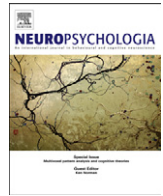




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## Research Report

# Brain regions involved in the retrieval of spatial and episodic details associated with a familiar environment: An fMRI study <sup>☆</sup>

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## ABSTRACT

Functional magnetic resonance imaging (fMRI) was used to compare brain activity during the retrieval of coarse- and fine-grained spatial details and episodic details associated with a familiar environment. Long-time Toronto residents compared pairs of landmarks based on their absolute geographic locations (requiring either coarse or fine discriminations) or based on previous visits to those landmarks (requiring episodic details). An ROI analysis of the hippocampus showed that all three conditions activated the hippocampus bilaterally. Fine-grained spatial judgments recruited an additional region of the right posterior hippocampus, while episodic judgments recruited an additional region of the right anterior hippocampus, and a more extensive region along the length of the left hippocampus. To examine whole-brain patterns of activity, Partial Least Squares (PLS) analysis was used to identify sets of brain regions whose activity covaried with the three conditions. All three comparison judgments recruited the default mode network including the posterior cingulate/retrosplenial cortex, middle frontal gyrus, hippocampus, and precuneus. Fine-grained spatial judgments also recruited additional regions of the precuneus, parahippocampal cortex and the supramarginal gyrus. Episodic judgments recruited the posterior cingulate and medial frontal lobes as well as the angular gyrus. These results are discussed in terms of their implications for theories of hippocampal function and spatial and episodic memory.

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## 1. Introduction

I (MM) was delighted to have been invited to a Festschrift for Andrew Mayes in Manchester and to contribute a paper to a special issue honoring him. Andrew and I began our careers at about the same time, in the early 1970s, and he was among the handful of people whose work I followed diligently. He was in the thick of things from the beginning, contributing significantly to all the important topics on the neuropsychological basis of memory in humans: the distinction between amnesia as an encoding, retrieval or storage deficit, the roles of hippocampus and diencephalic structures in memory, the nature and neural substrates of priming, the distinction between recollection and familiarity, the

neural representations of recent and remote memory, and the medial temporal lobe's involvement in spatial memory. It was the confluence of the latter two topics, which Mayes also tackled in a seminal paper (Mayes, Montaldi, Spencer, & Roberts, 2004), that serves as the point of departure of the present paper.

The hippocampus plays a well documented role in the acquisition of new spatial memories, but its role in the long-term maintenance and retrieval of such memories has been widely debated. Some investigators believe that memories based on allocentric spatial information always depend on the hippocampus (Maguire, Frackowiak, & Frith, 1996, 1997; O'Keefe, Burgess, Donnett, Jeffery, & Maguire, 1998; O'Keefe & Dostrovsky, 1971; O'Keefe & Nadel, 1978; Spiers et al., 2001), whereas others have noted that deficits following hippocampal damage are more selective (Milner, Corkin, & Teuber, 1968; Bohbot, Iaria, & Petrides, 2004; Corkin, 2002; Eichenbaum & Cohen, 2001). Recent studies in humans (Hirshhorn, Grady, Rosenbaum, Winocur, & Moscovitch, 2012; Rosenbaum et al., 2000; Rosenbaum, Ziegler, Winocur, Grady, & Moscovitch, 2004; Rosenbaum, Gao, Richards,

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Black, & Moscovitch, 2005; Teng & Squire, 1999; see review in Spiers & Maguire, 2007) and rodents (Winocur, Moscovitch, Fogel, Rosenbaum, & Sekeres, 2005; see also reviews by Rosenbaum, Winocur, & Moscovitch, 2001; Winocur, Moscovitch, & Bontempi, 2010; Winocur & Moscovitch, 2011) provide evidence that coarse schematic, yet allocentric, spatial representations can become independent of the hippocampus following extended experience in the environment. Such representations are sufficient to support navigation, and depend on a network of extra-hippocampal regions including the posterior parahippocampal cortex, lingual gyrus, posterior cingulate/retrosplenial cortex, and precuneus. Consistent with this observation, investigators have noted that the hippocampus always is needed for navigation along “minor” routes, but not on main thoroughfares (Maguire, Nannery, & Spiers, 2006). Even when navigation is spared following hippocampal lesions or deterioration, there is loss of perceptual details associated with a familiar environment (Hirshhorn, Newman, & Moscovitch, 2011) much like the type of loss for remote episodic memories reported after these lesions (Moscovitch et al., 2005; Rosenbaum, Gilboa, Levine, Winocur, & Moscovitch, 2009; St.-Laurent, Moscovitch, Levine, & McAndrews, 2009). The diminished ability of people with such damage even to imagine scenes in vivid detail (Hassabis, Kumaran, Vann, & Maguire, 2007) is ascribed either to loss of episodic memory, to impaired scene construction, or to both.

These findings, like current theories of hippocampal function, emphasize either episodic memory or spatial memory processing as a crucial function of the hippocampus. Mayes et al. (2004) were among the first to examine the effects that a memory’s age and spatial content have on the neural substrates mediating episodic and semantic memories. Summarizing a complex set of results, Mayes et al. (2004) noted that episodic memories, operationalized as an event associated with a spatial location or route, activated the medial temporal lobes more than did semantic memories, which were operationalized as knowledge of locations of towns on maps. The spatially richer recent memory, whether episodic or semantic, was associated with greater activation of the right posterior parahippocampal cortex, precuneus and posterior parietal cortex. Some of the episodic-semantic differences associated with memory age likely are due to the richness of the memory which typically is more pronounced for recent than remote episodic/event memories than for semantic/map memories. Following Mayes et al.’s (2004) example, our experiment aims to compare the role of the hippocampus in spatial and episodic memory by asking participants to make episodic or spatial comparison judgments about familiar Toronto landmarks. Departing further from Mayes et al.’s procedure, we held location constant across spatial and episodic conditions, allowing us to match all aspects of the task except for differences related to making spatial and episodic memory judgements, thereby affording us greater control and precision when comparing the two conditions.

It is generally accepted that, with respect to spatial memory, the hippocampus is preferentially involved in allocentric spatial memory (Holdstock et al., 2000; O’Keefe & Nadel, 1978). Therefore, an important element of this experiment is that participants were asked to make spatial memory judgments that strongly promoted the use of an allocentric frame of reference. This was done by asking participants to compare the relative locations of two landmarks based on their absolute positions with respect to cardinal spatial co-ordinates, independently of one’s viewpoint, e.g., “Which building is farther North, South, East or West?” If the hippocampus is in fact important for allocentric representations of space, it is necessary to determine whether it is equally implicated for all allocentric representations regardless of the density of information contained in the representation (i.e., whether the representation is coarse- or fine-grained). This

question is motivated by findings that suggest that the hippocampus may be crucially involved in fine-grained spatial representations. For example, patients with hippocampal lesions are impaired in recalling fine details of an environment such as individual houses in a familiar neighborhood or cities on a world-map, although they are able to recognize coarse details such as salient neighborhood landmarks and continents on a world map (Rosenbaum et al., 2000). The difficulty people with hippocampal lesions have in making fine, but not coarse, spatial discriminations may account for the impairment Maguire et al. (2006) observed in a London taxi-driver who could navigate the larger A routes but not the smaller, more tortuous, B routes. In addition, patients with hippocampal lesions are impaired at making fine-grained discriminations amongst scenes, suggesting that the hippocampus may also be involved in higher-order spatial perception (Lee, Barense, & Graham, 2005). These reports are consistent with the animal literature showing that the hippocampus is crucial for spatial pattern separation (e.g. Gilbert, Kesner, & DeCoteau, 1998). Further, work with rats has shown that the size of place fields increases progressively with the distance from the dorsal pole (corresponding to the posterior hippocampus in humans) (Jung, Wiener, & McNaughton, 1994; Kjelstrup et al., 2008; Maurer, Van Rhoads, Sutherland, Lipa, & McNaughton, 2005). Place cells in the dorsal hippocampus have smaller receptive fields, consistent with the notion that they code fine-grained spatial details (see Brun et al., 2008, for review).

If the hippocampus is required to distinguish between spatially similar information, it may be more active when participants are required to discriminate between two locations that are close together. Therefore, we wished to know whether the need for more fine-grained representations would recruit the hippocampus to a greater extent than for coarse discriminations. To test this idea, we included a difficulty manipulation for the allocentric judgments such that each pair of landmarks was presented with both an easy and a difficult question. Difficult questions were defined as those that required a comparison along the axis with the shortest distance between the two landmarks. These questions were expected to require the use of a more fine-grained representation than the easy ones. If the posterior hippocampus in humans is required for fine-grained representations of space (similar to the dorsal hippocampus in rats), the difficult questions should activate the posterior hippocampus to a greater extent than the easy ones.

The easy allocentric questions are expected to recruit a set of brain regions that are thought to support a coarse representation of a familiar environment. Such brain regions have been shown to support mental navigation independently of the hippocampus and include the parahippocampal cortex (PHC), lingual gyrus, posterior cingulate/retrosplenial cortex, and lateral temporal cortex (Hirshhorn et al., 2012; Rosenbaum et al., 2004, 2007). It is likely that the difficult allocentric condition will also recruit these brain regions, as they are important for representing the layout of a familiar environment. However, the difficult condition is expected to recruit additional regions, such as the precuneus, that reflect the need for detailed inspection of mental imagery.

Previous studies have shown that a coarse representation of an environment can become independent of the hippocampus with a year of experience in that environment (Hirshhorn et al., 2012). Building on this finding, we wished to compare the time course of hippocampal involvement in retrieving coarse- and fine-grained spatial details and episodic details associated with a familiar environment. To do so, we tested participants who had lived in Toronto for several years (mean=15.71 years; SD=9.83 years) and included this as a factor in the analysis of hippocampal activation during each condition.

For the episodic memory task, participants had to decide which of two landmarks they had visited most recently, a decision that was

expected to promote the vivid recollection of a specific event. The landmarks were the same as those used in the spatial tasks. Based on many reports of hippocampal activation during episodic retrieval of recent and remote memories (Addis, McIntosh, Moscovitch, Crawley, & McAndrews, 2004; Addis, Moscovitch, Crawley, & McAndrews, 2004; Gilboa, Winocur, Grady, Hevenor, & Moscovitch, 2004; for review see Moscovitch et al., 2005; Winocur, Moscovitch, Rosenbaum, & Sekeres, 2010), we expected that the hippocampus would be activated when participants retrieved episodic details associated with familiar landmarks. The question remained whether the location, extent, or degree of activation would be similar to that found in either or both of the spatial tasks. Thus, though the procedures are different, the design of this study resembled that used by Mayes et al. (2004) to contrast recent and remote episodic memories that occurred in a particular location with map-like “semantic” spatial memories.

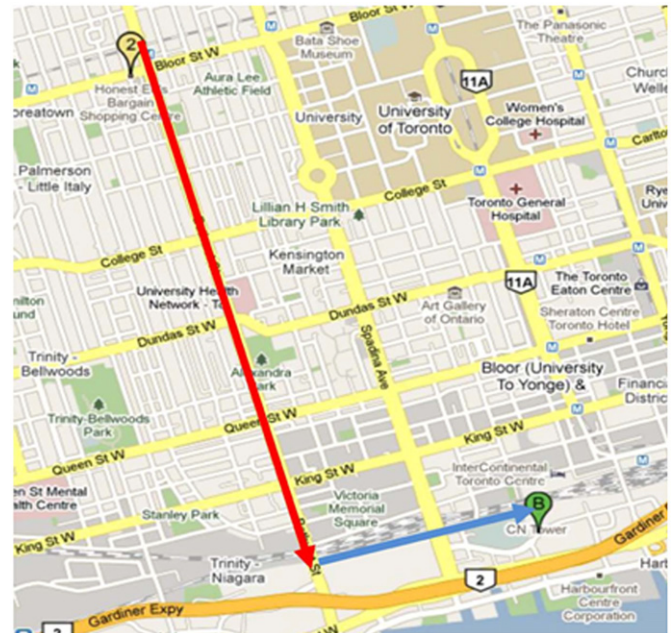
By asking participants to retrieve both episodic and spatial information about the same environment, we were able to contrast directly the role of the hippocampus in episodic and spatial memory. More specifically, we wished to answer the following question: is the hippocampus differentially activated during the long-term retrieval of episodic and spatial information about highly familiar environments? In a recent study, Hoscheidt, Nadel, Payne, and Ryan (2010) found that the hippocampus was differentially activated when participants were tested for their memory of spatial and non-spatial aspects of past autobiographical episodes, with the former activating the anterior region and the latter, the posterior region. The study, however, did not specifically test their memory of large-scale environments needed for navigation, but rather focused on memory for the location at which an event occurred or for spatial relations within the event (e.g., During the wedding, Sally sat to your right). Given the central role that memory for navigational space plays in theories of hippocampal function, and the controversy surrounding remote memory in general, it is important to determine whether similar hippocampal involvement will be observed for episodic and spatial memories associated with large scale, highly familiar environments (Moscovitch, 2008).

A complementary goal of this experiment was to detect whole-brain patterns of activation, in addition to those in the hippocampus, that would be common to and/or distinguish between the three memory conditions. Extensive overlap between the network of brain regions recruited by episodic memory and mental navigation tasks has been reported (Mayes et al., 2004; for review see Hassabis & Maguire, 2007, and Spreng, Mar, & Kim, 2009). Since the three tasks require some degree of episodic memory and mental navigation, we predicted that all three tasks would recruit, though not to the same extent, a set of brain regions commonly implicated in these functions, including the parahippocampal cortex, retrosplenial/posterior cingulate cortex, and precuneus which are involved in geometric spatial representations (Epstein, 2008; Mayes et al., 2004), translations between different perspectives (Maguire, 2001), and mental imagery (Fletcher et al., 1995), respectively. Other regions, such as medial prefrontal cortex and posterior parietal cortex (inferior parietal lobule, supramarginal gyrus, angular gyrus) may be preferentially activated for the episodic tasks (see Spreng et al., 2009; Svoboda, McKinnon, & Levine, 2006), whereas the precuneus and parahippocampal cortex may be preferentially activated for the spatial tasks (Epstein, 2008).

## 2. Materials and methods

### 2.1. Participants

Fourteen young, healthy, right-handed adults (6 male; mean age=26.43; SD=2.68) who had lived in the city of Toronto for a minimum of five years ( $M=15.71$  year;  $SD=9.83$  year) participated in this experiment. All participants provided informed written consent in accordance with the ethics review board at



**Fig. 1.** An illustration of the difference between easy and difficult allocentric judgments. Shown above are two of the landmarks used in the study: Honest Ed's (2) and the CN Tower (B). Looking at North–South coordinates designated by the red arrow, Honest Ed's is further North in a cardinal direction from the CN Tower, whereas looking at East–West co-ordinates, Honest Ed's is further West. For this example, the corresponding easy allocentric question is “Which landmark is farther North (or South)?” as the distance between these two landmarks along the North/South axis (shown in red) is relatively large. The more difficult allocentric question is “Which landmark is farther East (or West)?” as this distance (shown in blue) is relatively small.

the Rotman Research Institute. Prior to participation in the study, participants completed a screening questionnaire to ensure that they were familiar with the landmarks and had visited them.

### 2.2. Stimuli

The written names of 52 pairs of Toronto landmarks were used as stimuli. Landmarks were selected on the basis of high familiarity ratings (most frequently visited) in a pilot study.

### 2.3. Procedure

The fMRI session consisted of four 12.6 min runs of 52 trials each. Each trial was 12 s in duration. On each trial participants were presented with a pair of Toronto landmarks and a question pertaining to those landmarks. This information remained on the screen for the duration of the trial. Each pair of landmarks was presented four times during the experiment (once in each condition), but never in sequence or more than once in the same scanning run. Participants were instructed to emphasize accuracy over speed when answering each question. On each trial, participants made their response by pressing ‘1’, ‘2’, or ‘3’ on an fMRI-compatible number pad. The numbers ‘1’ and ‘2’ corresponded to the presented landmarks. The number ‘3’ was used to indicate a response of “I don't know.” Each question was followed by a two second fixation cross presented at the center of the screen. Four types of questions, corresponding to one control and three experimental conditions, were presented as follows:

**Task 1: episodic judgments.** Participants indicated which of the two landmarks they had visited most recently. Prior to the scanning session, participants were instructed to interpret the term “visited” in a liberal sense, which could include passing by a landmark without entering it. Participants were instructed to respond “I don't know” if they had never visited either landmark.

**Task 2: easy allocentric judgments.** Participants selected the landmark that is located farther North, South, East, or West with respect to cardinal directional coordinates. Easy allocentric questions required participants to compare the locations along the cardinal axis with the greatest distance between the two landmarks (see Fig. 1 for illustration). In Fig. 1, when asked which is further North, Landmark 2 (Honest Ed's)<sup>1</sup> or B (CN Tower), the difference between the two is large in comparison to being asked which is further West (see Task 3).

**Task 3: difficult allocentric judgments.** Participants selected the landmark that is located farther North, South, East, or West. Difficult allocentric questions required

**Table 1**  
Accuracy and reaction time for the four conditions.

Task	Accuracy (% correct) Mean (SD)	Reaction time (ms) Mean (SD)
Episodic	91.86 (0.92)	3758.56 (1033.47)
Easy allocentric	92.50 (0.93)	3387.95 (711.63)
Difficult allocentric	74.85 (0.75)	3558.92 (734.10)
Control (vowel comparison)	88.66 (0.89)	4086.06 (1078.62)

participants to compare the locations along the cardinal axis with the smallest distance between the two landmarks (see Fig. 1). As Table 1 shows, accuracy and RTs in making these judgements were consistent with estimates of difficulty.

*Task 4: vowel comparison baseline.* Participants indicated which landmark name had more or fewer vowels.

### 2.3.1. Post-scan interview

Following the fMRI session, participants completed a paper-and-pencil questionnaire to gather more information about the episodic condition. Participants were presented with a list of the same landmark pairs that were used during scanning. Participants were asked to circle the landmark that they had visited most recently, and to try to provide answers that were consistent with the ones given during scanning. We adapted the remember-know paradigm that is used to distinguish between memories that are based on recollection from those that are based on familiarity (Tulving, 1985; Yonelinas, 2001, 2002) and applied it to our task. For each pair of landmarks, participants were asked to make a Remember/ Know judgment by circling 'R' or 'K' respectively. Participants were instructed to make an 'R' response if they were able to recall their most recent visit to the selected landmark. Participants were instructed to make a 'K' response if they did not remember the specific instance of visiting that particular landmark, but answered the question using general knowledge—they strongly believed they had visited one landmark more recently because they knew that they passed it weekly whereas the other landmark they visited rarely. (see Yonelinas, 2002 for a review of R/K procedure). For example, "I know that I have visited Honest Ed's<sup>1</sup> most recently because I pass it every day on the way to work." The distinction between recollected memories and merely familiar ones is important because recollection of an event and the accompanying conscious awareness of episodic details is presumed to be dependent on the hippocampus (Eichenbaum, Yonelinas, & Ranganath, 2007; Yonelinas, Otten, Shaw, & Rugg, 2005). Familiarity, in contrast, is presumed to be supported by the perirhinal cortex (Brown & Aggleton, 2001; Wan, Aggleton, & Brown, 1999).

We included this procedure because of our specific prediction that hippocampal activation during the episodic condition would be related to the recollection of specific details about visiting that particular landmark. Therefore, it was necessary to exclude trials for which participants made a response based on more semantic/familiarity information. Only trials that were given an 'R' response were included in the subsequent analyses. For all other conditions, only correct responses were included in the analyses. Although this is not the conventional sense in which R/K is used, we thought it was an appropriate application of the procedure for this purpose. The average number of trials used was 48 for the episodic condition, 48 for the easy allocentric condition, 39 for the difficult allocentric condition, and 46 for the control condition.

In addition, participants were asked to rate how recently they had visited the selected landmark by circling one of five options: within the past week, past month, past year, past five years, and over five years ago.

### 2.3.2. Image acquisition

Anatomical and functional images were acquired at Baycrest with a 3 T Siemens scanner with a standard head coil. For each participant, we acquired a T1-weighted volumetric anatomical MRI (30 axial slices, TE=2.63 ms, 5 mm thick, FOV=256 cm). Brain activation was assessed using the blood oxygenation level-dependent (BOLD) effect. For functional imaging, twenty six, 5 mm thick axial slices were obtained using a T2\*-weighted pulse sequence with an echoplanar imaging (EPI) readout (TR=2000 ms, TE=30 ms, FOV=200 mm, 64 × 64 matrix).

Visual stimuli were presented on a back-projection screen using E-prime software (Psychology Software Tools, Pittsburgh, PA), viewed with a mirror mounted on the head coil. Responses were collected with an fMRI-compatible response box.

### 2.4. Behavioral analysis

Repeated measures ANOVAs were used to compare mean accuracy and mean reaction time (correct trials only) across the four conditions. Since we had no means to verify the responses given in the episodic condition, all responses other

than "I don't know" that were rated as 'Remember' in the post-scan questionnaire were counted as accurate. Therefore, accuracy in the episodic condition refers to the percentage of trials for which the participant was able to select one of the two landmarks based on an episodic memory. In addition, for the episodic condition, a repeated measures ANOVA was used to compare the mean number of visits from each time period (e.g. past week, past month, etc.) as reported in the post-scan questionnaire.

### 2.5. Data processing

Images were reconstructed and pre-processed using the Analysis of Functional Neuroimages (AFNI, version 2.0) software package (Cox, 1996). 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. Images were first reconstructed, then they were corrected for movement due to heart rate and respiration, slice-timing corrected to the first slice and motion corrected using a 3-D Fourier transform interpolation with a functional volume that minimized the amount of motion to approximately 1.5 mm. The four scanning runs were then concatenated and each condition was modeled, using the general linear model, with a tent function (20 s epoch, 8 lags), including the motion-correction parameters as regressors of no interest. Activation maps of the BOLD signal for each subject then were calculated for each memory condition with respect to the vowel control condition. The resulting individual activation images were normalized to the Montreal Neurological Institute (MNI) template (resampled at 1 mm × 1 mm × 1 mm voxels) and smoothed with a Gaussian filter of 6-mm full-width-at-half-maximum (FWHM) to increase the signal-to-noise ratio. The contrast images of each condition relative to the baseline condition were used for ROI analysis in AFNI. For PLS analysis, the original preprocessed images were used (2 mm isotropic voxel size), without any contrasts (i.e. the vowel control condition was included as a separate condition in the PLS analysis)

### 2.6. ROI analysis

An anatomical ROI was used as a mask to confine the conjunction and disjunction analysis to the hippocampus. A mask of the bilateral hippocampus was created using the automatic drawing feature based on anatomical templates in AFNI.

#### 2.6.1. Conjunction analysis

The contrast maps for each task (taken from the output of the group analysis) were thresholded liberally ( $p < 0.01$ ) and multiplied by each other in order to determine which brain regions were active for all three tasks. The resulting map has a significance level equal to the product of the  $p$ -values of each contrast map ( $p < 0.01 \times 0.01 \times 0.01 = p < 0.000001$ ) (not only see Cabeza, Dolcos, Graham, & Nyberg, 2002; Cabeza et al., 2004 for discussion of this method, but also see Lazar, Luna, Sweeney, & Eddy, 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. We were also interested in comparing the degree of hippocampal activation across the three conditions. Because the episodic and difficult allocentric conditions activated different regions of the hippocampus, we chose not to average the signal across the entire hippocampus. In order to compare the degree of activation, we used the bilateral clusters that were commonly activated by all three conditions (see Section 3 for locations of these regions). That is, we used the clusters identified by the conjunction analysis as a mask to extract the mean percentage signal change during each task from each individual subject. Repeated measures ANOVAs were used to compare the mean per cent signal change across the three conditions for the left and right hippocampus.

#### 2.6.2. Disjunction analysis

A disjunction analysis was used to identify regions of activation in the hippocampal ROI that were unique to each of the three tasks. Disjunction analysis is a conventional analysis that complements conjunction analysis and permits the identification of regions that are uniquely engaged by a condition relative to a common baseline (Braver, Barch, Gray, Molfese, & Snyder, 2001; Chikazoe et al., 2009). The contrast maps were multiplied so as to create an output map of the brain regions active for the episodic condition, but not the easy or difficult allocentric conditions. This procedure was repeated to create output maps of brain regions that were uniquely activated for the easy and difficult allocentric conditions. The significance of each output map is equal to the product of the  $p$ -values of each contrast map ( $p < 0.01 \times 0.01 \times 0.01 = p < 0.000001$ ). The coordinates of the peak voxel for regions of activation were determined using the average  $t$ -statistic from the three contrasts as described above.

#### 2.6.3. Correlation analysis

We were interested in the relationship between degree of familiarity with the environment and hippocampal activation. To assess this relationship, we extracted the mean percentage signal change for each participant from each of the clusters

<sup>1</sup> Honest Ed's is a well known department store in Toronto.

identified in the disjunction analysis. For each cluster, we correlated the mean percentage signal change during the task that uniquely activated that cluster, and the number of years each participant had lived in Toronto. Given that participants completed a screening questionnaire to ensure that they frequently visited the majority of landmarks tested, we took the number of years spent living in Toronto as a rough estimate of general familiarity with the environment. One participant had a mean percentage signal change that was over two standard deviations from the mean for two of the posterior clusters, and was excluded from the analysis of the difficult allocentric condition. For all correlations, we calculated the Pearson correlation and computed 1000 bootstraps to calculate the 95% confidence interval for each one.<sup>2</sup>

### 2.7. PLS analysis

Whole-brain neuroimaging data were analyzed with partial least squares (PLS; McIntosh, Bookstein, Haxby, & Grady, 1996; McIntosh, Chau, & Protzner, 2004; for tutorial and review see Krishnan, Williams, McIntosh, & Abdi, 2011). PLS is based on the assumption that cognitive processes result from the activity of an integrated neural network, rather than the activation of any independent brain region. With PLS, no assumptions are made about the shape of the hemodynamic response function (HRF), allowing the algorithm to determine the response that best characterizes the conditions of interest. Furthermore, PLS is a data-driven approach such that no *a priori* contrasts are specified, and thereby examines the entire brain, in a theory-neutral way, to see which voxels emerge as similar to or different from one another in different conditions. As such, it provides a novel assessment of covarying whole-brain patterns of brain activity, not obtainable from univariate or ROI approaches; it complements these other approaches. Thus, mean-centered PLS allows us to assess those patterns of brain activity that most closely covary with the experimental design. The result of this analysis is a set of orthogonal variables (latent variables; LVs) that describe brain regions that covary together across the experimental conditions at different time points (lags). Each LV has an associated linear contrast between the tasks and a brain image that shows the regions that covary with the contrast at each lag.

The statistical significance of each LV was determined by permutation tests (McIntosh et al., 1996). In this study 500 permutations were computed, which makes the smallest *p* value possible for any LV  $p < 0.002$ . The amount of covariance accounted for by each LV is given by the singular value. In addition, each brain voxel has a weight (or salience) that indicates how strongly each voxel covaries with the pattern seen on each LV. The reliability of the saliences for the brain voxels that covaried with each pattern identified by the LVs was computed by a bootstrap estimation of the standard errors. This bootstrap estimation procedure was carried out 300 times. Clusters of 100 or more voxels with a bootstrap ratio (saliency/SE ratio) greater than 3.0 were considered to be reliable as this is roughly equal to  $p < 0.005$ . The maximum value for each cluster is reported in MNI space.

Analysis was conducted on the 20 s period after stimulus onset (i.e. 10 lags). Activity at each time point in the analysis was normalized to the first lag of each trial. We first ran mean-centered PLS analysis on all three task conditions and the vowel control condition. The first significant LV distinguished between the three experimental tasks and the control. Since this LV accounted for much of the covariance, we ran a second mean-centered PLS analysis excluding the vowel condition, to allow greater sensitivity with which to detect differences between the experimental tasks. We refer here to the LV identified from the analysis of all four conditions as LV1, and the one resulting from the analysis of the three memory conditions as LV2.

In PLS analysis, each participant has an associated “brain score” for each lag of each LV. The brain score is an index of the degree to which that participant expresses the pattern of activity associated with that LV, for each condition. We plotted the mean brain scores for each LV across the 10 lags that were analyzed (i.e. the “temporal brain scores”). The resulting plots are analogous to hemodynamic response functions and show how the pattern of whole-brain activity associated with each condition is expressed over the window of 10 lags. These plots were used to identify the lags with the peak brain score for each LV. Because this peak activity was mostly at lag 5, we report cluster maxima at this lag in the tables. To assess differences between tasks for each significant LV, PLS calculates the mean brain score over the 10 lags for each task and determines the 95% confidence interval for these means. If the confidence interval for a task overlaps

with zero this indicates that this task is not significantly different from the mean across conditions. If the confidence intervals of two tasks overlap, this indicates that the tasks are not significantly different from each other. Conversely, if the confidence intervals from two conditions do not overlap, then activity in these two conditions reliably differs from one another.

## 3. Results

### 3.1. Behavioral performance

Mean accuracy and reaction times for each task are summarized in Table 1. A repeated measures ANOVA revealed a main effect of task on accuracy [ $F(3,13)=21.43, p < 0.001$ ]. Pairwise *t* tests with Bonferroni corrections for multiple comparisons showed, as expected, that accuracy in the difficult allocentric condition ( $M=74.72\%$ ,  $SD=8.26$ ) was significantly lower than accuracy for all other tasks ( $p < 0.05$ ) (episodic:  $M=91.86\%$ ,  $SD=9.33$ ; easy allocentric:  $M=92.50\%$ ,  $SD=5.96$ ; vowel control:  $M=88.66\%$ ,  $SD=9.11$ ).

A second repeated measures ANOVA revealed a main effect of task on reaction time [ $F(3,13)=5.63, p < 0.005$ ]. Pairwise *t* tests with Bonferroni corrections for multiple comparisons showed, as expected, that reaction time was significantly faster only in the easy allocentric condition ( $M=3387.9$  ms,  $SD=711.6$  ms) compared to the control condition ( $M=4086.1$  ms,  $SD=1078.6$  ms) ( $p < 0.05$ ).

The mean percentage of episodic trials involving visits from each of the five time periods (as reported in the post-scan questionnaire) is summarized in Table 2. A repeated measures ANOVA was used to compare the mean number of visits reported from each time period, and revealed a main effect of time period [ $F(4,13)=6.03, p < 0.001$ ]. Pairwise *t* tests with Bonferroni corrections for multiple comparisons showed that the percentage of visits reported from the past week was significantly greater than the percentage of visits from over five years ago ( $p < 0.05$ ). The percentage of visits reported from the past month was significantly greater than the percentage of visits from five years ago ( $p < 0.05$ ) and the percentage of visits from over five years ago ( $p < 0.05$ ).

### 3.2. ROI analysis results

The conjunction of all three spatial memory tasks showed a common activation in posterior hippocampal regions in the right (30, −34, −6) and left hemispheres (−31, −36, −6) (see Fig. 2). The mean per cent signal change during each task was extracted from the left and right clusters (Fig. 2) separately. Repeated measures ANOVAs showed no main effect of task on the mean per cent signal change in either the left [ $F(2,26)=3.07, p=0.06$ ] or right cluster [ $F(2,26)=1.27, p=0.30$ ]. Clusters of activation unique to each of the three tasks are listed in Table 3. The episodic task uniquely activated a cluster extending along the length of the left HPC with the peak in the anterior HPC (peak coordinates = −29, −17, −18) (Fig. 3) and a cluster in the right anterior HPC (27, −15, −15) (Fig. 3). The easy allocentric condition did not show any unique activations within the hippocampus. The hard allocentric condition uniquely activated two clusters in the mid-posterior right HPC (31, −27, −10 and 33, −22, −14) (Fig. 4).

The mean percentage signal change during the episodic task in the left and right clusters identified in the disjunction analysis did not correlate with the number of years participants had lived in Toronto (left:  $r = -0.40, p = 0.18$ , confidence intervals (CIs) = −0.80, 0.089; right:  $r = -0.29, p = 0.34$ , CIs = −0.82, 0.20) or the accuracy (left:  $r = 0.35, p = 0.21$ , CIs = −0.06, 0.72; right:  $r = 0.45, p = 0.11$ , CIs = 0.17, 0.89) or reaction time (left:  $r = 0.21, p = 0.47$ , CIs = −0.19, 0.61; right:  $r = 0.19, p = 0.69$ , CIs = −0.42, 0.55) on the episodic task.

Because the easy allocentric condition did not uniquely activate any clusters in the hippocampus, we made use of the clusters

<sup>2</sup> Unfortunately, it was not possible to examine the relationship between hippocampal activation during the episodic memory task and recency of the recovered memories. Although this analysis would have been informative, the decision during the task was based on a comparison between two events, one recent and one more remote, making it difficult to know to which of the two memories (or to both) hippocampal activation was related. Because the vast majority of sites were visited within the recent month, and because we did not collect detailed descriptions of these memories, it was unlikely that we could distinguish clearly between the effects of time and memory vividness on hippocampal activation.

that were active in the conjunction of all tasks, and collapsed across right and left hemispheres, to assess the correlation between activation during the easy allocentric task and time living in Toronto. The mean percentage signal change during the easy condition did not correlate with the number of years participants had lived in Toronto ( $r = -0.25$ ,  $p = 0.40$ , CIs =  $-0.73$ ,  $0.34$ ), or the accuracy ( $r = 0.22$ ,  $p = 0.45$ , CIs =  $-0.24$ ,  $0.57$ ), or reaction time ( $r = 0.44$ ,  $p = 0.11$ , CIs =  $-0.16$ ,  $0.83$ ) on the easy allocentric questions. The mean percentage signal change in the two posterior hippocampal clusters during the difficult allocentric task showed a significant negative correlation with the number of years participants had lived in Toronto ( $r = -0.75$ ,  $p < 0.01$ , two-tailed, CIs =  $-0.92$ ,  $-0.52$ ; see Fig. 4). The mean percentage signal change in these two clusters was not correlated with accuracy ( $r = 0.07$ ,  $p = 0.81$ , CIs =  $-0.41$ ,  $0.56$ ) or reaction time ( $r = 0.20$ ,  $p = 0.50$ , CIs =  $-0.37$ ,  $0.73$ ) for the difficult allocentric condition.

The negative correlation between time lived in Toronto and change in hippocampal activation in the difficult allocentric task fell just short of being significantly greater than that observed for right hemisphere activity in the episodic task ( $Z = 1.51$ ,  $p = 0.065$ , one-tailed) and R/L combined activity in the easy spatial task ( $Z = 1.60$ ,  $p = 0.055$ , one-tailed).

**Table 2**

The percentage of episodic trials grouped into each time period in post-scan questionnaire.

Time period	Percentage of trials Mean (SD)
Past week	41.02 (34.19)
Past month	29.40 (13.62)
Past year	18.77 (22.34)
Past five years	9.80 (10.77)
Over five years ago	1.02 (3.52)

### 3.3. PLS results

The first LV from the mean-centered PLS was significant at  $p < 0.002$ . LV1 accounted for 63.08% of the variance and identified brain regions that differentiated between all three memory conditions and the vowel comparison task (Fig. 5). There were no significant differences between the three memory conditions (Fig. 5C).

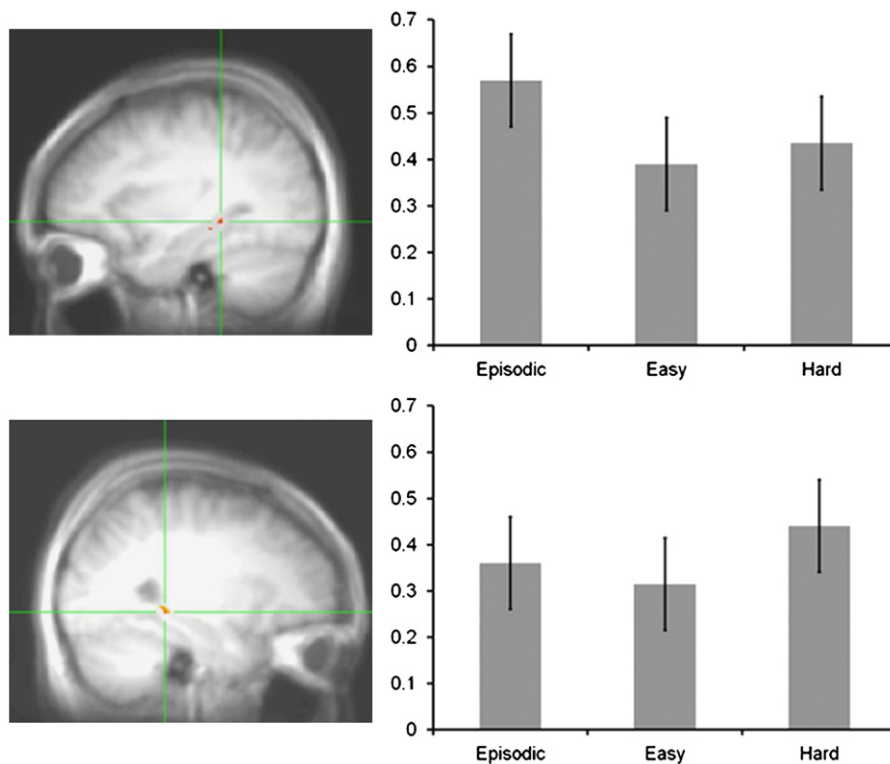
Brain regions that showed significant activation in response to the three memory conditions are shown in Table 4 and Fig. 5A. These regions include the bilateral hippocampus, lingual gyrus, superior temporal gyrus, angular gyrus, posterior cingulate gyrus/precuneus, and the middle frontal gyrus. Decreased activity in the memory conditions compared to the vowel control condition was seen in the bilateral precentral gyrus, middle frontal gyrus, middle occipital gyrus and superior parietal lobule.

The second mean-centered PLS analysis, in which the vowel task was excluded, revealed one significant LV at  $p < 0.002$ . LV2 accounted for 60.12% of the covariance and identified brain regions differentiating the episodic condition from the difficult

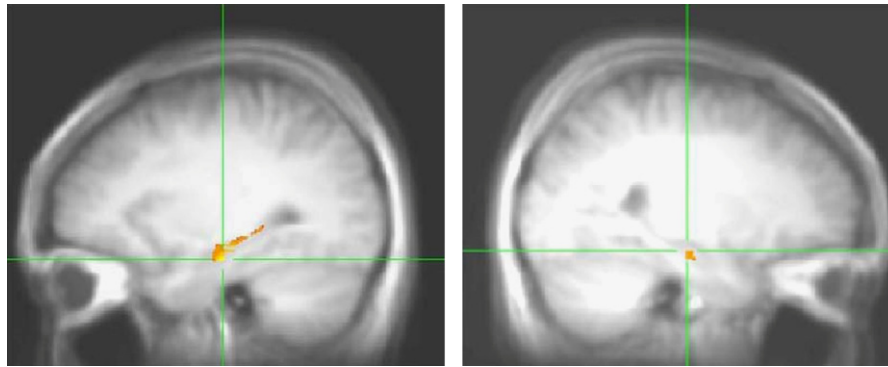
**Table 3**

Regions within the hippocampus that were uniquely activated by each of the three conditions.

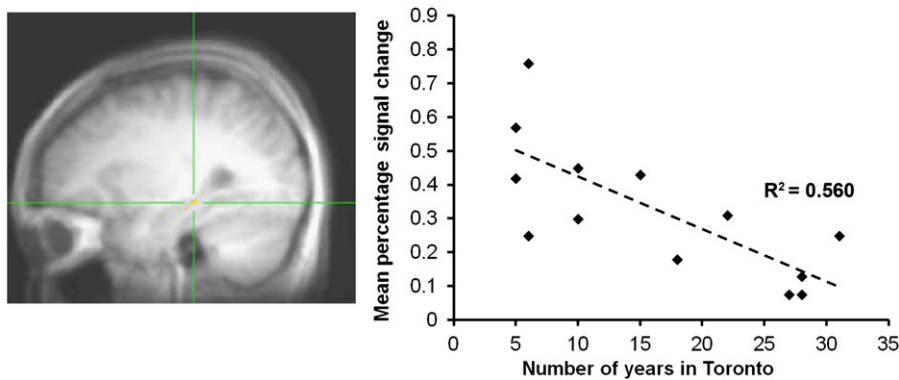
Task	L/R	Talairach coordinates			Cluster size
		x	y	z	
Episodic	L	-29	-17	-18	403
	R	27	-15	-15	176
Easy allocentric	-	-	-	-	-
Difficult allocentric	R	31	-27	-10	38
	R	33	-22	-14	11



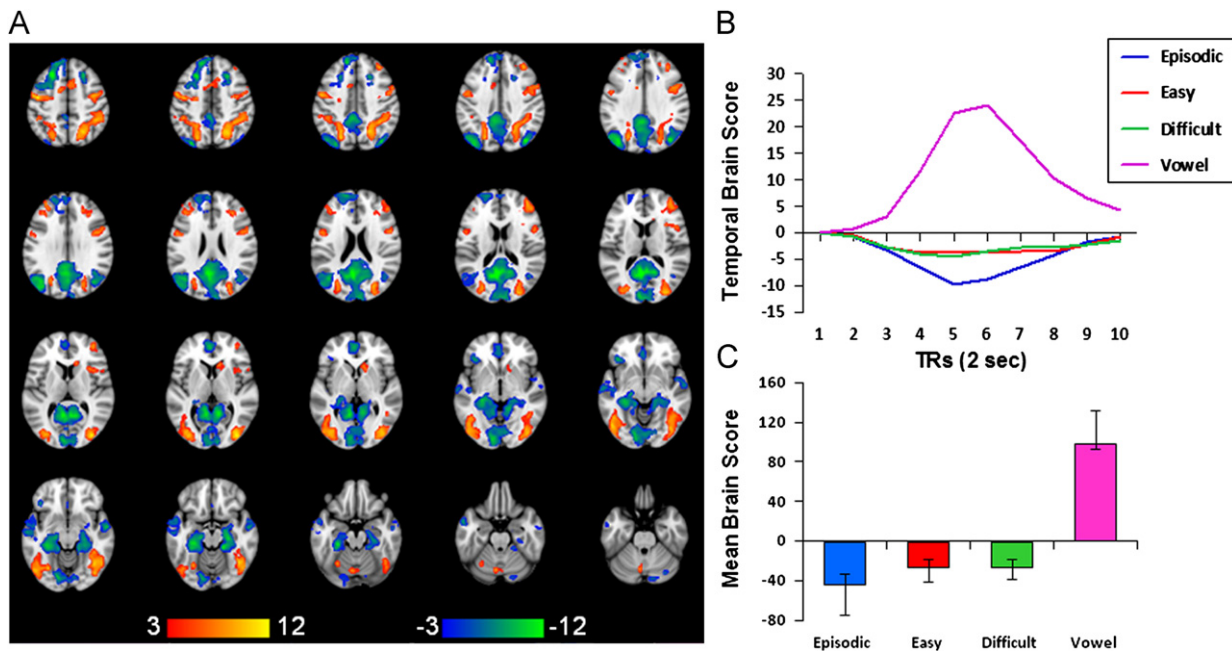
**Fig. 2.** A cluster in the left hippocampus (top) ( $-31$ ,  $-36$ ,  $-6$ ; 46 voxels) and one in the right hippocampus (bottom) ( $30$ ,  $-34$ ,  $-6$ ; 54 voxels) commonly activated by all three spatial memory conditions. The mean per cent signal change during each task is shown for each cluster on the right.



**Fig. 3.** A region in the left hippocampus uniquely activated by the episodic condition. (−29, 17, −18; 403 voxels) is shown on the left. On the right is an anterior region of the right hippocampus uniquely activated by the episodic condition. (27, −15, −15; 176 voxels).



**Fig. 4.** A posterior region of the right hippocampus uniquely activated by the difficult allocentric condition (31, −27, −10; 38 voxels) is shown on top. Shown below is the correlation between the mean per cent signal change in this cluster in response to the difficult allocentric task and the number of years participants had lived in Toronto ( $r = -0.75$ ,  $p < 0.01$ , two-tailed).



**Fig. 5.** (A) Brain regions that showed significant activation in response to the three spatial memory conditions are shown in cool colors, and those areas with more activity for the vowel task are shown in warm colors (bootstrap data from TR5). Areas of activity are shown on a standard structural image in MNI space. (B) The temporal brain scores for each condition on LV1 are shown. These scores can be thought of as whole-brain hemodynamic responses, as the brain scores are summary measures of activity in all brain voxels. Positive brain scores and bootstrap ratios were associated with the vowel condition; negative scores and bootstrap ratios were associated with the three memory conditions. (C) The mean brain scores for each condition are shown with the 95% confidence intervals. These scores were mean-centered prior to averaging, so that 0 on this graph represents the mean activity across all 4 conditions. The color bars indicate the range of bootstrap ratio values for both positive and negative values.

allocentric condition. The easy allocentric condition did not make a reliable contribution to this LV (Fig. 6C). Brain regions that show increased activation in response to the episodic condition compared to the difficult allocentric condition are shown in Table 5 and Fig. 6A (blue regions). These regions include the bilateral superior frontal gyrus, middle frontal gyrus, middle and superior temporal gyri, and the posterior cingulate gyrus on the left. Brain regions that show increased activation in response to the difficult allocentric condition compared to the episodic condition are shown in Table 6 and Fig. 6A (red regions). These regions include the right precuneus and parahippocampal cortex, and the caudate, superior frontal gyrus, and supramarginal gyrus on the left.

**Table 4**  
Brain Activations, identified in the PLS analysis, that differentiated the three memory conditions from the vowel baseline.

Region	Talairach coordinates			BSR
	x	y	z	
R middle/superior frontal gyrus	24	24	48	-7.0
L superior frontal gyrus	-24	26	50	-11.7
L anterior cingulate	-2	48	4	-6.7
L posterior cingulate	-4	-58	14	-11.7
R angular gyrus	38	-74	36	-9.2
L angular gyrus	-38	-78	32	-7.8
R hippocampus	26	-24	-14	-7.0
L parahippocampus/hippocampus	-26	-32	-18	-8.8
L lingual gyrus	-12	-92	-6	-6.8
R cerebellum	6	-48	-36	-7.9
R temporal pole	58	-6	-12	-7.0
L temporal pole	-60	-14	-12	-5.0

Data are from LV1 and all maxima are from TR5 where activity peaks. BSR=bootstrap ratio, indicating robust activity. Regions correspond to those shown in cool colors in Fig. 5.

#### 4. Discussion

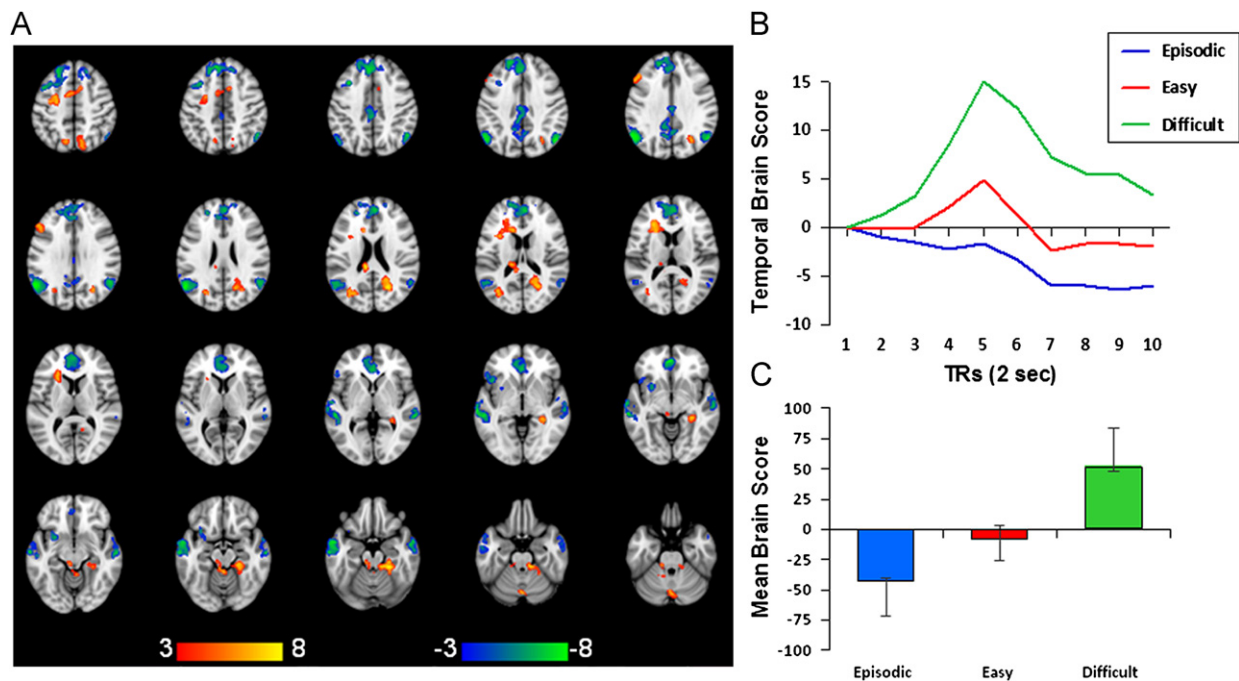
##### 4.1. Differences between episodic and spatial memory

A primary goal of this experiment was to compare the role of the hippocampus in spatial and episodic memory associated with a familiar environment. We found that the hippocampus was activated by retrieval of both types of memory, even when the spatial memories were acquired long ago. In addition, an ROI analysis of the hippocampus identified several regions that differentiated between these two types of memory. First, there were differences in the location of activation along the

**Table 5**  
Brain areas, identified in the PLS analysis, with more activity during the episodic condition than the easy and difficult allocentric conditions.

Region	Talairach coordinates			BSR
	x	y	z	
R superior frontal gyrus	16	24	60	-5.8
L superior frontal gyrus	-22	26	52	-6.2
L superior frontal gyrus	-16	46	36	-5.3
L anterior cingulate	-2	48	-8	-6.8
L middle cingulate gyrus	-6	-38	36	-4.3
R middle temporal gyrus	62	-34	0	-6.1
R temporal pole	60	2	-18	-5.8
L temporal pole	-66	-14	-18	-7.5
R angular gyrus	52	-66	36	-6.5
L angular gyrus	-54	-62	26	-6.5
L striatum	-28	6	-10	-4.2

Data are from LV2 and all maxima are from TR5 where activity peaks. BSR=bootstrap ratio, indicating robust activity. Regions correspond to those shown in cool colors in Fig. 6.



**Fig. 6.** (A) Brain regions that differentiate the episodic condition from the difficult allocentric condition are shown in cool colors. Brain regions that differentiate the difficult allocentric condition from the episodic one are shown in warm colors. Areas of activity are shown on a standard structural image in MNI space (bootstrap data from TR5). (B) The temporal brain scores for each task on LV2 are shown. Positive brain scores and bootstrap ratios were associated with the difficult allocentric condition; negative scores and bootstrap ratios were associated with the episodic condition (activity in the easy allocentric condition was not different from the mean). (C) The mean brain scores for each condition for LV2 with 95% confidence intervals are shown. These scores were mean-centered prior to averaging, so that 0 on this graph represents the mean activity across the 3 conditions. The color bars indicate the range of bootstrap ratio values for both positive and negative values.



**Table 6**  
Brain areas, identified in the PLS analysis, with more activity during the difficult allocentric condition than the easy allocentric and episodic conditions.

Region	Talairach coordinates			BSR
	x	y	z	
L middle frontal gyrus	−24	−10	52	5.6
L middle frontal gyrus	−50	28	32	4.9
L inferior frontal gyrus	−26	28	12	5.8
R precuneus	22	−62	20	6.0
R precuneus	10	−78	52	5.2
L middle temporal gyrus	−34	−68	20	5.1
R parahippocampal gyrus	28	−34	−18	7.0

Data are from LV2 and all maxima are from TR5 where activity peaks. BSR=bootstrap ratio, indicating robust activity. Regions correspond to those shown in warm colors in Fig. 6.

rostrocaudal axis of the right hippocampus for each task, with the difficult allocentric task uniquely activating a posterior region, and the episodic task uniquely activating an anterior region. In addition, the episodic condition uniquely activated a region that extended along the length of the left hippocampus. The easy allocentric condition did not show any unique regions of activation within the hippocampus. Although Mayes et al. (2004) did not employ procedures that distinguished between easy and difficult allocentric spatial comparisons, and their episodic and spatial tasks were different than ours, the results we obtained are broadly aligned with theirs.

These results suggest that the hippocampus is in fact differentially involved in episodic and spatial memory, and are consistent with several other reports of differences in function along the anterior–posterior axis. In a study that also examined memory for spatial and non-spatial information associated with autobiographical episodes, Hoscheidt et al. (2010) found a similar pattern to ours, with memory for spatial and non-spatial information being associated with posterior and anterior hippocampal activation, respectively, and both types of information associated with activation in a middle region of the hippocampus. In another study, Ryan, Lin, Ketcham, and Nadel (2010) had participants recall spatial, non-spatial, episodic and semantic relations in a laboratory-based recognition task of a pictorial display of an array of objects. The researchers found that the posterior right hippocampus was preferentially involved in the recall of spatial relations in that array, whereas non-spatial conditions activated the left hippocampus and the right middle hippocampus. Taken together, these findings suggest that the posterior hippocampus is implicated in memory for spatial relations regardless of whether they pertain to highly familiar large-scale environments, to smaller-scale scenes, or to recently encountered pictorial arrays.

Other recent neuroimaging studies also report that the anterior hippocampus is implicated in non-spatial relational memory encoding or episodic aspects of memory (e.g. Chadwick, Hassabis, Weiskopf, & Maguire, 2010; Davachi, 2006; Davachi & Wagner, 2002; Lepage, Habib, & Tulving, 1998; Prince, Daselaar, & Cabeza, 2005), whereas the posterior hippocampus is preferentially involved in spatial memory (e.g., Maguire et al., 2000). For example, Liang, Wagner, and Preston (in press) used multivariate pattern analyses to investigate hippocampal sensitivity to scenes as compared to non-spatial stimuli such as faces and words. They found that the posterior hippocampus bilaterally, but not the anterior hippocampus, was differentially sensitive to memory for scenes but not for other stimuli. When comparing sensitivity to novel vs. repeated stimuli, it was the anterior hippocampus bilaterally that showed the greater sensitivity.

Similar conclusions regarding the function associated with the posterior hippocampus emerged from studies correlating regional

hippocampal volumes with spatial memory. Maguire and her colleagues found that experienced London taxi drivers have greater gray matter volume in the posterior hippocampus compared to healthy controls, and this increased volume is correlated with the number of years spent working as a taxi driver, and with accumulated knowledge of the spatial relationships between London landmarks (Maguire et al., 2000; Woollett & Maguire, 2009). Taxi drivers also have reduced gray matter volume in the anterior hippocampus, which has been associated with a decreased ability to learn new visual associations (Woollett & Maguire, 2009). The anterior hippocampus is also thought to be important for novelty detection and encoding (Bunzeck & Duzel, 2006; Poppenk & Moscovitch, 2011). These findings are consistent with the current results, as retrieving one's most recent visit to a particular landmark may be accompanied by additional episodic details, which would pose added demands on relational processing.

The differential activation along the rostro-caudal axis of the hippocampus during retrieval of spatial and episodic memories corresponds with its neuroanatomical projections. The posterior hippocampus, which showed preferential activation, particularly on the right in the difficult spatial task, is strongly connected to parahippocampal and retrosplenial cortex, and indirectly to parietal cortex, all of which are implicated in processing spatial information (Rosenbaum et al., 2004). By comparison, retrieval of episodic memories is associated with activation that is distributed along much of the longitudinal axis of the left hippocampus, and in the posterior and anterior portions of the right hippocampus. This pattern is consistent with the multifaceted aspects of episodic memories which draw on (1) spatial and perceptual information represented in posterior neocortex and projecting to posterior and mid-portions of the hippocampus (Poppenk & Moscovitch, 2011; Spaniol et al., 2009 and references therein), (2) semantic information represented in anterior temporal and inferior frontal cortex and projecting to anterior hippocampus (Rogers et al., 2006) and (3) emotion-related information mediated by the amygdala, which also has strong projections to the anterior hippocampus (Olson, Plotzker, & Ezzyat, 2007; see also Duvernoy, 2005). As we discuss below, the multifaceted aspects of episodic memory, in combination with scene construction processes that may be implicated in episodic retrieval, also help account for the patterns of overlap in hippocampal activation across the various tasks.

The only study whose findings departed from this pattern of greater sensitivity to spatial information in the right, posterior hippocampus is that of Morgan, MacEvoy, Aguirre, and Epstein (2011). Using an adaptation paradigm to pictures of locations on a university campus, they found that activation levels in the left, anterior hippocampus corresponded to real-world distances between landmarks on successive trials, suggesting that this region codes for distance relations of even very familiar stimuli. At the same time, no hippocampal region was found to be sensitive to repetition. We have no ready explanation for this anomaly, except that pictures of very familiar landmarks in their study may have also elicited autobiographical and general memories in most of the participants (Morgan et al., 2011, p. 1243), both of which are associated with left, anterior hippocampal activation.

In addition to these differences in hippocampal activation, the PLS analysis revealed a set of other brain regions that differentiated between the episodic and difficult allocentric conditions. The episodic condition was associated with activity in the medial frontal and middle frontal gyrus, as well as the anterior and posterior cingulate gyrus. The medial frontal cortex is often activated in autobiographical memory tasks and is thought to be involved in self-referential processing (see Svoboda et al., 2006 for review) as well as post-retrieval monitoring and verification (see Gilboa, 2004 for review). The episodic condition also was associated with activation in the angular gyrus and inferior

parietal lobule, consistent with many reports of posterior parietal engagement in episodic memory tasks (see Wagner, Shannon, Kahn, & Buckner, 2005 for review). In contrast, the difficult allocentric condition was associated with increased activity in the right precuneus and parahippocampal cortex, and the left superior frontal gyrus and supramarginal gyrus. The finding of right precuneus activation during the difficult allocentric task is consistent with the idea that this task requires detailed inspection of mental imagery (Fletcher et al., 1995). The landmark pairs in this condition were being compared along the dimension with the least distance between them, which requires a more fine-grained spatial representation and may, in addition, depend on geometric spatial representations mediated by parahippocampal cortex (Epstein, 2008). The supramarginal gyrus activation may reflect the need for increased spatial attention (Chambers, Payne, Stokes, & Mattingley, 2004), while the superior frontal gyrus may reflect increased spatial working memory processes (Courtney, Petit, Maisog, Ungerleider, & Haxby, 1998).

Notwithstanding the above-mentioned task differences, there was considerable overlap in the brain regions activated during the three conditions. First, ROI analysis of the hippocampus revealed a bilateral cluster in the mid-posterior hippocampus that responded equally to both episodic and spatial memory demands. Others have noted extensive overlap in the brain regions that are commonly implicated in episodic and spatial memory (Hoscheidt et al., 2010; see Buckner & Carroll, 2007, and Hassabis & Maguire, 2007 for review). Hassabis and Maguire (2007) suggested that scene construction may be a common process underlying these two memory functions, and that this process may account for the observed overlap in brain regions supporting episodic and spatial memory. They define scene construction as “the process of mentally generating and maintaining a complex and coherent scene or event. This is achieved by the retrieval and integration of relevant informational components...the product of which has a coherent spatial context, and can then later be manipulated and visualized,” (Hassabis & Maguire, 2007, p. 300). The region of the hippocampus that was commonly activated by all three tasks was located between the posterior region engaged by the difficult allocentric task and the anterior region engaged by the episodic task. Therefore this region is ideally situated to integrate spatial and episodic details in the service of scene construction.

It is likely that the episodic condition in this experiment engaged scene construction processes as it required participants to recall a specific event in which they visited a particular landmark (Mayes et al., 2004). Post-scan reports confirmed that participants did in fact recall a high percentage (94%) of these events in vivid detail. It is also likely that the difficult allocentric condition engaged scene construction processes as it required participants to construct and inspect a representation of the environment at a fine-grained level of detail. The easy allocentric questions could be answered with reference to a coarse representation of the environment that may not necessitate a coherent and vivid mental image. It is possible that these participants, like the others, engaged in scene construction processes for reasons incidental to the task itself. The results of the PLS analysis are also consistent with a scene construction interpretation. All three spatial memory tasks engaged a set of brain regions including retrosplenial/posterior cingulate cortex, hippocampus, and middle frontal gyrus, which are commonly regarded as part of the default mode network (Raichle et al., 2001). The default mode network describes a set of brain regions that are more active during rest periods and often show deactivation during externally oriented tasks. This network is thought to support functions such as monitoring of the internal environment and mind-wandering (Gusnard, Akbudak, Shulman, & Raichle, 2001). Many of these brain regions are also commonly activated in studies of episodic

and autobiographical memory (Burianova & Grady, 2007; St-Laurent, Abdi, Burianova, & Grady, 2011) and self-projection (Buckner & Carroll, 2007; Spreng et al., 2009; Spreng & Grady, 2010). This finding is consistent with the notion that all three tasks involve some degree of internal reflection and inspection of mental imagery, all of which are elements of scene construction. Activation was also observed in the angular gyrus, a region of the ventral parietal cortex, which is postulated to be involved when attention is captured in a bottom-up manner by a retrieved memory (see Cabeza, Ciaramelli, Olson, & Moscovitch, 2008; Ciaramelli, Grady, & Moscovitch, 2008; Hutchinson, Uncapher, & Wagner, 2009 for this and other theories of recruitment of this region in memory tasks).

The shared processing and representational components among the tasks is reflected in overlap of hippocampal activation, both in the ROI analysis and the PLS analysis. The PLS analysis, which examines covarying patterns of brain activity across all voxels, was less sensitive than ROI analysis in distinguishing among the distinct aspects of each task that uniquely activated different parts of the hippocampus. However, it did identify a region of parahippocampal activity that distinguished the difficult allocentric task, consistent with a role for this region in spatial processing, together with the posterior hippocampus.

#### 4.2. Differences between coarse- and fine-grained spatial representations or judgments

A second goal of this experiment was to compare the brain regions involved in coarse- and fine-grained spatial representations. This was assessed by using two types of spatial questions, easy and difficult, that were designed to require coarse- and fine-grained representations, respectively. An ROI analysis of the hippocampus showed that the difficult questions uniquely recruited the right posterior hippocampus, consistent with animal work showing smaller receptive fields in the dorsal hippocampus (Jung et al., 1994; Kjelstrup et al., 2008; Maurer et al., 2005). In contrast, the easy allocentric questions did not recruit any hippocampal regions outside of the ones commonly activated by all three tasks. Therefore, the requirement for fine-grained spatial details recruits the right, posterior hippocampus to a greater extent than coarse spatial representations (but see above for discussion of Morgan et al., 2011).

One interpretation of this finding is that the easy allocentric questions could be answered with reference to a coarse schematic representation that is supported by extra-hippocampal structures, and only engaged the hippocampus for reasons incidental to the task. Indeed, previous work suggests that basic navigation can be supported by a hippocampally independent representation that is likely to be schematic in nature, containing only the major landmarks and the relations between them (Hirshhorn et al., 2012). This explanation is consistent with the idea that the region of the hippocampus that was activated by the easy allocentric task is necessary for scene construction. This region was equally implicated in the episodic memory condition, which suggests that this activation is not due to the retrieval of spatial details per se, but perhaps with retrieval of scenes associated with the episode. It is possible that while retrieving the coarse spatial information required to answer the question, participants also were automatically engaged in scene construction or episodic processes associated with the landmarks.

The differential activation of the posterior hippocampus for fine-grained judgements can be interpreted to mean that the hippocampus is always needed to retain or retrieve detailed information of the environment that can support such fine-grained judgements, akin to similar processes, in other parts of the posterior hippocampus associated with temporal and episodic memory. Alternatively, the posterior regions may be implicated in

pattern separation processes that are needed to make fine grained judgements both about episodes and space, and for constructing such fine grained representations from information represented in other structures (Gilbert et al., 1998). Both interpretation would help reconcile the differences between Maguire et al. (2006; and review by Spiers & Maguire, 2007) and Rosenbaum et al. (2000, 2004, 2007) on the role of the hippocampus in navigation. As long as navigation requires fine-grained discrimination of streets and routes, the hippocampus will be needed regardless of whether one is navigating the winding, small streets of London's B routes, or the grid-like layout of streets in Toronto.

The PLS analysis did not reveal any brain regions that robustly characterized the easy condition, relative to the difficult allocentric condition. Based on previous studies (Hirshhorn et al., 2012; Rosenbaum et al., 2004, 2007), one might have expected regions such as the posterior PHC, lingual gyrus, caudate, and lateral temporal cortex to be more active during the easy task than the difficult one. These regions are commonly implicated in studies of mental navigation and are thought to support a coarse schematic representation of space. If the easy allocentric questions could in fact be answered by referring to coarse representations supported by the abovementioned extra-hippocampal regions, it is surprising that such regions did not differentiate the easy task from the others in the PLS analysis. However, it is possible that the coarse representation that supports the easy allocentric judgments can also support the difficult allocentric and episodic judgments, with these two tasks recruiting additional brain regions that represent more fine-grained spatial or episodic details.

#### 4.3. Changes in activation with experience

We wished to know whether the hippocampus plays a time-limited role for both coarse- and fine-grained spatial representations. Right posterior hippocampal activation during the difficult allocentric task was negatively correlated with the number of years participants had lived in Toronto. Importantly, this activation did not correlate with accuracy or reaction time, suggesting that this effect is related to experience in the environment. In contrast, there was no relationship between hippocampal activation during the easy allocentric task and participants' experience in the city, though the difference between the correlation in the two conditions only approached significance. Although we used bootstrapping techniques to overcome limitations caused by the small number of participants, these conclusions should still be interpreted cautiously, especially since there were only marginally significant differences between the correlations in the two spatial conditions.

Taken together with previous findings from our laboratory (for review see Winocur et al., 2010; Winocur & Moscovitch, 2011) and that of others (Spiers & Maguire, 2007) regarding hippocampal activation during mental navigation, the present results suggest that with experience, schematic representations of the environment are formed in extra-hippocampal structures within a relatively short time. These schematic representations are sufficient to support navigation and judgments about spatial relations as long as fine discriminations among routes and locations are not required. Our results suggest that more extensive experience and time may be needed to create extra-hippocampal representations that can support these fine spatial judgements, though performance in such conditions may not ever be completely independent of the hippocampus (Spiers & Maguire, 2007). Alternatively, there may be only one type of representation in extra-hippocampal structures, but the hippocampal pattern separation processes that operate on these representations benefit from increased knowledge of the environment that comes with time and experience.

There was no relationship between activation during the episodic memory task and the number of years participants had lived in Toronto. However, the episodic memory task asked participants to recall a specific event in which they visited familiar landmarks. Therefore, the length of time that elapsed since the recalled visit may have a stronger influence on hippocampal activation than the number of years one has lived in Toronto. Although there is some evidence for such a recency effect on hippocampal activity (Mayes et al., 2004; Niki & Luo, 2002), other studies have reported that the vividness and personal significance of a retrieved episodic memory are more strongly related to hippocampal activation than the recency of the recalled memory (Addis and Moscovitch, 2004; Gilboa et al., 2004; St-Laurent et al., 2009).

#### 4.4. Summary and theoretical implications

The results of this experiment show that the hippocampus is differentially involved in spatial and episodic memory associated with a familiar environment. Fine-grained spatial representations recruit a posterior region of the right hippocampus, while episodic memories recruit the anterior hippocampus on the right and a region extending along the rostrocaudal axis of the left hippocampus. Coarse spatial representations were found to recruit a bilateral region in the middle of the hippocampus that is also engaged by episodic memory and fine-grained spatial discriminations. We suggest that this region is not involved in the retrieval of spatial information *per se*, but in integrating spatial and episodic details to construct a coherent and vivid scene, consistent with the observations of Liang et al. (in press) and Hoscheidt et al. (2010) that as one moves toward the anterior hippocampus, the representations become less content-specific. Consistent with this idea, all three tasks recruited a set of brain regions including the posterior cingulate/retrosplenial cortex and middle frontal gyrus, which are commonly implicated in self-projection and the inspection of mental imagery. These results are consistent with theoretical accounts which posit that scene construction is a crucial function of the hippocampus.

According to Multiple Trace Theory (MTT), the hippocampus plays a time-limited role in semantic memory, but is continually required to retrieve episodic details (Nadel & Moscovitch, 1997; Nadel, Samsonovich, Ryan, & Moscovitch, 2000). Multiple Trace Theory also predicts that the distinction between semantic and episodic memory has its analog in spatial memory, and that semantic aspects of spatial memory can become independent of the hippocampus with experience in an environment (Moscovitch et al., 2005). The interpretation that the hippocampal activation during the easy allocentric task is incidental and does not reflect the retrieval of spatial information, but rather scene construction processing, is consistent with this hypothesis. This suggests that coarse spatial representations do not require the hippocampus once an environment has become familiar. However, the hippocampus may be recruited if participants engage in elaborative processing and recall episodic details associated with the familiar environment. Also consistent with MTT's prediction that the degree of retrieved detail is a crucial determinant of hippocampal function is the finding that the hippocampus was continually involved in the retrieval of episodic memories, regardless of familiarity with the environment.

The results of this experiment also extend previous work to show that with more extensive experience in an environment, even fine-grained spatial representations, or judgments, become less dependent on the hippocampus. This finding, which needs to be interpreted cautiously as it depends on correlational analyses on a small sample, is consistent with Standard Consolidation Theory (SCT), which predicts that with time, all memories can become independent of the hippocampus, not just the semanticized ones

(Alvarez & Squire, 1994; Cermak & O'Connor, 1983). Therefore, the results of this experiment offer partial support for several theories of hippocampal function (MTT, SCT), as well as scene construction accounts, consistent with the conclusions drawn by Mayes et al. (2004) that the network of structures implicated in retrieval of remote episodic and spatial memory is influenced by a variety of factors including the age of the memory, and the type of information that is retrieved.

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