes in accuracy.

Toronto Public Places Test (Rosenbaum et al., 2004)

The Toronto Public Places Test (TPPT; Rosenbaum et al., 2004, 2005) is a spatial memory test of a $3 \text{ km} \times 5 \text{ km}$ region of downtown Toronto, which contains many of Toronto's most familiar landmarks and routes (Fig. 1 for a map of the region). Names of landmarks selected from the prescan interview were presented as stimuli using Eprime v1.1 software (Psychology Software Tools, Pittsburgh, PA) on a back-projection screen using an LCD projector external to the magnet room. Responses were collected using fMRI compatible keypads.

Participants performed mental navigation tasks using the names of landmarks as cues. Each trial consisted of a pair of

words denoting familiar Toronto landmarks. Landmark names were presented side by side in the center of the screen and participants made right and left button press responses according to the task instructions, indicated by a written cue at the beginning of each block of trials.

Each scanning run was 5 min long and consisted of four blocks, with each block representing one of the four tasks and lasting 60 s. Each block consisted of three trials lasting 30 s each, interleaved with a 30-s visuomotor control task (passive viewing of a string of x's in place of words while subjects pressed both response buttons). A block of each task was presented once within each of six scanning runs in a counterbalanced order.

Mental Navigation Tasks

Task 1: Proximity judgments

Participants indicated which of two landmarks is closer 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 is greater or less than 2.5 km with left and right button presses, respectively. Participants were informed prior to the scanning session that the distance between the northern and southern limits of downtown Toronto is approximately 5 km.

Task 3: Landmark sequencing

Participants determined whether each pair of landmarks was presented in the true order in which they would appear if one were to walk from west to east. A left button press was used to indicate a “yes” response and a right button press was used to indicate a “no” response (opposite for half the participants).

Task 4: Blocked-route navigation

Participants were told that a 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 responded “yes” if a second street specified in the instructions would be passed along the detour and “no” if not (right button press to a “yes” response for half of the participants).

Prescan Practice Session

Each task was explained to the participants one week prior to the scanning session. Participants were familiarized with each task by performing the equivalent of one scanning run on a desktop computer.

Image Acquisition

Participants were scanned with a GE Signa 3 Tesla MRI scanner. A standard high-resolution 3D T1-weighted pulse sequence image (124 axial slices, 1.4 mm thick, FOV = 22 cm) 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). Functional scans were acquired with a single-shot T2*-weighted pulse sequence with a spiral readout (26 axial slices, 5 mm thick, TR = 2,000, TE = 30 ms, flip angle = 30°, FOV = 20 cm).

Data Analysis

Accuracy (percentage correct) was analyzed with a 2×4 repeated measures analysis of variance (ANOVA) with session (session 1, session 2) and task (distance judgment, proximity judgment, landmark sequencing, and blocked route problem solving) as factors.

Image processing and analysis were performed using the Analysis of Functional Neuroimages (AFNI, version 2.0) soft-

ware package (Cox, 1996; Cox and Hyde, 1997). The initial ten 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 coregistered to correct for head motion using a 3D Fourier transform interpolation (the peak range of head motion was <1.5 mm for all participants). The four scanning runs were then concatenated and activation maps of the BOLD signal for each subject were calculated for each condition with respect to the visuomotor baseline condition. The resulting individual activation images 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 (S/N) 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.

Session 1 (N = 13)

Because there were a number of tasks, each of which had to be compared across two time periods, for simplicity and ease of exposition, we chose to examine the brain regions that are activated in common across the various tasks. To do so, we performed a conjunction analysis, which would identify the core regions implicated in spatial navigation, rather than task-specific variations. The contrast maps for each task (taken from the output of the group analysis) were thresholded liberally ($P < 0.1$) and multiplied by each other to determine which brain regions were active for all four tasks. The resulting map had a significance level equal to the product of the P -values of each contrast map ($P < 0.1 \times 0.1 \times 0.1 \times 0.1 = P < 0.0,001$) (see Cabeza et al., 2002, 2004 for discussion of this method, but also Lazar et al., 2002). Although this map shows brain regions that are active for all task contrasts, it does not provide information about the degree of activation in any of these regions. To calculate the peak of activation in these brain regions, the conjunction map was multiplied by a map of the average value of the t -statistics from each contrast.

Conjunction analysis of the four mental navigation tasks only revealed one region of common activation in the right insula (42, -10, 2, BA 13). Further inspection of the contrast maps for each task revealed that this result was driven by the landmark sequencing task, which did not share any other regions of common activation with the other three tasks. The power of this task was much lower than that of the other three (there were few activations or deactivations at $P < 0.05$, uncorrected), which we suspect is because of differences in task demands. For now, we have excluded this task from subsequent analysis because of our interest in characterizing the set of brain regions involved in mental navigation and how the involvement of particular regions may change with time and experience in an environment.

A second conjunction analysis was done to look at areas of common activation across the remaining three tasks (distance and proximity judgments, and blocked-route problem solving).

The contrast maps were thresholded at $P < 0.05$ and multiplied to create a conjunction map with a significance level of $P < 0.05 \times 0.05 \times 0.05 = P < 0.000125$. This map was multiplied by a map of the average value of the t -statistics for the three tasks, and the resulting map was used to report the coordinates of the peak voxel of the regions of shared activation across the three tasks.

Session 1 ($N = 8$)

The conjunction analysis described above was repeated for the subset of eight participants who returned for the second fMRI session. This was done to ensure that the pattern of activation observed in these eight subjects was consistent with the larger group and suitable for further analysis.

Session 2 ($N = 8$)

Conjunction analysis was done in the manner described above to look at regions of shared activation for the distance and proximity judgments and blocked-route problem solving in the second scanning session.

Comparison of Session 1 and Session 2

ROI analysis

A cluster of 170 voxels in the right hippocampus was functionally defined based on the conjunction of the distance judgment, proximity judgment, and blocked-route tasks for all thirteen participants in the first session. This cluster was then used as a mask for a region of interest analysis comparing right hippocampal activation in the first and second sessions. Mean percentage signal change was calculated for all three tasks for each session, and the two sessions were compared using a paired-samples t -test.

Conjunction and disjunction analysis

Conjunction analysis was used to identify areas of common activation across the distance judgment, proximity judgment, and blocked-route tasks for both sessions. This was done by multiplying the contrast maps for each of the three tasks for each session. We used a liberal threshold of $P < 0.5$ for the contrast maps that were input into this analysis. The significance of the output map is equal to the product of the P -values of each contrast map ($P < 0.5 \times 0.5 \times 0.5 \times 0.5 \times 0.5 \times 0.5 = P < 0.0156$). To calculate the peak of activation in these brain regions, the conjunction map was multiplied by a map of the average value of the t -statistics from the six contrasts. The output of this analysis was used to report the coordinates of the peak voxel of the regions of activation common to all three tasks and both sessions.

A disjunction analysis was used to identify regions of activation that were unique to the second session. The contrast maps were multiplied so as to create an output map of the brain regions active for all three tasks in session 2 but not session 1. The significance of this output map is equal to the product of

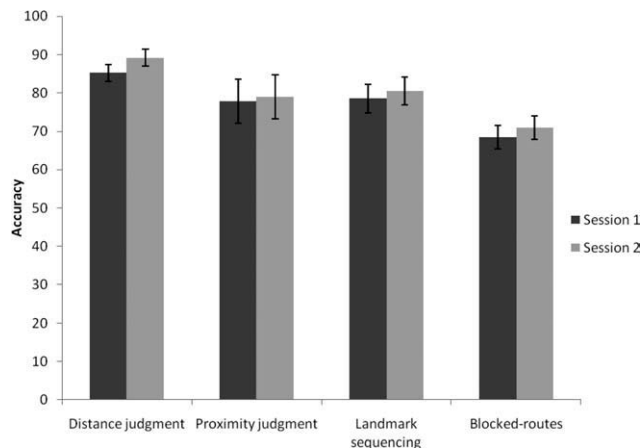


FIGURE 2. The mean accuracy for the four mental navigation tasks is shown for session one and session two. The means are based on the eight participants who were present for both sessions.

the P -values of each contrast map ($P < 0.0156$). The coordinates of the peak voxel for regions of activation were determined using the average t -statistic from the three task contrasts from session 2.

RESULTS

Accuracy data for the four mental navigation tasks and both sessions is shown in Figure 2. Only the eight participants who were present for both scanning sessions were included in this analysis. A 2×4 repeated measures ANOVA (with session (1, 2) and task (Distance judgment, Proximity judgment, Blocked-route problem solving, and Landmark sequencing) as factors did not reveal a main effect of session ($F(1,7) = 1.39$). There was no interaction between session and task ($F(3,21) = 0.17$). A main effect of task was observed ($F(3,21) = 4.16$, $P = 0.018$). Given this main effect of task, we investigated differences between tasks using simpler planned comparisons with Bonferroni's correction for multiple comparisons. Accuracy for distance judgments was significantly higher than accuracy for blocked-route problem solving ($P < 0.001$).

Reaction time (RT) data for the four mental navigation tasks and both sessions is shown in Table 1. RT data were missing due to computer error for two subjects in the second session, therefore the data shown represents the six subjects who were present for both sessions and for whom RT data were available at both time points. A 2×4 repeated measures ANOVA (with session (1, 2) and task (Distance judgment, Proximity judgment, Blocked-route problem solving, and Landmark sequencing) as factors revealed main effects of session ($F(1,5) = 1.32$, $P < 0.02$) and task ($F(3,15) = 10.98$, $P < 0.0001$) with no interaction between session and task ($F(3,15) = 2.85$, $P = 0.07$). Given the main effects of session and task, we investigated differences between sessions and tasks using simpler planned comparisons with Bonferroni's correction for multiple

TABLE 1. *Reaction Time Data for the Four Conditions for Sessions One and Two*

Task	Mean RT (ms) (SD)	
	Session 1	Session 2
Distance judgment	3.62 (0.50)	3.24 (0.28)
Proximity judgment	3.73 (0.58)	3.30 (0.43)
Landmark sequencing	4.38 (0.91)	3.47 (0.28)
Blocked-routes	4.77 (0.62)	3.64 (0.26)

comparisons. Reaction time was significantly longer in session two than session one ($P < 0.05$). Reaction time for the blocked-route task was significantly longer than RT for both the distance ($P < 0.005$) and proximity ($P < 0.01$) tasks.

Session 1 (N = 13)

Conjunction analysis of the distance judgment, proximity judgment, and blocked-route problem solving tasks revealed regions of common activation in the right hippocampus, left parahippocampal gyrus as well as other brain regions commonly implicated in mental navigation tasks, including the left precuneus and right cuneus (Table 2 and Fig. 3). Several regions of common activation were observed in the frontal lobes, including the middle (BA 8), inferior (BA 45), and superior gyri (BA 6) on the left, and the postcentral gyrus bilaterally.

TABLE 2. *Regions of Common Activation for Distance and Proximity Judgment and Blocked-Route Problem-Solving in Session 1 (N = 13) (P < 0.001)*

Region	Talairach coordinates			Volume (voxels)
	x	y	z	
R middle temporal gyrus	54	-52	6	6,481
L superior temporal gyrus	-56	-60	27	4,623
R cuneus	15	-91	32	1,698
R precentral gyrus	45	-10	57	1,607
L precuneus (BA 31)	-11	-50	32	1,567
L middle frontal gyrus	-25	35	42	895
R hippocampus	31	-23	-9	505
R fusiform gyrus (BA 20)	41	-36	-17	501
L parahippocampal gyrus and hippocampus	-33	-14	-16	295
L middle temporal gyrus (BA 21)	-54	0	-10	158
L inferior frontal gyrus (BA 45)	-57	27	4	137
L superior temporal gyrus	-51	-18	0	136
L superior frontal gyrus (BA 6)	-21	20	62	133
L postcentral gyrus	-10	-38	68	108
R postcentral gyrus (BA 2)	60	-24	37	103

Session 1 (N = 8)

Conjunction analysis of the distance judgment, proximity judgment, and blocked-route problem-solving tasks was repeated excluding the five participants who were unable to return for a second testing session. The results of this analysis were consistent with the pattern of activations observed when all thirteen participants were included. Regions of shared activation included the right hippocampus (32, -20, -14), the right middle temporal gyrus (54, -53, 7 and 63, -18, -12), the left and right postcentral gyrus (-12, -45, 68 and 9, -41, 70, respectively), and the left supramarginal gyrus (-62, -54, 36).

Session 2 (N = 8)

Conjunction analysis of the distance judgment, proximity judgment, and blocked-route problem-solving tasks revealed only one region of common activation in the left inferior frontal gyrus (-23, 33, -4; $t = 2.06$).

Comparison of Session 1 and Session 2

ROI analysis

Since we had a specific hypothesis regarding the right hippocampus, we defined a functional ROI using the cluster of voxels active in the conjunction of the distance and proximity judgment and blocked-route problem solving tasks for the thirteen participants in session 1 (Fig. 4). The mean percentage signal change for this cluster was extracted for each task and for each session. A paired-sample t -test revealed a significant decrease in the mean percentage signal change from session 1 to session 2

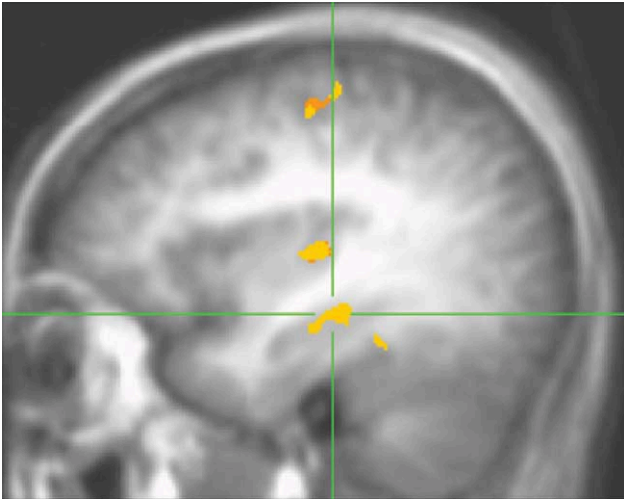


FIGURE 3. Regions of activation common to the distance judgment, proximity judgment, and blocked-route problem-solving tasks in session one include the hippocampus, lingual gyrus (BA 20), insula, and precentral gyrus on the right. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

across the three mental navigation tasks ($t = 3.16$, $P = 0.004$, two-tailed) (Fig. 5).

Conjunction analysis (Session 1 and Session 2)

A conjunction analysis of the distance judgment, proximity judgment, and blocked-route problem-solving tasks in session 1 and session 2 revealed regions of activation that were common to all three tasks and both testing sessions. Regions of common activation were observed in the middle and inferior frontal lobes, bilaterally, the inferior temporal gyrus on the left, and

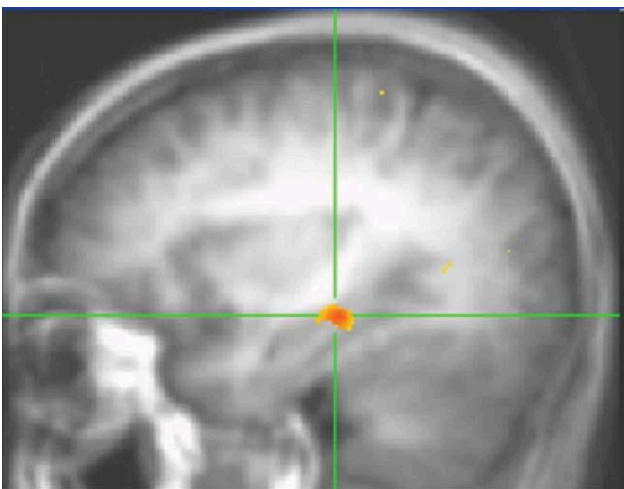


FIGURE 4. A region of interest analysis was performed for the cluster of activation in the right hippocampus. (170 voxels, peak coordinates: 31, -23, -9). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Hippocampus

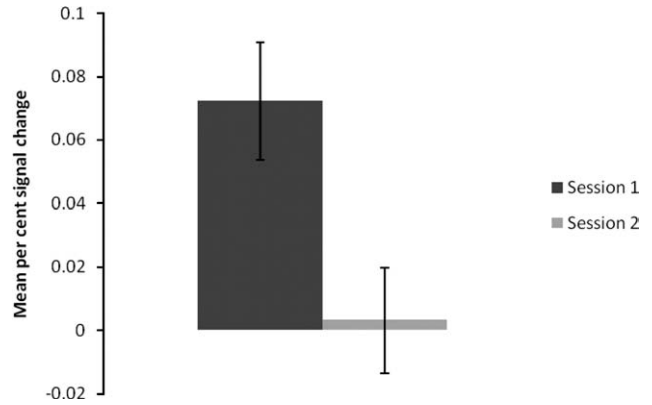


FIGURE 5. The mean percent signal change in the right hippocampus in response to the three mental navigation tasks is shown for session one and two.

the middle temporal gyrus bilaterally right (Table 3 and Fig. 6). The clusters in the temporal lobes extended into the parietal cortex, such that there was also bilateral activation of the precuneus.

Disjunction analysis: Regions of activation unique to Session 2

A disjunction analysis revealed regions of activation that were unique to the second session, including the posterior parahippocampal gyrus, lingual gyrus, and superior temporal gyrus on the right, as well as the caudate and inferior frontal gyrus on the left (Table 4). The superior temporal activation on the right also extended into the posterior cingulate/retrosplenial cortex.

DISCUSSION

Our results show that as participants gained familiarity with downtown Toronto over the course of a year, there was a significant decrease in right hippocampal activation during the performance of mental navigation tasks, with no evidence of activation above baseline during the second fMRI session. This decrease in right hippocampal activation was accompanied by a corresponding increase in activation in the posterior parahippocampal cortex, lingual gyrus, and superior temporal gyrus on the right, and the caudate and inferior frontal gyrus on the left.

This study is the first to track brain regions involved in spatial memory for large scale environments at both short and very long retention intervals. The use of a longitudinal design ensures that the changes in brain activation over time and experience cannot be attributed to environment- or participant-related factors, as may have been the case in interpreting differences based on cross-sectional studies across different laboratories. Although it is possible that the changes in hippocampal activation observed in the present study may be explained by

TABLE 3. *Regions of Common Activation for Distance and Proximity Judgment and Blocked-Route Problem-Solving in Both Session 1 and Session 2 (P < 0.0156)*

Region	Talairach coordinates			Volume (voxels)
	x	y	z	
L middle occipital gyrus	-41	-73	2	63,610
L middle frontal gyrus and inferior frontal gyrus	-22	33	-5	20,476
L inferior temporal gyrus	-49	-4	-35	13,416
L middle frontal gyrus (BA 6)	-27	20	54	3,601
R medial frontal gyrus (BA 10)	5	66	8	2,551
R insula (BA 13)	41	-10	11	1,144
L middle temporal gyrus	-51	-19	-9	717
L caudate	-1	15	7	439
L insula (BA 13)	-42	-3	1	259
L superior temporal gyrus (BA 38)	-46	20	-18	180
R inferior frontal gyrus	48	29	5	130
R middle temporal gyrus	51	-33	0	123

the increased accuracy in mental navigation as participants gained familiarity with the environment, we believe that this is unlikely, as accuracy did not change significantly over time for the items tested. In fact, we attempted to minimize changes in accuracy by using individualized stimuli that each participant rated as familiar prior to the first fMRI session. An additional possibility is that the hippocampal activity observed in the first session is because of active encoding of the task and the novel experience of being in the scanner. Such activation would also be expected to decrease in the second fMRI session, as both the task and environment of the scanner have become familiar to participants. We consider this explanation unlikely as no

such activity was observed the very first time that long-term Toronto residents were exposed to the exact same task and scanning environment (Rosenbaum et al., 2004). However, it is still possible that the hippocampal activation we reported in the first session is because of the relative novelty of the landmarks for our participants, compared to the participants in Rosenbaum’s study. Although the landmarks were of greater novelty in the current study, participants had still been living in the city for an average of three months and the landmarks used were ones that participants rated as being familiar. This degree of familiarity is much greater than that reported for typical novelty effects within the hippocampus (e.g., Tulving et al., 1994). Therefore, although the landmarks were relatively more novel for our participants than those in Rosenbaum’s study, we argue that the participants still had sufficient familiarity with the landmarks that the hippocampal activation cannot be solely because of landmark novelty.

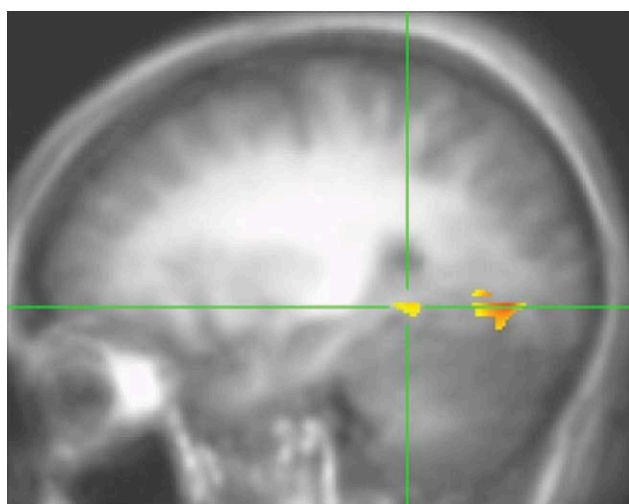


FIGURE 6. Brain regions that were active in session two, but not session one, includes the parahippocampal gyrus and lingual gyrus on the right. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE 4. *Regions of Activation Unique to Session 2 (P < 0.0156)*

Region	Talairach coordinates			Volume (voxels)
	x	y	z	
R lingual gyrus	30	-71	-3	50,620
L inferior frontal gyrus	-20	33	-5	7,871
R superior temporal gyrus (BA 22)	61	-15	2	4,370
L caudate head	-2	17	7	356
R parahippocampal gyrus	23	-41	0	304
R superior temporal gyrus	46	16	-20	151

Another possibility is that the reported decrease in hippocampal activation is an artifact of a whole-brain decrease in activation that accompanies lowered attention or arousal as participants become familiar with the task. The finding that several brain regions (e.g., posterior parahippocampal gyrus, lingual gyrus, caudate, and inferior frontal gyrus) showed increased activation in the second session argues against this interpretation.

It is important to note that the regions that increased in activation over time are the same regions that Rosenbaum et al. (2004) showed to be part of a network that supports navigation in a familiar environment. The parahippocampal cortex is commonly activated in neuroimaging studies of spatial memory (Aguirre et al., 1996; Maguire et al., 1998; Shelton and Gabrieli, 2002; Rosenbaum et al., 2004; Epstein, 2008) and patients with lesions to the parahippocampal gyrus are unable to learn new spatial relations (Habib and Sirigu, 1987; Barrash et al., 2000). It has been suggested that its function is related to the geometrical representation of spatial layouts (Epstein, 2008). The lingual gyrus has also been activated in neuroimaging studies of spatial memory (Committeri et al., 2004) and is thought to play a role in the identification of familiar landmarks in a familiar environment (Takahashi and Kawamura, 2002). Lesions to the lingual gyrus result in landmark agnosia, an inability to recognize landmarks and use them to guide navigation (Aguirre and D'Esposito, 1999; Rosenbaum et al., 2005). Activity in the caudate nucleus during mental navigation tasks has been correlated with the speed of navigation (Maguire et al., 1998) and the use of nonspatial, stimulus-response based strategies (McDonald and White, 1994; Packard and McGaugh, 1996; Iaria et al., 2003; Etchamendy and Bohbot, 2007). The caudate may also play a role in the spatial working memory required to support navigation (Postle and D'Esposito, 1999). The retrosplenial cortex is commonly implicated in mental navigation (e.g., Ghaem et al., 1997; Mellet et al., 2000; Parslow et al., 2004; Rosenbaum et al., 2004), and is thought to mediate transitions between egocentric representations supported by the posterior parietal cortex and allocentric representations supported by the medial temporal lobes (Maguire, 2001). In addition, the precuneus which was active during both session one and two may mediate the inspection of imagery in service of mental navigation (Fletcher et al., 1995).

Some of these regions (parahippocampal gyrus and inferior frontal gyrus) were already active in session one, suggesting that they serve a general function, which increases in importance with time. However, it is important to note that the areas active in session one and two were different (i.e., distinct clusters within the same brain regions were active during both sessions). More specifically, the parahippocampal activation reported in session two was posterior to the region reported in session one. The parahippocampal activation observed at both time points in the current study is consistent with the notion that this structure is crucial for the acquisition and long-term retention of spatial information and representation of spatial layouts. The changes observed between the two sessions suggest that it is not simply that the hippocampus is no longer needed,

but that areas implicated at time one assume increased responsibility for spatial memory processing.

Others regions (caudate, lingual gyrus, superior temporal gyrus, posterior cingulate/retrosplenial cortex), however, were newly recruited in session two. The fact that new areas were recruited suggests that the nature of the representation has changed. What remains to be done is to conduct cognitive/behavioral studies to determine exactly what the change in representation has been. Work with animals suggests that this new representation is more schematic than the initial one (Winocur et al., 2005, 2010), relying only on learned spatial layouts, major landmarks, and practiced routes among them, consistent with our finding of increased caudate activation (McDonald and White, 1994; Packard and McGaugh, 1996; Iaria et al., 2003; Etchamendy and Bohbot, 2007). The schematic representation of space that is supported by extra-hippocampal, neocortical regions is presumed to be less detailed, flexible, cohesive, and well-integrated than the one that is dependent on the hippocampus (Hassabis et al., 2007; Winocur et al., 2010).

The finding of early hippocampal involvement followed by later caudate activation is consistent with work in rats showing that the hippocampus supports an allocentric navigational strategy during initial training in a T maze, while the striatum supports a habit-based strategy after extensive training (Packard and McGaugh, 1996). Work with human subjects has also demonstrated hippocampal involvement in spatial navigation strategies and caudate involvement in nonspatial navigational strategies (Iaria et al., 2003). It is possible that the changes in brain activation we report reflect a change in navigational strategy rather than a change in representation. However, it is also likely that a change in navigational strategy (i.e., from allocentric or place-based navigation to a habit-based navigation) would lead to the use of a different spatial representation. The relationship between navigational strategy and spatial representation will be an interesting topic for future research.

The present results are relevant to the current debate between Consolidation and Multiple Trace Theories of hippocampal function. According to Consolidation Theory all explicit memories (including spatial ones) are temporarily dependent on the hippocampus until a stable representation is established in the neocortex. There is no predicted change in the representation over time. Changes in brain activation should reflect the decreased requirement of the hippocampus, and increased requirement of the same neocortical regions that were initially implicated. Thus, Consolidation Theory would predict only quantitative changes in brain activation (i.e., the degree of activity in the hippocampus and extra-hippocampal regions). Multiple Trace Theory distinguishes between two types of spatial representations in memory—a map-like representation sufficient for navigation and a rich representation for re-experiencing the environment. In the case of the former, the information is represented schematically so that only major landmarks and the relations among them are preserved. In the latter which entails re-experiencing, the representation is perceptually detailed and includes sensory features of the environ-

ment, such as the color and texture of buildings, and incidental entities not needed for navigation. This representation is analogous to episodic memory of an environment and, as such, is likely to be dependent on the hippocampus whereas the schematic representation, which is akin to semantic memory, is likely to become independent of the hippocampus with time and experience in an environment. As a spatial memory becomes independent of the hippocampus, there is also a change in the representation, such that it becomes more schematic in nature. Thus, in contrast to Consolidation Theory, Multiple Trace Theory predicts both *quantitative* and *qualitative* changes in brain activation (i.e., changes in the degree of hippocampal and extra-hippocampal activity, as well as changes in brain regions which are activated). This prediction was confirmed in the present study.

The idea that there is a fundamental change in the spatial representation over time is consistent with neuroimaging studies that demonstrate that the hippocampus is crucially involved in the recollection of highly detailed memories (Addis et al., 2004; Gilboa et al., 2004; Viard et al., 2007), even those that are spatial (Hirshhorn et al., in press). This account is also consistent with reports of hippocampal patients who are able to navigate successfully in premorbidly familiar environments, but are unable to recognize fine-grained details such as individual houses (Rosenbaum et al., 2000).

The role of the hippocampus in the long-term retention of spatial information has been widely debated, and the variety of methods, participants, and environments used in neuroimaging studies of spatial memory has made comparisons across studies difficult. One explanation of the discrepant findings in studies of remote spatial memory, proposed by Spiers and Maguire (2007), is that there is an important difference in the layout of the two cities commonly tested. For example, Toronto is grid-like in its layout and may lend itself more readily to the formation of a schematic representation, whereas the layout of London is comparatively irregular and navigation in such a city may always require a detailed, hippocampally dependent representation. An additional possibility is that the many studies that do report hippocampal activation during mental navigation use virtual reality environments (Maguire et al., 1998; Hartley et al., 2003; Parslow et al., 2004; Spiers and Maguire, 2006), which may impose task demands that recruit the hippocampus, but that are peripheral to navigation.

The results reported here demonstrate that the hippocampus is not necessarily required to support mental navigation in a familiar environment. Instead, at least under some circumstances, mental navigation can be supported by a network of extrahippocampal regions including the parahippocampal cortex, lingual gyrus, caudate, posterior cingulate/retrosplenial cortex, and prefrontal cortex. The tasks used in this study could be accomplished with the use of a schematic representation of the environment and did not promote detailed re-experiencing. However, we expect that if experiential components were added to the task then the hippocampus would be recruited once again. It will be important for future work to determine which factors (environments, task demands, experience) promote re-experi-

encing of the environment and how such factors modulate hippocampal involvement in long-term spatial memory.

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