Brain Regions Involved in Long-term Spatial Memory:

fMRI and Behavioural Studies

by

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Brain regions involved in long-term spatial memory: fMRI and behavioural studies
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Abstract

In this thesis, I investigated the role of the hippocampus and other brain regions in long-term spatial memory. I used neuroimaging and behavioural techniques to compare spatial representations that are dependent on the hippocampus and those that rely on extra-hippocampal structures.

In Experiment 1, I demonstrated that at least some spatial memories that are initially dependent on the hippocampus can become independent of it with time. This was done by looking at changes in brain activation as participants became familiar with a real-world environment over a year. Hippocampal activation was found during mental navigation tasks when participants were new to Toronto, but not after they had lived there for a year. This change was accompanied by an increase in activation in the posterior parahippocampal gyrus, lingual gyrus, cuneus, and superior temporal gyrus.

In Experiment 2, I used neuroimaging to compare hippocampal involvement during the retrieval of coarse- and fine-grained spatial details, and episodic details associated with a familiar environment. I showed that hippocampally-mediated representations contain more fine-grained spatial details than extra-hippocampal spatial representations. Further, I demonstrated that fine-grained details become less dependent on the hippocampus with experience, but episodic details require the hippocampus throughout the lifetime of the memory.

In Experiment 3, I provided behavioural evidence that the role of hippocampus in episodic memory associated with a familiar environment is crucially related to the degree of
detail retrieved. Older adults were asked to recall walking routes from their daily lives and the number of details retrieved was correlated with tests sensitive to hippocampal function.

Finally, I showed that the extra-hippocampal regions implicated in spatial memory depend on task demands. Basic navigation can be supported by the posterior parahippocampal gyrus, lingual gyrus, superior temporal gyrus, caudate and inferior frontal gyrus, independently of the hippocampus. When navigation requires fine-grained spatial details, additional regions including the precuneus and supramarginal gyrus will be recruited. When the task requires the retrieval of episodic details, the posterior cingulate, angular gyrus, and medial frontal lobes will be required, along with the hippocampus.
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General Introduction

Overview of Spatial Memory

Spatial memory, broadly defined, describes one’s knowledge of the layout of an environment. Such knowledge is not only crucial for daily navigation along well-travelled paths, but also supports the use of novel routes, such as when the most direct path between two locations is blocked. Spatial memory can exist in a variety of perspectives, although the most common distinction is between egocentric and allocentric frames of reference. Egocentric representations contain information about the location of landmarks with respect to the viewer, while allocentric representations store information about the relative locations of landmarks with respect to each other (see King, Burgess, Hartley, Vargah-Kadem, & O’Keefe, 2002). In addition to its well-documented role in supporting navigation, spatial memory also provides a context for the retrieval of episodic memories (Nadel, 1992; Burgess, Maguire, & O’Keefe, 2002). For example, visualizing the layout of the classroom on your first day of school may help you to recall other non-spatial details associated with the event.

Research on spatial memory, both in the animal and human literature, has focused largely on understanding which brain regions support this function. The hippocampus has been identified as crucial for the acquisition of new spatial memories, where its role has been well-documented (see below). However, the role of the hippocampus in the long-term maintenance and retrieval of spatial memories is widely debated (see Rosenbaum, Ziegler, Winocur, Grady, & Moscovitch, 2004 for review). At issue is whether spatial memories, after an initial period of hippocampal dependence, can come to be supported by a set of extra-hippocampal structures. A corollary to this question is which (if any) extra-hippocampal regions are capable of supporting
long-term spatial memory and whether the spatial representations mediated by these extra-hippocampal structures differ from those that depend on the hippocampus.

In this thesis, I will examine the role of the hippocampus and other brain regions in long-term spatial memory in two neuroimaging studies and one behavioural study outlined below. I will demonstrate that at least some spatial memories that are initially dependent on the hippocampus can become independent of it with time and experience in an environment. Next, I will explore the differences between long-term spatial representations that are dependent on the hippocampus and those that have become independent of it. I will show that hippocampally-mediated representations contain more fine-grained spatial details than extra-hippocampal spatial representations. However, I will also demonstrate that these fine-grained spatial details can be incorporated into an extra-hippocampal representation with more extensive experience in an environment.

This thesis will also provide evidence that as spatial memories become independent of the hippocampus they lose the rich episodic details associated with them. Unlike fine-grained spatial details which can become less dependent on the hippocampus with extensive experience, episodic details associated with a familiar environment require the hippocampus throughout the lifetime of a memory. In addition, I will show that fine-grained spatial details and episodic details differentially engage the hippocampus in terms of both the location and extent of the regions they activate.

Finally, I will show that the extra-hippocampal brain regions implicated in long-term spatial memory are influenced by task demands. Basic navigation that depends on a coarse representation of the environment can be supported by the posterior parahippocampal cortex, lingual gyrus, superior temporal cortex, caudate, posterior cingulate / retrosplenial cortex, and
inferior frontal cortex. These regions can support basic navigation in a familiar environment independently of the hippocampus. When navigation requires fine-grained spatial details, additional regions including the precuneus and supramarginal gyrus will be recruited. These regions may work together with the hippocampus, or independently of it, depending on one’s degree of experience with the environment. When the task requires the retrieval of episodic details in order to visualize a coherent scene, the posterior cingulate cortex, angular gyrus, and medial frontal lobes will be required, along with the hippocampus.

**Spatial Memory Acquisition**

The idea that the layout of an environment can be represented internally as a cognitive map is rooted in comparative cognition, and dates back to E.C. Tolman’s seminal work with rats in the 1940s. Tolman observed that rats allowed to explore a maze without any reward showed evidence of latent learning of the environment when food was introduced at a later time – they quickly navigated toward the food reward, demonstrating knowledge of the layout of the maze (Tolman, 1948). Tolman interpreted this finding as evidence that rats store comprehensive maps of the environment which allow for flexible behaviour, beyond the confines of stimulus-response learning. This hypothesis was supported by the discovery of place cells in the rat hippocampus which respond maximally when the rat is in a particular location in the environment (O’Keefe & Dostrovsky, 1971; O’Keefe, Burgess, Donnett, Jeffery, & Maguire, 1998). This finding provided the impetus for Cognitive Map Theory which proposes that the hippocampus is required for the acquisition and long-term retention of allocentric representations of space (O’Keefe & Nadel, 1972). Since the discovery of place cells, lesion studies in animals have provided corroborating evidence that the hippocampus is essential for the acquisition of new spatial memories. Rats with hippocampal lesions have demonstrated impairments in learning new environments such as the
Morris water maze (Morris, Garrud, Rawlins, O’Keefe, 1982; Morris, Schenk, Tweedie, Jarrad, 1990; Moser, Moser, & Anderson, 1993; Sutherland, Whishaw, Kolb, 1983) and Olton’s eight arm radial maze (Jarrad, 1978; Olton, Walker, Gage, 1978). Despite this impairment in learning new spatial information, rats with hippocampal lesions are still able to retain knowledge about the layout of an environment for which they have extensive pre-operative experience (Winocur, Moscovitch, Fogel, Rosenbaum, & Sekeres, 2005; 2010). This preserved ability is thought to be based on a schematic representation that relies on learned spatial layouts, major landmarks, and practiced routes among them (discussed in more detail below).

Studies of spatial learning in humans also demonstrate the importance of the hippocampus for the acquisition of new spatial memories. Patients with hippocampal lesions often present with impairments in learning the layout of new real-world (Milner, Corkin, & Teuber, 1968; Teng & Squire, 1999; Rosenbaum, Prieslac, Kohler, Black, Gao, Nadel et al., 2000; Holdstock, Mayes, Cezayirli, Isaac, Aggleton, & Roberts, 2000) and virtual environments (Spiers, Burgess, Maguire, Baxendale, Hartley, Thompson et al., 2001; Bohbot, Iaria, & Petrides, 2004; Bohbot, Kalina, Stepankova, Spackova, Petrides, Nadel, 1998; Bohbot, Jech, Ruzicka, Nadel, Kalina, Stepankova et al., 2002). Such findings mirror the deficits described in the animal literature.

Converging evidence also comes from neuroimaging studies that report hippocampal activation when participants learn the layout of a new environment (Maguire, Frackowiak, & Frith, 1996; Mellet, Bricogne, Tzourio-Mazoyer, Ghaem, Petit, Zago et al., 2000; Shelton & Gabrieli, 2002; Bohbot et al., 2004). This has been demonstrated using a variety of environments and learning strategies. For example, greater hippocampal activation has been reported when participants viewed a film depicting navigation through city streets than when they viewed static
footage of people passing by a street corner (Maguire et al., 1996). Another study also demonstrated hippocampal activation when participants viewed a navigation movie from a ground-level perspective (Shelton & Gabrieli, 2002). Hippocampal activation was also reported when participants mentally navigated between landmarks in a park that they had learned by actually navigating in it (Mellet et al., 2000). More recently, a study using cellular recordings has demonstrated an analogue of place cells in the human hippocampus (Ekstrom, Kahana, Caplan, Fields, Isham, Newman et al., 2003). When participants freely explored and navigated in a virtual town, hippocampal cells responded preferentially to the participants’ location, irrespective of their viewpoint (Ekstrom et al., 2003).

**Long-term Retention of Spatial Memories**

Although the animal and human literature provide consistent evidence that the hippocampus is required to learn the layout of a new environment and represent it as a cognitive map (O’Keefe & Nadel, 1978) in the service of navigation (e.g. Bohbot et al., 1998; Maguire et al., 1996; Shelton, & Gabrieli, 2002), its role in the long-term storage and retrieval of such representations is disputed.

A number of investigators have shown that retention of spatial information is impaired in rodents with hippocampal lesions made as long as nine months after learning spatial locations (Becker, Olton, Anderson, & Breitlinger, 1981; Morris et al., 1982; Clark, Broadbent, & Squire, 2005; Winocur, Moscovitch, Caruana, & Binns, 2005). However, some authors have suggested that these impairments reflect the necessity of the hippocampus for navigation itself and not spatial memory per se (Clarke et al., 2005). Other recent studies have demonstrated that spatial memory can be preserved in rats with hippocampal lesions, following extensive pre-operative training and experience in a complex environment, although the hippocampus is needed for
acquisition (see Winocur, Moscovitch, Fogel, Rosenbaum, & Sekeres, 2005; Winocur et al., 2010 for a full review). These latter findings are consistent with reports that humans with extensive medial temporal lobe damage have preserved spatial memory and navigational abilities for environments learned prior to their brain damage (Corkin, 2002; Teng & Squire, 1999; Rosenbaum et al., 2000; Rosenbaum, Gao, Richards, Black, & Moscovitch, 2005; Maguire, Nannery, & Spiers, 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; the hippocampus is dispensable for retention and retrieval of spatial memories acquired long ago.

Neuroimaging findings, while strongly supporting a role for the hippocampus in the acquisition and initial storage of spatial memories (e.g. Maguire et al., 1996), remain equivocal about the role of the hippocampus in the retention and retrieval of such memories long after they are acquired. Some studies report hippocampal activation during mental navigation tasks in a well-learned environment (Maguire, Frackowiak, & Frith, 1997), but careful examination suggests that the reported activation is on the border between the hippocampus and parahippocampal cortex, not in the hippocampus proper. More recent studies with long-time residents of London report hippocampal activation when participants mentally navigated between friends’ homes (Kumaran & Maguire, 2005) and when participants planned routes prior to navigating in a virtual simulation of the city of London (Spiers & Maguire 2006). Other studies that report hippocampal activation during spatial memory retrieval have used virtual environments (Newman, Caplan, Kirschen, Korolev, Sekuler, Kahana, 2007; Maguire, Burgess, Donnet, Frackowiak, Frith, O’Keefe, 1998; Parslow, Rose, Brooks, Fleminger, Gray,
Giampietro, et al., 2004; Spiers & Maguire, 2006), or small-scale environments that were learned within a day (Ghaem, Mellet, Crivello, Tzourio-Mazoyer, Berthoz, et al., 1997; Mellet et al., 2000).

In contrast to the above findings, a study with long-time Toronto residents did not report any hippocampal activation during a variety of Toronto-based 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, another study reports that a hippocampal patient’s preserved remote spatial memory was supported by the PHC, rather than residual hippocampal tissue (Rosenbaum, Winocur, Grady, Ziegler, & Moscovitch, 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 (Bohbot et al., 1998; Aguirre, Detre, Alsop, & D’Esposito, 1996).

**Factors that May Influence Hippocampal Involvement in Long-term Spatial Memory**

The role of the hippocampus in long-term spatial memory has been investigated using a wide range of methods. Different studies have used environments of varying scale and complexity, and participants ranging from average adults to experienced London taxi drivers. Such variance in methodologies makes comparison across studies difficult. As a result, the role of the hippocampus in the long-term maintenance of spatial memory remains unknown.

Differences in the learning and retention intervals may be able to explain some of the differences in hippocampal activation reported across studies. Many of the studies that do report hippocampal activation use small-scale environments that are tested after one day or less (e.g. Ghaem et al., 1997). The few studies that do not report hippocampal activation have tested retrieval for highly familiar large-scale environments that participants had learned at least ten...
years prior to being scanned (Rosenbaum et al., 2004). It is possible that studies using shorter retention intervals find hippocampal activation because not enough time has yet elapsed for a spatial representation to be consolidated in the neocortex. However, there are still many studies with equally extensive retention intervals as those described above that do report hippocampal activation (e.g. Maguire et al., 1998; Spiers & Maguire, 2006). It appears, therefore, that although the retention interval may be important, it is not able to account for all of the different findings. One study that did test the effect of retention interval had participants recall places they visited within the past two years and places visited over seven years ago in as much detail as possible (Niki & Luo, 2002). Greater medial temporal activation was reported for recent compared to remote spatial memories that were highly detailed. There was no difference in medial temporal activation for recent compared to remote memories for spatial memories with few details. This suggests that recency and the degree of detail retrieved may interact.

Another important methodological difference amongst studies of long-term spatial memory is the type of environment used. Many of the studies that report hippocampal activation, even at longer retention intervals, have used virtual reality environments (e.g. Bohbot et al, 2004; Parslow et al, 2004; Spiers & Maguire, 2006), while the studies that do not report hippocampal activation have tested memory for real-life ones (Rosenbaum et al., 2004). It is possible that the use of virtual reality may impose additional demands on encoding that would engage the hippocampus for reasons other than spatial memory per se. With that said, there are still a number of studies that have tested memory for real-life environments and do report hippocampal activation (e.g. Kumaran & Maguire, 2005; Maguire et al., 1997). Again, it seems that the difference between virtual and real-life environments does not provide a sufficient explanation for the variability in results reported.
Yet another important difference across studies of long-term spatial memory is the layout of the environment being tested. Spiers and Maguire (2007) described a significant difference between two cities that are commonly tested: London and Toronto. Toronto is grid-like in its layout and this regular arrangement of landmarks may lend itself more readily to the formation of a spatial representation that can be supported by extra-hippocampal structures. London is comparatively irregular, and navigation in such a city may always require a hippocampally-dependent representation. However, hippocampal activation has been reported during spatial memory retrieval for environments that are relatively simple (e.g. Ghaem et al., 1997; Mellet et al., 2000). As with the aforementioned factors, it appears that environmental layout and complexity are unable to account for the full range of results.

Last, there is wide variety in the range of tasks used to test long-term spatial memory. Different tasks are expected to promote the use of different perspectives (egocentric vs. allocentric; detailed vs. schematic) which may further explain observed differences in hippocampal activation. For example, one study directly contrasted brain activation when participants recalled an environment that was learned from either ground-level footage of navigation (egocentric) or footage taken from an aerial perspective (allocentric) (Shelton & Gabrieli, 2002). Greater activation was reported in the medial temporal lobes when participants engaged in egocentric learning, suggesting that the perspective at the time of learning also affects brain activation at the time of recall. That being said, studies that test spatial memory for familiar, real-world environments that have been learned outside of the laboratory have little control over how the environment is learned. As such, it is difficult to comment further on how perspective at the time of learning interacts with brain activation at the time of recall.
In order to come to a satisfying understanding of the role of the hippocampus in long-term spatial memory it is necessary to conduct, first, a longitudinal neuroimaging study that tracks brain activation as the same participants develop familiarity with the same environment over time. Second, to understand the role of different tasks in engaging the hippocampus, it is necessary to compare memory for the same environment using a variety of tasks that are thought to promote the use of different spatial representations. In this thesis, I will describe a set of experiments that are designed to clarify the role of the hippocampus in long-term spatial memory.

Overview of Chapters

In the following chapters I will present two neuroimaging experiments and one behavioural experiment aimed at clarifying the role of the hippocampus in long-term spatial memory. In combination, these experiments will provide evidence that coarse schematic representations of space can become independent of the hippocampus with time and experience in an environment. With even more extensive experience, it is possible for fine-grained spatial details to be incorporated into an extra-hippocampal representation. I will also show that the hippocampus is continually required to retrieve episodic details associated with a familiar environment throughout the lifetime of the memory. Finally, I will show that the hippocampus is differentially involved in the retrieval of fine-grained spatial details and episodic details for a familiar environment.

In the General Discussion, I will consider the implications of these findings for theories of hippocampal function and hippocampal-neocortical interaction, ultimately suggesting that an account of hippocampal function based on Multiple Trace Theory (Moscovitch, Rosenbaum, Gilboa, Addis, Westmacott, Grady et al., 2005) and scene construction (Hassabis & Maguire,
2007) is best able to account for the results presented in this thesis. Lastly, I will address limitations of the experiments presented and consider how future research may address these limitations and build on the findings presented in this thesis.

Chapter One examines whether spatial memories that are initially dependent on the hippocampus can become independent of it with time and experience in an environment. This question was addressed with a longitudinal fMRI study on participants who were new to Toronto and following them over the course of a year as they became familiar with the city. Scanning the participants as they performed mental navigation tasks, I show that the hippocampus was engaged when participants were new to Toronto, but not after a year of living in the city. 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. I conclude that at least some forms of spatial memory can come to be represented outside the hippocampus with sufficient experience in an environment.

Having established in Chapter One that some long-term spatial memories can be mediated by extra-hippocampal structures, Chapter Two further explores the differences between these extra-hippocampal representations and spatial memories that continue to involve the hippocampus in a familiar environment. This question was addressed with a second fMRI study using participants who were highly familiar with Toronto. Participants were scanned as they made comparison judgments about pairs of Toronto landmarks. The comparison judgments were of three types, designed to require either coarse- or fine-grained spatial details, or episodic details associated with the environment. Hippocampal involvement in the spatial memory judgments was greater when they required a fine-grained representation. However, these fine-grained
spatial representations were less dependent on the hippocampus, the more experience
participants had in Toronto. The retrieval of episodic details associated with Toronto activated a
more anterior region of the hippocampus on the right, and a more extensive region along the
length of the left hippocampus. Hippocampal involvement in these episodic judgments did not
vary with participants’ experience in Toronto or the recency of the events retrieved. Lastly,
judgments based on coarse spatial details also recruited the hippocampus, but it is suggested that
this activity reflects elaborative processing or scene construction, rather than the retrieval of
spatial details per se.

Chapter Two demonstrated that the hippocampus is differentially involved in the retrieval
of spatial and episodic details associated with a familiar environment. Chapter Three explores
this idea further using behavioural tests of episodic and spatial memory. Older adult participants
were asked to describe walking routes from their daily lives in as much detail as possible. The
number of details provided in these descriptions correlated with tests that are sensitive to
hippocampal function, corroborating the finding in Chapter Two that the hippocampus is
continually involved in the retrieval of episodic details associated with a familiar environment.
Participants also completed a test of memory for Toronto landmark locations (an abbreviated
version of the one used in Chapter Two). Performance on this test was not correlated with any
tests sensitive to hippocampal function. This was the case, even for questions that required a
fine-grained spatial representation (i.e. the questions that activated the hippocampus in Chapter
Two). However, the participants in this experiment had far more extensive experience with
Toronto than those in the previous experiment. This extends Chapter Two’s finding that fine-
grained spatial representations become less dependent on the hippocampus with experience in an
environment, to show that with even more experience these representations may actually become independent of it.

**Theoretical Considerations**

The findings of this thesis are relevant to current theories of hippocampal function and hippocampal neocortical interaction. In the General Discussion I will consider which theories are best able to account for the range of findings presented. I will show that an account of hippocampal function based on Multiple Trace Theory (MTT) and scene construction is most consistent with the present results. Briefly, MTT proposes that the distinction between episodic and semantic forms of memory has its analogue in spatial memory (Moscovitch et al., 2005). Coarse, schematic representations that retain only major landmarks and the relations between them are considered analogous to semantic memory. These representations are sufficient to support navigation and can become consolidated in the neocortex. In contrast, detailed representations of space that support the vivid re-experience of an environment are considered analogous to episodic memory and are expected to be continually dependent on the hippocampus. Other theoretical accounts of hippocampal function propose that it is crucial in integrating spatial information with episodic details to create a vivid and coherent mental scene (Hassabis & Maguire, 2007).

I will also consider how the results of this thesis relate to other prominent theories including Cognitive Map Theory (CMT), Relational Memory Theory (RMT), and Standard Consolidation Theory (SCT). Briefly, CMT posits that the hippocampus is essential for the long-term representation of space in an allocentric perspective (O’Keefe & Nadel, 1978). Relational Memory Theory argues that spatial memory is merely a specific example of the hippocampus’ more general function in relational processing (Eichenbaum & Cohen, 2001). Standard
Consolidation Theory proposes that spatial memory, like all forms of declarative memory can become consolidated in the neocortex after an initial period of hippocampal dependence (Alvarez & Squire, 1994).
Chapter 1

Introduction

The role of the hippocampus in the acquisition of new spatial information has been well documented; however, its role in the long-term retention and retrieval of spatial representations is still debated. 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, Experiment 1 aims to determine whether a spatial representation that is initially dependent on the hippocampus can become independent of it with time. This question is addressed with a longitudinal neuroimaging study that tracks changes in brain activation as participants become familiar with a large-scale environment over time. 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 one year. The mental navigation tasks involved judging the relative distance between pairs of landmarks, judging the relative proximity of two landmarks to a reference point, and planning an alternative route between two landmarks when the most direct one was blocked.

Based on reports of hippocampal patients who retain the ability to navigate in pre-morbidly familiar environments (Corkin, 2002; Teng & Squire, 1999; Rosenbaum et al., 2000; Rosenbaum et al., 2005; Maguire, Nannery, & Spiers, 2006), and fMRI evidence that the hippocampus is not necessary for spatial memory retrieval at long retention intervals
(Rosenbaum et al., 2004), hippocampal activation is expected to decrease from the first to the second session.

A complementary goal of Experiment 1 is to identify brain regions such as the parahippocampal cortex (PHC) and posterior parietal cortex, which may support spatial representations at one or both time intervals. In addition to the predicted decrease in hippocampal activation with time, a corresponding increase in activation is expected in the PHC, reflecting the role of this region in the long-term maintenance of spatial relations (Bohbot et al., 1998; Epstein, 2008). In addition to these predicted changes in activity in the medial temporal lobe, the rest of the brain is expected 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 one year.

**Method**

**Participants.**

Thirteen participants (5 male; mean age 26.7 yrs, SD = 4.0; 2 left-handed) who had three or fewer months of experience with downtown Toronto participated in the first session. Eight of these participants (1 male; mean age 27.0 yrs, 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.

**Pre-scan interview.**

All participants completed a survey assessing their degree of familiarity with a list of 60 downtown Toronto landmarks on a scale of 1 to 5 (see Appendix A). 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.

**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 x 5 km region of downtown Toronto, which contains many of Toronto’s most familiar landmarks and routes (see Figure 1.1 for a map of the region). Names of landmarks selected from the pre-scan 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 centre 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 four tasks and lasting 60 s. Each block consisted of three trials lasting 30s
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.

The four mental navigation tasks were as follows:

**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).

When participants who were highly familiar with Toronto performed these tasks they reported the use of an allocentric strategy for the distance and proximity judgments, and an egocentric strategy for the landmark sequencing and blocked-route problem-solving tasks.
It is not known whether these tasks will promote the use of similar strategies in participants who are new to Toronto.

**Pre-scan 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 = 2000, TE = 30 ms, flip angle = 30 degrees, FOV = 20 cm).

**Data analysis.**

Accuracy (percentage correct) was analyzed with a 2x4 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) software package (Cox, 1996; Cox & 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 co-registered 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 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, I chose to examine the brain regions that are activated in common across the various tasks. To do so, I 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 in order 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 x 0.1 x 0.1 x 0.1 = p < 0.0001) (see Allan, Dolan, Fletcher, & Rugg, 2000; Cabeza, Dolcos, Graham, & Nyberg, 2002; Cabeza, Prince, Daselaar, Greenberg, Budde, Dolcos, LaBar, et al., 2004 for discussion of this method, but also 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.
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 is likely due to differences in task demands. For now, I 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 x 0.05 x 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. I 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 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 1.2. Only the eight participants who were present for both scanning sessions were included in this analysis. A 2x4 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, I 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).

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 (see Table 1.1 and Figure 1.3). 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.

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 I had a specific hypothesis regarding the right hippocampus, I 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 (see Figure 1.4). 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 across the three mental navigation tasks (\( t = 3.16, p = 0.004, \) two-tailed) (see Figure 1.5).

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 the middle temporal gyrus bilaterally right (see Table 1.2) 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 (see Table 1.3. and Figure 1.6). The superior temporal activation on the right also extended into the posterior cingulate / retrosplenial cortex.

**Discussion**

The results of Experiment 1 show that as participants gained familiarity with the downtown Toronto environment 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 long retention intervals. The use of a longitudinal design ensures that the changes in brain activation over time and experience cannot be attributed to peculiarities of the environment or of the participants, 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 the increased accuracy in mental navigation as participants gain familiarity with the environment, this is unlikely, as accuracy did not change significantly over time for the items tested. In fact, changes in accuracy were purposefully minimized 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 due to 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. However, it is unlikely that the observed hippocampal activity is due to active encoding of this nature, 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). Another possibility is that the reported decrease in hippocampal activation is an artefact 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) show increased activation in the second session argues against this possibility.

It is important to note that the regions that increased in activation over time are the same regions that have been demonstrated by Rosenbaum et al. (2004) to be part of a network that supports navigation in a familiar environment. The PHC is commonly activated in neuroimaging studies of spatial memory (Aguirre et al., 1996; Maguire et al., 1998; Rosenbaum et al., 2004; Shelton & Gabrieli, 2002) and patients with lesions to the parahippocampal gyrus are unable to learn new spatial relations (Habib & Sirigu, 1987; Barrash, Damasio, Adolphs & Tranel, 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, Galati, Paradis, Pizzamiglio, Berthoz, & LeBihan, 2004) and is thought to play a role in the identification of familiar landmarks in a familiar environment (Takahasi & Kawamura, 2002). Lesions to the lingual gyrus result in landmark agnosia, an inability to recognize landmarks and use them to guide navigation (Aguirre & 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 non-spatial, stimulus-response based strategies (Etchamendy & Bohbot, 2007; Iaria, Petrides, Dagher, Pike, & Bohbot, 2003; McDonald & White, 1994; Packard & McGaugh, 1996). The caudate may also play a role in the spatial working memory required to support navigation (Postle & 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, 2001b). 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, Frith, Baker, Shallice, Frackowiak, & Dolan, 1995).

Some of these regions (parahippocampal gyrus, inferior frontal gyrus) were already active in session one, suggesting that they serve a general function, which increased 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, are newly recruited in session two. The fact that new areas are
recruited suggests that the nature of the representation has changed. What remains to be done is
to conduct cognitive/behavioural studies, to determine exactly what the change in representation
has been. Work from the animal literature suggests that this new representation is more
schematic than the initial one (Winocur, Moscovitch, Fogel, Rosenbaum, & Sekeres, 2005),
relying only on learned spatial layouts, major landmarks, and practiced routes among them. In
fact, studies on both spatial discrimination (Maviel, Durkin, Menzaghi, & Bontempi, 2004) and
contextual fear conditioning (Frankland, Bontempi, Talton, Kaczmarek, & Silva, 2004) in rats
reveal a similar shift in activation from the hippocampus to cortical structures. When researchers
tracked activity-dependent gene expression in the hippocampus and neocortex at short and long
delays, hippocampal activity is observed shortly after learning, but then decreases. In contrast,
activity in the prefrontal cortex and retrosplenial cortex (for the spatial task) and anterior
cingulate cortex (for the fear conditioning) are found to increase with time (Maviel et al., 2004;
Frankland et al., 2004).

The present results are relevant to the current debate between Consolidation and Multiple
Trace Theories of hippocampal function (see Winocur, Moscovitch, & Bontempi, 2010 for
review). Multiple Trace Theory predicts that memories that are no longer supported by the hippocampus are more schematic in nature than those that continually rely on the hippocampus (Moscovitch et al., 2005). In contrast, Consolidation Theory predicts that what is altered is only the neural substrate that mediates the representations as memories become independent of the hippocampus, not that the representations themselves are changed (Alvarez & Squire, 1994). The former account is favoured partly because it is consistent with neuroimaging studies that demonstrate that the hippocampus is crucially involved in the recollection of highly detailed memories (Addis, McIntosh, Moscovitch, Crawley, & McAndrews, 2004; Gilboa, Winocur, Grady, Hevenor, & Moscovitch, 2004), even those that are spatial (Hirshhorn, Newman, & Moscovitch. In press.). This account is also consistent with reports of hippocampal patients who are able to navigate successfully in pre-morbidly 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. 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 (Spiers et al., 2001; Bohbot et al., 2004; Bohbot et
al., 1998; Bohbot et al., 2002) 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 required to support mental navigation in a familiar environment. Instead, mental navigation is supported by a network of extra-hippocampal regions including the parahippocampal cortex, lingual gyrus, caudate, and prefrontal cortex. The tasks used in this study could be accomplished with the use of a coarse representation of the environment and did not promote detailed re-experiencing. However, I expect that if experiential components were added to the task then the hippocampus would be recruited once again. This hypothesis will be tested in Experiment 2, by having participants recall specific experiences associated with familiar landmarks while in the scanner. I will also explore in more detail the role of the hippocampus in long-term spatial representation by comparing activity during mental navigation that can be supported by coarse- and fine-grained representations of space.
Table 1.1

Regions of common activation for distance and proximity judgment and blocked-route problem-solving in session 1 (N=13) (p < 0.001)

<table>
<thead>
<tr>
<th>Region</th>
<th>Talairach coordinates</th>
<th>Volume (voxels)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>x  y  z</td>
<td></td>
</tr>
<tr>
<td>R middle temporal gyrus</td>
<td>54 -52 6</td>
<td>6481</td>
</tr>
<tr>
<td>L superior temporal gyrus</td>
<td>-56 -60 27</td>
<td>4623</td>
</tr>
<tr>
<td>R cuneus</td>
<td>15 -91 32</td>
<td>1698</td>
</tr>
<tr>
<td>R precentral gyrus</td>
<td>45 -10 57</td>
<td>1607</td>
</tr>
<tr>
<td>L precuneus (BA 31)</td>
<td>-11 -50 32</td>
<td>1567</td>
</tr>
<tr>
<td>L middle frontal gyrus</td>
<td>-25 35 42</td>
<td>895</td>
</tr>
<tr>
<td>R hippocampus</td>
<td>31 -23 -9</td>
<td>505</td>
</tr>
<tr>
<td>R fusiform gyrus (BA 20)</td>
<td>41 -36 -17</td>
<td>501</td>
</tr>
<tr>
<td>L parahippocampal gyrus &amp; hippocampus</td>
<td>-33 -14 -16</td>
<td>295</td>
</tr>
<tr>
<td>L middle temporal gyrus (BA 21)</td>
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<td>158</td>
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<td>L inferior frontal gyrus (BA 45)</td>
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<td>L superior temporal gyrus</td>
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</tr>
<tr>
<td>L superior frontal gyrus (BA 6)</td>
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<td>133</td>
</tr>
<tr>
<td>L postcentral gyrus</td>
<td>-10 -38 68</td>
<td>108</td>
</tr>
<tr>
<td>R postcentral gyrus (BA 2)</td>
<td>60 -24 37</td>
<td>103</td>
</tr>
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</table>
Table 1.2

Regions of common activation for distance and proximity judgment and blocked-route problem-solving in both session 1 and session 2 (p < 0.0156)

<table>
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<th>Region</th>
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<th>Volume (voxels)</th>
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</thead>
<tbody>
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<tr>
<td>L middle frontal gyrus</td>
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<td>20476</td>
</tr>
<tr>
<td>&amp; inferior frontal gyrus</td>
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<td></td>
</tr>
<tr>
<td>L inferior temporal gyrus</td>
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<td>13416</td>
</tr>
<tr>
<td>L middle frontal gyrus (BA 6)</td>
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<td>3601</td>
</tr>
<tr>
<td>R medial frontal gyrus (BA 10)</td>
<td>5 66 8</td>
<td>2551</td>
</tr>
<tr>
<td>R insula (BA 13)</td>
<td>41 -10 11</td>
<td>1144</td>
</tr>
<tr>
<td>L middle temporal gyrus</td>
<td>-51 -19 -9</td>
<td>717</td>
</tr>
<tr>
<td>L caudate</td>
<td>-1 15 7</td>
<td>439</td>
</tr>
<tr>
<td>L insula (BA 13)</td>
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<td>259</td>
</tr>
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<td>180</td>
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<tr>
<td>R inferior frontal gyrus</td>
<td>48 29 5</td>
<td>130</td>
</tr>
<tr>
<td>R middle temporal gyrus</td>
<td>51 -33 0</td>
<td>123</td>
</tr>
</tbody>
</table>
Table 1.3

Regions of activation unique to session 2 (p < 0.0156)

<table>
<thead>
<tr>
<th>Region</th>
<th>Talairach coordinates</th>
<th>Volume (voxels)</th>
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</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>R lingual gyrus</td>
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<td>-71</td>
</tr>
<tr>
<td>L inferior frontal gyrus</td>
<td>-20</td>
<td>33</td>
</tr>
<tr>
<td>R superior temporal gyrus (BA 22)</td>
<td>61</td>
<td>-15</td>
</tr>
<tr>
<td>L caudate head</td>
<td>-2</td>
<td>17</td>
</tr>
<tr>
<td>R parahippocampal gyrus</td>
<td>23</td>
<td>-41</td>
</tr>
<tr>
<td>R superior temporal gyrus</td>
<td>46</td>
<td>16</td>
</tr>
</tbody>
</table>
Figure 1.1. 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-pwgsc.gc.ca/images/Toronto-DT-Final.gif)
Figure 1.2. 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.
Figure 1.3. 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.
Figure 1.4. A region of interest analysis was performed for the cluster of activation in the right hippocampus. (170 voxels, peak coordinates: 31, -23, -9).
Figure 1.5. The mean per cent signal change in the right hippocampus in response to the three mental navigation tasks is shown for session one and two.
Figure 1.6. Brain regions that were active in session two, but not session one include the parahippocampal gyrus and lingual gyrus on the right.
Chapter 2

Introduction

Having established in Experiment 1 that at least some spatial representations can be supported by extra-hippocampal structures after an environment is well learned, I wished to explore further which factors may influence the involvement of the hippocampus in long-term spatial memory. Experiment 2 was motivated by current theories of hippocampal function which emphasize either episodic memory or spatial memory processing as a crucial function of the hippocampus. This experiment aims to compare the role of the hippocampus in these two forms of memory by asking participants to make episodic or spatial comparison judgments about familiar Toronto landmarks. Episodic judgments required participants to decide which of two landmarks they had visited most recently and were expected to promote the vivid recollection of a specific event. Spatial judgments required participants to compare the relative allocentric locations of landmarks (“Which building is farther North, South, East or West?”). By asking participants to retrieve both episodic and spatial information from the same environment, I was able to contrast directly the role of the hippocampus in episodic and spatial memory. More specifically, I wished to answer the following question: Is the hippocampus differentially activated during the retrieval of episodic and spatial information? This may refer to the location, extent, or degree of activation. Based on many reports of hippocampal activation during episodic retrieval (Addis et al., 2004; Gilboa et al., 2004), and recent reports that the hippocampus is preferentially engaged in episodic memory retrieval compared to spatial memory retrieval (Hoscheidt, Nadel, Payne, & Ryan, 2010) I predict that the hippocampus will be more active when participants retrieve episodic details associated with familiar landmarks.
An important limitation of Experiment 1 is that I did not explicitly manipulate the perspective (egocentric or allocentric) from which spatial memories were retrieved. This is important because theories that emphasize a role for the hippocampus in spatial memory postulate that it is preferentially involved in allocentric spatial memory (O’Keefe & Nadel, 1978). Therefore an important element of this experiment is that the spatial memory judgments 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, independently of one’s viewpoint.

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 neighbourhood or cities on a world-map, although they are able to recognize coarse details such as salient neighbourhood landmarks and continents on a world map (Rosenbaum et al., 2000). 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, and Graham, 2005). These reports are consistent with the animal literature showing that the hippocampus is crucial for spatial pattern separation (e.g. Gilbert, Kesner, and 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;
Maurer, Van Rhoads, Sutherland, Lipa, & McNaughton, 2005; Kjelstrup, Solstad, Brun, Hafting, Leutgeb, Witter, et al., 2008). Place cells in the dorsal hippocampus have smaller receptive fields, consistent with the notion that they code fine-grained spatial details (see Brun, Solstad, Kjelstrup, Fyhn, Witter, Moser 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, I 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, Experiment 2 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 requirement for course- or fine-grained representations was not manipulated in Experiment 1. Therefore it is possible that after a year of experience in Toronto, participants were able to rely on a coarse representation of the environment that did not require the hippocampus. If such coarse representations can be supported by extra-hippocampal regions, then the easy allocentric condition should activate similar brain regions to those that were active in session 2 of Experiment 1 (PHC, lingual gyrus, caudate, lateral temporal cortex). 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 also
expected to recruit additional regions that reflect the need for detailed inspection of mental imagery, such as the precuneus.

Experiment 1 demonstrated that a coarse representation of an environment can become independent of the hippocampus with a year of experience in that environment. Building on this finding, I 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, I tested participants who had lived in Toronto for a range of years (mean = 15.71 years; SD = 9.83 years) and included this as a factor in the analysis of hippocampal activation during each condition.

A complementary goal of this experiment was to detect whole-brain patterns of activation that would 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 (see Hassabis & Maguire, 2007 for review). Since the three tasks require both episodic memory and mental navigation processes, I predicted that all three tasks would recruit a set of brain regions commonly implicated in these processes, including the medial temporal lobes, retrosplenial / posterior cingulate cortex, and precuneus. Medial temporal lobe activations are commonly reported for both episodic and spatial memory recollection (see Buckner & Carroll, 2007 and Hassabis & Maguire, 2007 for review; also Burgess et al., 2002; Maguire, 2001a; Rugg, Otten, & Henson, 2002; Svoboda, McKinnon, & Levine, 2006). The precuneus is often activated during tasks that require the inspection of mental imagery, a process which the three conditions are expected to promote (Fletcher et al., 1995). The retrosplenial / posterior cingulate cortex is thought to mediate the transition between different perspectives, and is also commonly active in mental navigation and episodic memory tasks (Maguire, 2001b). The episodic task was
expected to recruit additional brain regions that are implicated in episodic memory, such as the medial prefrontal cortex and posterior parietal cortex (inferior parietal lobule, supramarginal gyrus, angular gyrus) (see Spreng, Marr, & Kim, 2009; Svoboda et al., 2006). The difficult allocentric task was expected to require detailed inspection of mental imagery. This may recruit additional regions of the precuneus (beyond those expected to be active for all three conditions) and the parahippocampal cortex (PHC). The PHC is often implicated in studies of long-term spatial memory, and is thought to support the long-term representation of spatial relations (Epstein, 2008).

Method

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 yrs.; SD = 9.83 yrs.) participated in this experiment. All participants provided informed written consent in accordance with the ethics review board at Rotman Research Institute. Prior to participation in the study, participants completed a screening questionnaire to ensure that they visit the majority of the landmarks used in the test at least once per week.

Stimuli.

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

Procedure.

The fMRI session consisted of four 12.6 minute runs of 52 trials each. Each trial was 12 seconds 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. Easy allocentric questions required participants to compare the locations along the cardinal axis with the greatest distance between the two landmarks (see Figure 2.1 for illustration).

Task 3: Difficult allocentric judgments. Participants selected the landmark that is located farther North, South, East, or West. Difficult allocentric questions required participants to compare the locations along the cardinal axis with the smallest distance between the two landmarks (see Figure 2.1).

Task 4: Vowel comparison baseline. Participants indicated which landmark name had more or less vowels.
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. For each pair, participants were then 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 (see Yonelinas, 2002 for a review of R/K procedure). For example, “I know that I have visited Honest Ed’s ¹ most recently because I pass it every day on the way to work.” This is based on the remember-know paradigm, which is a process dissociation procedure used to distinguish between memories that are based on recollection and those that are based on familiarity (see Yonelinas, 2001). This distinction is important because recollection of an event and the accompanying conscious awareness of episodic details is dependent on the hippocampus (Yonelinas, Otten, Shaw, & Rugg, 2005). Familiarity, in contrast, is supported by the perirhinal cortex (Brown & Aggleton, 2001; Wan, Aggleton, & Brown, 1999).

I included this procedure because of the 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 semantic information. Only trials that were given an ‘R’

¹ Honest Ed’s is a well known department store in Toronto.
response were included in the subsequent analyses. For all other conditions, only correct responses were included in the analyses. 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.

**Image acquisition.**

Anatomical and functional images were acquired at Baycrest with a 3T Siemens scanner with a standard head coil. For each participant, a T1-weighted volumetric anatomical MRI (30 axial slices, TE = 2.63 ms, 5 mm thick, FOV = 256 cm) was acquired. 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 = 2000ms, TE =30 ms, FOV = 200 mm, 64 x 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.

**Behavioural analysis.**

Repeated measures ANOVAs were used to compare mean accuracy and mean reaction time (correct trials only) across the four conditions. Since I 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.

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.

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 activation maps of the BOLD signal for each subject were calculated for each condition with respect to the vowel comparison baseline condition. The resulting individual activation images were normalized to the Montreal Neurological Institute (MNI) template (resampled at 1mm x 1mm x 1mm 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 pre-processed images were used, without any contrasts (i.e. the baseline condition was included as a separate condition in the PLS analysis).

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.

**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 ($p < 0.01 \times 0.01 \times 0.01 = p < 0.000001$) (see Allan et al., 2000; Cabeza et al., 2002; Cabeza et al., 2004 for discussion of this method, but also Lazar et al., 2002). (Please note: a higher threshold was used for the conjunction and disjunction analyses than in Experiment 1. This was done to be more conservative so that only robust hippocampal differences would be found.) 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.

I was 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, I chose not to average the signal across the entire hippocampus. In order to compare the degree of activation, I used the bilateral cluster that was commonly activated by all three conditions. To do so, I 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.
**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. 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 allocentric 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 x 0.01 x 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.

**Correlation analysis.**

I was interested in the relationship between degree of familiarity with the environment and hippocampal activation. To assess this relationship, I extracted the mean percentage signal change for each participant from each of the clusters identified in the disjunction analysis. For each cluster, I 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, I 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.

I was also interested in the relationship between hippocampal activation during the episodic memory task and the recency of the retrieved memories. To assess this relationship, I first calculated a recency score for each participant based on the number of trials that he/or she
grouped into each time period in the post-scan questionnaire. I converted the percentage of trials in each time period to a value out of 100. I then weighted the number of trials in each time period by their recency with the highest weight given to the most recent events. More specifically, the number of trials in the most recent period (past week) was multiplied by five and the number of trials in the past month period was multiplied by four, and so forth. Finally, the number of trials in the greater than five years ago period was multiplied by one. The weighted number of trials in each time period were then summed to give each participant a weighted mean recency score. The maximum possible score was 500 and would indicate a participant who rated all of the episodic memory trials as being based on an event within the past week. I then correlated the weighted recency scores with the mean percent signal change during the episodic condition. This was done for all clusters that were uniquely activated by the episodic condition, as identified in the disjunction analysis.

**PLS analysis.**

Whole-brain neuroimaging data were analyzed with partial least squares (PLS; McIntosh, Chau, & Protzner, 2004; McIntosh, Bookstein, Haxby, & Grady, 1996). Mean-centered PLS is a multivariate analysis technique that allows one to assess covariance between brain activity and the experimental design without the specification of a priori contrasts. 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 \( p < .002 \).

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 is proportional to the singular value for 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 320 or more voxels with a bootstrap ratio (salience/SE ratio) greater than 3.0 were considered to be reliable as this is roughly equal to \( p < .005 \). PLS uses MNI format, therefore the output coordinates from the PLS analysis were converted from MNI space to Talairach coordinates by the algorithm developed by Lacadie, Fulbright, Rajeevan, Constable, and Papademetris (2008) (www.bioimagesuite.org).

Analysis was conducted on the 20 second 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 (labelled lag 0). Mean-centered PLS analysis was run first on all three task conditions and the vowel baseline condition. The first significant LV distinguished between the three experimental tasks and the baseline. Since this LV accounted for much of the covariance, I ran a second mean-centered PLS analysis excluding the baseline condition, to allow greater sensitivity with which to detect differences between the experimental tasks.

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. I plotted the mean brain scores for each LV across the 10 lags that were analyzed. 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. The significant clusters of activity from these lags are reported. To assess differences between tasks for each significant LV, PLS uses a plot of the mean brain score over the 10 lags for each task with a 95% confidence interval. 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.

**Results**

**Behavioural Performance.**

Mean accuracy and reaction times for each task are summarized in Table 2.1. 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 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 that reaction time was significantly faster 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 2.2. 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 ($M = 41.02, SD = 34.19$) was significantly greater than the percentage of visits from over five years ago ($M = 1.02, SD = 3.52$) ($p < 0.05$). The percentage of visits reported from the past month ($M = 29.40, SD = 13.62$) was significantly greater than the percentage of visits from five years ago ($M = 9.80, SD = 10.77$) ($p < 0.05$) and the percentage of visits from over five years ago ($p < 0.05$).

**ROI Analysis Results.**

The conjunction of all three spatial memory tasks commonly activated posterior hippocampal regions in the left (-31, -36, -6) and right hemispheres (30, -34, -6) (see Figure 2.2 and Figure 2.3). The mean percent signal change during each task was extracted from the left (Figure 2.4) and right clusters (Figure 2.5) separately. Repeated measures ANOVAs showed no main effect of task on the mean percent 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 2.3. 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) (Figure 2.6) and a cluster in the right anterior HPC (27, -15, -15) (Figure 2.7). The easy allocentric condition did not show any unique activation within the hippocampus. The hard allocentric condition uniquely activated two clusters in the mid-posterior right HPC (31, -27, -10 and 33, -22, -14) (Figure 2.8).

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: $r = -0.35$, $p = 0.22$; right: $r = -0.29$, $p = 0.31$) or the accuracy (left: $r = 0.32$, $p = 0.26$; right: $r = 0.44$, $p = 0.12$) or reaction time (left: $r = 0.21$, $p = 0.47$; right: $r = 0.12$, $p = 0.69$) on the episodic task. I also assessed whether activation during the episodic task was correlated with the average recency of the recalled events. The mean percentage signal change during the episodic task in the left and right clusters did not correlate with the weighted recency scores (left: $r = -0.25$, $p = 0.43$; right: $r = 0.40$, $p = 0.20$).

Because the easy allocentric condition did not uniquely activate any clusters in the hippocampus, I made use of the clusters that were active in the conjunction of all tasks 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 in the left and right clusters did not correlate with the number of years participants had lived in Toronto (left: $r = -0.19$, $p = 0.89$; right: $r = -0.47$, $p = 0.10$), or the accuracy (left: $r = 0.04$, $p = 0.89$; right: $r = 0.27$, $p = 0.35$) or reaction time (left: $r = 0.47$, $p = 0.10$; right: $p = 0.15$, $r = 0.61$) 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; see Figure 2.9). The mean percentage signal change in these two clusters was not correlated with accuracy ($r = 0.07$, $p = 0.83$) or reaction time ($r = 0.20$, $p = 0.50$) for the difficult allocentric condition.

**PLS Results.**

The first LV from the mean-centered PLS was significant at $p < 0.0001$. LV1 accounted for 63.08% of the variance and identified brain regions that differentiated between all three spatial memory conditions and the vowel baseline task. There were no significant differences
between the three spatial memory conditions. The mean brain scores for each condition are plotted with 95% confidence intervals in Figure 2.10.

The temporal brain score plot for LV1 is shown in Figure 2.11. Brain regions that showed significant activations in response to the three spatial memory conditions between lags 3 and 5 are shown in Table 2.4 and Figure 2.12. 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 spatial memory conditions compared to the control 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 variance and identified brain regions differentiating the episodic condition from the difficult allocentric condition. The easy allocentric condition did not make a reliable contribution to this LV (see Figure 2.13 for a plot of the mean brain scores for each condition with 95% confidence intervals). The temporal brain score plot for LV2 is shown in Figure 2.14. Brain regions that show increased activation in response to the episodic condition compared to the difficult allocentric condition are shown in Table 2.5 and Figure 2.15 for lags 4 and 5. 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 2.6 and Figure 2.15 for lags 4
and 5. These regions include the right precuneus, and the caudate, superior frontal gyrus, and supramarginal gyrus on the left.

**Discussion**

**Differences between episodic and spatial memory.**

A primary goal of Experiment 2 was to compare the role of the hippocampus in spatial and episodic memory associated with a familiar environment. 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 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.

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. For example, Ryan and colleagues had participants recall spatial, non-spatial, episodic and semantic relations and found that the posterior right hippocampus was preferentially involved in the recall of spatial relations, while non-spatial conditions activated the left hippocampus and the right middle hippocampus (Ryan, Lin, Ketcham, & Nadel, 2010). Other recent neuroimaging studies report that the anterior hippocampus is implicated in relational memory encoding or episodic aspects of memory (e.g. Chadwick, Hasssabis, Weiskopf, & Maguire, 2010; Davachi, 2006; Davachi & Wagner, 2002; Lepage, Habib, & Tulving, 1998; Prince, Daselaar, & Cabeza, 2005), while the posterior hippocampus is preferentially involved in spatial memory (e.g. Maguire, Gadian, Johnsruide, Good, Ashburner,
Frackowiak et al., 2000). For example, experienced London taxi drivers have greater grey 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 accumulated knowledge of the spatial relationships between London landmarks (Maguire et al., 2000; Woollett & Maguire, 2009). Taxi drivers also have reduced grey 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). This is 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.

In addition to these differences in hippocampal activation, the PLS analysis also revealed a set of brain regions that differentiate 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 on the left. 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., 2002 for review) as well as post-retrieval monitoring and verification (see Gilboa, 2004 for review). The episodic condition was also 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). The difficult allocentric condition was associated with increased activity in the right precuneus 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. 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
working memory processes (Courtney, Petit, Maisog, Ungerleider, & Haxby, 1998).

Despite the above-mentioned task differences, there was also considerable overlap in the
brain regions activated by 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 (see Buckner & Carroll, 2007 and
Hassabis & Maguire, 2007 for review). Hassabis and Maguire (2007) have 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 tasks. 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. 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 participants engaged in elaborative processing which would recruit 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, MacLeod, Snyder, Powers, Gusnard, & Shulman, 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 memory and self-projection (Spreng et al., 2009). 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).

**Differences between coarse- and fine-grained spatial representations.**

A second goal of Experiment 2 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; Maurer et al., 2005; Kjelstrup et al., 2008). 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 hippocampus to a greater extent than coarse spatial representations.

One interpretation of this finding is that with experience in an environment, spatial memories can become independent of the hippocampus (consistent with the results of Experiment 1). The results of Experiment 1 suggest that such hippocampally-independent representations are likely to be schematic in nature, containing only the major landmarks and the relations between them. It is possible 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. 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. It is possible that once participants had retrieved the coarse spatial
information required to answer the question, they elaborated to create a vivid image, incidentally engaging the hippocampus.

The PLS analysis did not reveal any extra-hippocampal brain regions that differentiated between the easy and difficult allocentric conditions. Based on the results of Experiment 1, one might have expected regions such as the posterior PHC, lingual gyrus, caudate, and lateral temporal cortex to differentiate the easy task from the difficult one. These regions took on an increased role when participants in Experiment 1 became familiar with Toronto, and were thought to support a coarse schematic representation of space. If the easy allocentric representations could in fact be answered with a coarse representation 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 or episodic details. Another possible explanation for this discrepancy is that the results from Experiment 1 were based on a univariate analysis, while the current experiment employed a multivariate approach. Perhaps there was not enough variability in brain activation between the two allocentric conditions for PLS to detect any significant patterns. The difficulty manipulation was indeed subtle, and so it is likely that differences in brain activation between these two tasks were minimal.

Another possibility is that there were important differences in the spatial memory tasks used in these two experiments. The tasks in this experiment strongly promoted the use of an allocentric perspective. The tasks in Experiment 1 required participants to consider not only the relative locations of familiar landmarks, but the distance and possible routes between them. Such
differences in task demands may help to explain the differences in extra-hippocampal regions reported in these two experiments.

**Changes in activation with experience.**

Experiment 1 provided evidence that the role of the hippocampus in some forms of spatial memory decreases as one gains experience in an environment. In Experiment 2, I wanted to know whether the same is true 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.

Experiment 1 provided evidence that coarse representations of space can become independent of the hippocampus after a year of experience in an environment. All of the participants in the current experiment had lived in Toronto for a minimum of five years. Therefore, if the easy allocentric questions make use of a similar coarse representation, one would expect no hippocampal activation, or at least for the activation to be negatively correlated with participants’ experience in the city. However, if we consider that the hippocampal activation during the easy allocentric condition was incidental to the spatial demands (as described above), we can reconcile these findings. If the hippocampal involvement in the easy allocentric task reflects scene construction or other elaborative processes, then hippocampal involvement should not vary with the amount of experience one has with Toronto.

Experiment 1 suggests that spatial memories can become independent of the hippocampus over the course of one year. The negative correlation between activation during the
difficult allocentric task and years living in Toronto suggests a much longer time course for such consolidation. In fact, the participant with the greatest experience in Toronto had lived there for over 30 years, and still showed some hippocampal activation during this task. However, the spatial representations studied in Experiment 1 were likely more coarse than the ones required by the difficult allocentric task in the current experiment. One way to reconcile these two findings is with the idea that with longer periods of time even more fine-grained details can become incorporated into an extra-hippocampal representation.

I also wanted to determine whether hippocampal involvement in the episodic memory condition was related to participants’ degree of experience with Toronto. 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 has elapsed since the recalled visit may have a stronger influence on hippocampal activation than the number of years one has lived in Toronto. Previous studies have reported that the vividness and personal significance of a retrieved episodic memory are related to hippocampal activation, though the recency of the recalled memory is less important (Addis et al., 2004; Gilboa et al., 2004; St.-Laurent, Moscovitch, Levine, & McAndrews, 2008). To test this, I looked at the relationship between hippocampal activation during the episodic memory task and a weighted recency score based on each participant’s post-scan report. Consistent with previous work, there was no relationship between hippocampal activation and the recency of the retrieved episodic memories. This suggests that, unlike the findings on spatial memory, the hippocampus is continually involved in the retrieval of episodic details associated with a familiar environment.

**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. I suggest that this region is not involved in the retrieval of spatial information \textit{per se}, but in integrating spatial and episodic details to construct a coherent and vivid scene. 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 role of the hippocampus.

Multiple Trace Theory also predicts that the distinction between semantic and episodic memory has its analogue 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, similarly to what was found in Experiment 1, 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 or the recency of the events being retrieved.

The results of this experiment also extend those of Experiment 1 to show that with more extensive experience in an environment, even fine-grained spatial representations become less dependent on the hippocampus. This finding is consistent with a Standard Consolidation view of hippocampal function and the prediction that with time, all memories can become independent of the hippocampus (Alvarez & Squire, 1994). Therefore, the results of this experiment offer partial support for several theories of hippocampal function (MTT, SCT), as well as scene construction accounts. These theoretical positions are contrasted in detail in the General Discussion.
Table 2.1

Accuracy and reaction time for the four conditions

<table>
<thead>
<tr>
<th>Task</th>
<th>Accuracy (% correct)</th>
<th>Reaction Time (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Episodic</td>
<td>91.86 (0.92)</td>
<td>3758.56 (1033.47)</td>
</tr>
<tr>
<td>Easy Allocentric</td>
<td>92.50 (0.93)</td>
<td>3387.95 (711.63)</td>
</tr>
<tr>
<td>Difficult Allocentric</td>
<td>74.85 (0.75)</td>
<td>3558.92 (734.10)</td>
</tr>
<tr>
<td>Control (vowel comparison)</td>
<td>88.66 (0.89)</td>
<td>4086.06 (1078.62)</td>
</tr>
</tbody>
</table>
Table 2.2
The percentage of episodic trials grouped into each time period in post-scan questionnaire

<table>
<thead>
<tr>
<th>Time period</th>
<th>Percentage of trials</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Past week</td>
<td>41.02 (34.19)</td>
</tr>
<tr>
<td>Past month</td>
<td>29.40 (13.62)</td>
</tr>
<tr>
<td>Past year</td>
<td>18.77 (22.34)</td>
</tr>
<tr>
<td>Past five years</td>
<td>9.80 (10.77)</td>
</tr>
<tr>
<td>Over five years ago</td>
<td>1.02 (3.52)</td>
</tr>
</tbody>
</table>
Table 2.3

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

<table>
<thead>
<tr>
<th>Task</th>
<th>L/R</th>
<th>Talairach coordinates</th>
<th>Cluster size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>x</td>
<td>y</td>
</tr>
<tr>
<td>Episodic</td>
<td>L</td>
<td>-29</td>
<td>-17</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>27</td>
<td>-15</td>
</tr>
<tr>
<td>Easy allocentric</td>
<td></td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Difficult allocentric</td>
<td>R</td>
<td>31</td>
<td>-27</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>33</td>
<td>-22</td>
</tr>
</tbody>
</table>
Table 2.4

Brain activations that differentiated the three memory conditions from the vowel baseline

<table>
<thead>
<tr>
<th>Region</th>
<th>lag</th>
<th>Talairach coordinates</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>x</td>
<td>y</td>
</tr>
<tr>
<td>L posterior cingulate</td>
<td>3</td>
<td>-3</td>
<td>-56</td>
</tr>
<tr>
<td>R angular gyrus</td>
<td>3</td>
<td>41</td>
<td>-70</td>
</tr>
<tr>
<td>L hippocampus</td>
<td>3</td>
<td>-19</td>
<td>-21</td>
</tr>
<tr>
<td>L angular gyrus</td>
<td>3</td>
<td>-40</td>
<td>-69</td>
</tr>
<tr>
<td>L middle frontal gyrus</td>
<td>3</td>
<td>-23</td>
<td>-26</td>
</tr>
<tr>
<td>R hippocampus</td>
<td>3</td>
<td>19</td>
<td>-19</td>
</tr>
<tr>
<td>L lingual gyrus</td>
<td>3</td>
<td>-10</td>
<td>-89</td>
</tr>
<tr>
<td>R cerebellum</td>
<td>3</td>
<td>6</td>
<td>-47</td>
</tr>
<tr>
<td>L superior temporal gyrus</td>
<td>3</td>
<td>-58</td>
<td>-16</td>
</tr>
<tr>
<td>L posterior cingulate</td>
<td>4</td>
<td>-4</td>
<td>-54</td>
</tr>
<tr>
<td>L middle frontal gyrus</td>
<td>4</td>
<td>-23</td>
<td>28</td>
</tr>
<tr>
<td>R angular gyrus</td>
<td>4</td>
<td>39</td>
<td>-70</td>
</tr>
<tr>
<td>R cerebellum</td>
<td>4</td>
<td>6</td>
<td>-49</td>
</tr>
<tr>
<td>L angular gyrus</td>
<td>4</td>
<td>-38</td>
<td>-75</td>
</tr>
<tr>
<td>R superior temporal gyrus</td>
<td>4</td>
<td>55</td>
<td>-9</td>
</tr>
<tr>
<td>L anterior cingulate</td>
<td>4</td>
<td>-2</td>
<td>43</td>
</tr>
<tr>
<td>R fusiform gyrus</td>
<td>4</td>
<td>33</td>
<td>-74</td>
</tr>
<tr>
<td>L temporal pole</td>
<td>4</td>
<td>-52</td>
<td>1</td>
</tr>
<tr>
<td>L middle frontal gyrus</td>
<td>5</td>
<td>-23</td>
<td>28</td>
</tr>
<tr>
<td>L posterior cingulate</td>
<td>5</td>
<td>-3</td>
<td>-56</td>
</tr>
</tbody>
</table>
Table 2.4 continued

<table>
<thead>
<tr>
<th>Region</th>
<th>lag</th>
<th>Talairach coordinates</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>x</td>
<td>y</td>
</tr>
<tr>
<td>R cerebellum</td>
<td>5</td>
<td>4</td>
<td>-48</td>
</tr>
<tr>
<td>L superior occipital gyrus</td>
<td>5</td>
<td>-30</td>
<td>-76</td>
</tr>
<tr>
<td>L lingual gyrus</td>
<td>5</td>
<td>-9</td>
<td>-87</td>
</tr>
<tr>
<td>R superior occipital gyrus</td>
<td>5</td>
<td>39</td>
<td>-70</td>
</tr>
<tr>
<td>R cerebellum</td>
<td>5</td>
<td>43</td>
<td>-66</td>
</tr>
</tbody>
</table>
Table 2.5

Brain activations that differentiated the episodic condition from the difficult allocentric condition

<table>
<thead>
<tr>
<th>Region</th>
<th>lag</th>
<th>Talairach coordinates</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>L middle temporal gyrus</td>
<td>4</td>
<td>-62 -16 -12</td>
<td>-7.5</td>
</tr>
<tr>
<td>L anterior cingulate</td>
<td>4</td>
<td>-2 42 -9</td>
<td>-6.8</td>
</tr>
<tr>
<td>L superior occipital cortex</td>
<td>4</td>
<td>-54 -60 27</td>
<td>-6.5</td>
</tr>
<tr>
<td>R angular gyrus</td>
<td>4</td>
<td>53 -63 35</td>
<td>-6.5</td>
</tr>
<tr>
<td>L superior frontal gyrus</td>
<td>4</td>
<td>-21 28 47</td>
<td>-6.2</td>
</tr>
<tr>
<td>L posterior cingulate gyrus</td>
<td>4</td>
<td>-5 36 34</td>
<td>-4.3</td>
</tr>
<tr>
<td>R superior frontal gyrus</td>
<td>5</td>
<td>18 28 56</td>
<td>-6.2</td>
</tr>
<tr>
<td>L medial frontal gyrus</td>
<td>5</td>
<td>-6 36 36</td>
<td>-6.2</td>
</tr>
<tr>
<td>L middle frontal gyrus</td>
<td>5</td>
<td>-21 25 49</td>
<td>-5.6</td>
</tr>
<tr>
<td>L middle temporal gyrus</td>
<td>5</td>
<td>-53 -11 -10</td>
<td>-5.1</td>
</tr>
<tr>
<td>L inferior parietal lobule</td>
<td>5</td>
<td>-53 -56 27</td>
<td>-5.0</td>
</tr>
<tr>
<td>L anterior cingulate</td>
<td>5</td>
<td>-10 43 -2</td>
<td>-5.0</td>
</tr>
<tr>
<td>Region</td>
<td>lag</td>
<td>Talairach coordinates</td>
<td>Ratio</td>
</tr>
<tr>
<td>------------------------------</td>
<td>-----</td>
<td>------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>L cerebellum</td>
<td>4</td>
<td>-15 -52 -36</td>
<td>7.4</td>
</tr>
<tr>
<td>R precuneus</td>
<td>4</td>
<td>22 -60 21</td>
<td>6.0</td>
</tr>
<tr>
<td>L superior frontal gyrus</td>
<td>4</td>
<td>-24 -7 58</td>
<td>5.6</td>
</tr>
<tr>
<td>R precuneus</td>
<td>5</td>
<td>26 -62 21</td>
<td>8.4</td>
</tr>
<tr>
<td>L supramarginal gyrus</td>
<td>5</td>
<td>-25 -37 24</td>
<td>5.5</td>
</tr>
</tbody>
</table>
Figure 2.1. 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). The corresponding easy allocentric question is “Which landmark is farther North (or South)?” as there is a greater distance between these two landmarks along the North/South axis (shown in red). The difficult allocentric question is “Which landmark is farther East (or West)?”
Figure 2.2. A cluster in the left hippocampus commonly activated by all three spatial memory conditions (-31, -36, -6; 46 voxels).
Figure 2.3. A cluster in the right hippocampus commonly activated by all three spatial memory conditions (30, -34, -6; 54 voxels).
Figure 2.4. The mean per cent signal change during each task in the left hippocampal cluster that was commonly activated by all three tasks.
Figure 2.5. The mean per cent signal change during each task in the right hippocampal cluster that was commonly activated by all three tasks.
Figure 2.6. A regions in the left hippocampus uniquely activated by the episodic condition. (-29, -17, -18; 403 voxels).
Figure 2.7. An anterior region of the right hippocampus uniquely activated by the episodic condition. (27, -15, -15; 176 voxels).
Figure 2.8. A posterior region of the right hippocampus uniquely activated by the difficult allocentric condition (31, -27, -10; 38 voxels).
Figure 2.9. The correlation between the mean per cent signal change in the posterior right hippocampus 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).
Figure 2.10. The mean brain scores for each condition for LV1 with 95% confidence intervals.
Figure 2.11. The temporal brain scores for each condition associated with LV1.
Figure 2.12. Brain regions that showed significant activation in response to the three spatial memory conditions are shown in blue.
Figure 2.13. The mean brain scores for each condition for LV2 with 95% confidence intervals.
Figure 2.14. The temporal brain scores for each task associated with LV2.
Figure 2.15. Brain regions that differentiate the episodic condition from the difficult allocentric condition are shown in blue. Brain regions that differentiate the difficult allocentric condition from the episodic one are shown in yellow.
Chapter 3

Introduction

Taken together, Experiments 1 and 2 showed that hippocampally-dependent spatial representations contain more fine-grained spatial details and more associated episodic details than spatial representations that are mediated by extra-hippocampal structures. In addition, Experiment 2 showed that episodic and spatial information engage the hippocampus differentially and further, that hippocampal involvement in these two types of memory has a different time course. More specifically, hippocampal involvement in spatial memory decreases with experience in an environment, but the hippocampus is continually required to retrieve episodic memories associated with a familiar environment.

However, it is possible that the hippocampal activation during the episodic condition of Experiment 2 was due to active encoding rather than the retrieval of episodic details per se. In Experiment 3, I wished to further explore the relationship between hippocampal function and the degree of episodic details associated with a spatial environment. To do so, I asked participants to describe walking routes from their daily lives in as much detail as possible. These descriptions were scored for detail content and the number of details provided was then correlated with tests sensitive to hippocampal and frontal lobe function. Based on the results of Experiment 2, and other studies showing that the degree of retrieved detail is crucially related to hippocampal function (Addis et al., 2004; Gilboa et al., 2004; St.-Laurent et al., 2008), I expected the number of details in the descriptions of walking routes to correlate with tests of hippocampal, but not frontal function.
An important limitation of Experiment 2 was that I was not able to assess the relationship between the temporal specificity of the episodic memories and hippocampal activation. That is, I was not able to control for whether participants recalled one specific instance in which they visited a given landmark, or several repeated visits over time. Recent evidence from lesion and functional neuroimaging studies on autobiographical memory indicates that it is the detailed representation of the remembered event, rather than its temporal specificity, that is crucially-dependent on the hippocampus (Addis et al., 2004; St.-Laurent et al., 2008). I wished to know whether the same applies to spatial memories. To compare hippocampal involvement in temporally specific and repeated memories, participants were asked to describe two routes, a familiar route that they habitually used at least three times a week in the past year (or longer), and a unique route that they had used only once.

Because Experiment 2 showed that the hippocampus is differentially involved in episodic and spatial memory, I also included a test of allocentric spatial memory for a familiar environment. Participants answered questions about the allocentric relationship between well-known Toronto landmarks (an abbreviated version of the test used in Experiment 2). As in Experiment 2, landmark pairs were presented with both an easy and a difficult question. In Experiment 2 the difficult questions were found to recruit the hippocampus to a greater extent than the easy questions. Therefore, I expected performance on the difficult questions to be more strongly correlated with tests of hippocampal function than performance on the easy questions.

I chose to test these predictions in a population of 20 healthy older adults because previous studies have shown that older adults have greater variability in hippocampal structure (Van Petten, 2004) and related memory function (Levine, Svoboda, Hay, Winocur, & Moscovitch, 2002). Normal aging is associated with volume decline in the hippocampus and its
related structures which, in turn, is hypothesized to lead to a decline in the ability to retrieve contextually-specific episodic details of autobiographical events (Levine et al., 2002). Previous research has documented a decline in the number of episodic details given in autobiographical memories in older adults, using the Autobiographical Interview (AI; Levine et al., 2002). Further, Addis, Wong, and Schacter (2008) found a correlation between performance on a relational memory task presumed to be mediated by the hippocampus, and the number of episodic details in descriptions of past, and imagined future, autobiographical events.

**Method**

**Participants.**

Twenty healthy older adults (6 male; aged 66 to 92 years, \( M = 77.25, \ SD = 7.07 \)) with no history of neurological or psychiatric impairment were recruited from the University of Toronto volunteer database. All participants gave informed written consent in a manner approved by the University of Toronto Ethics Review Board and were compensated upon completion of the study.

**Spatial Interview.**

Participants were asked to describe a familiar, 10-minute walking route, defined as one they have been walking at least 3 times a week for at least the past year. Participants were asked to give detailed description of the route, in which they were encouraged to provide as many details as possible so that the experimenter could visualize the route (see Appendix C for instructions given). The spatial interview concluded with three probe questions encouraging further description of specific entities mentioned in the detailed description.
Following the spatial interview for a familiar route, the entire spatial interview was repeated for a unique route, defined as one which the participant has walked only once, within the past year.

The spatial interviews were recorded by a typist who transcribed the spatial interviews as the participants spoke. These transcripts were used for later analysis.

**Tests Sensitive to Hippocampal Function.**

**Tabletop spatial task.**

A tabletop spatial task adapted from Smith and Milner (1984) was used. This task was chosen because of its sensitivity to spatial memory and right hippocampal function. Ten objects were placed on a 56 x 56 centimeter board. In the study phase, participants were asked to point to each item, name it, and estimate its price. After a 30-minute delay, during which time participants completed other non-spatial neuropsychological tests (details below), participants were asked to freely recall the objects that were presented on the board. Participants were then given an empty 56 x 56 cm board along with the original objects, and asked to place the objects in exactly the same position they occupied during the price estimation task. Participants were given a time limit of one minute for the object identity recall and two minutes for the object location recall. The displacement between each object and its original location was measured and the mean displacement across the ten items was used for later analysis.

**Verbal Paired Associates I.**

Participants completed the Verbal Paired Associates (VPA I) test from the Wechsler Memory Scale – Revised (Lezak, 1995). Eight word pairs were read aloud by the experimenter at the rate of one word per second. Participants were instructed to pay attention to the word pairs for a later memory test. At the end of the list, the experimenter paused for five seconds before
beginning the memory test. During the memory test, the experimenter would read one word from
the previous list and ask the participant to recall its associate, providing feedback on each trial.
This procedure was repeated four times. The total number of correctly recalled word pairs was
used for later analysis. Though the VPA is a test of relational memory, and as such is affected by
hippocampal lesions, there may be components that are affected by damage to other regions of
MTL and lateral temporal cortex (for discussion see Lowndes & Savage, 2007).

**Autobiographical Interview (Total Internal Details).**

Participants completed an adapted version of the Autobiographical Interview (AI) that
probes both repeated (familiar) and unique events from the participant’s past. Participants were
asked to describe the memory of a repeated event, which was defined as something repeated at
least once a week and from within the period of the past five years. Participants were also asked
to describe the memory of a unique event, defined as something that has occurred within the past
year. Descriptions were recorded for later analysis. The transcripts were scored according to the
methods described by Levine et al. (2002), and the number of internal and external details for
each event were tabulated for later analysis. I have chosen to include this test because the
number of internal, but not external details has been shown to be sensitive to hippocampal
function.

**Tests Sensitive to Frontal/Executive Function.**

**FAS Phonemic Fluency.**

Participants were asked to produce as many words as possible (excluding proper nouns
and repetitions) beginning with the letters ‘F’, ‘A’, and ‘S’. Participants were given one minute
for each letter. The total number of words produced was used for later analysis.

**Backwards Digit Span.**
The experimenter read aloud number strings at a rate of one number per second and asked the participant to repeat the digits in the reverse order. Number strings began at a length of two digits and increased in length by one digit after two correct trials at a given length. The total number of correctly recalled number strings in the reverse order was used for later analysis.

**Wisconsin Card Sort Task.**

Participants were given a pile of 64 cards with geometric shapes that varied along three dimensions: colour, form, and number. Participants were instructed to place the cards, one at a time, below one of four “key” cards. They were not informed of the correct sorting principle, but are given feedback after the placement of each card. The initial sorting rule was to match the cards according to colour. After ten cards had been sorted correctly, the experimenter changed the sorting rule without informing the participant. Perseverative errors are sorting errors in which the participant continues to sort by the previous rule. The total number of such errors was used for later analysis.

**Test of Spatial Memory.**

Participants completed a computerized test of allocentric Toronto landmark locations consisting of 30 trials. This was an abbreviated version of the test used in Experiment 2. On each trial, the participant was presented with a pair of Toronto landmarks at the center of the screen and asked to make a comparison judgment about their relative locations (e.g. “Which building is farther North?”). Participants responded by pressing the key corresponding to one of the landmarks. In addition, participants were given the option to respond with a third key representing the response “I don’t know” to prevent guessing. There was no time limit for response, and participants were encouraged to prioritize accuracy over speed of response. As in Experiment 2, a difficulty manipulation was included such that half of the questions were easy.
and the other half were difficult. Difficult questions were defined as those that required participants to compare the landmarks along the dimension with the shortest distance between them, and were expected to require a fine-grained spatial representation.

**Analysis.**

**Spatial Interview scoring.**

The detailed descriptions from the Spatial Interview were scored according to the protocol developed by Hassabis, Kumaran, Vann, and Maguire (2007). Descriptive details were classified as belonging to one of four main categories: entity presence (EP), spatial reference (SPA), sensory description (SD), or thought/emotion/action (TEA). The entity category is a simple count of how many distinct physical entities were mentioned (e.g., “there is a house”). The spatial reference category encompasses statements about the relative position of entities within the environment, with respect to the subject or to each other (e.g., “there is a house on my left”, “the library is north of the school”). The sensory category consists of perceptual details (in any modality) furthering the description of an entity (e.g., “there is a green house”, “it is a brick building”). Thought/emotion/action refers to any thoughts, emotions or actions of the subject or any other person in the scene. For the familiar route, thought/emotion/action points were only awarded for routine or common thoughts or occurrences (e.g., “the owner of the house is always sitting on the porch”). Inter-rater reliability was established on the basis of a ten familiar and ten unique routes, all randomly selected.

**Correlation analysis.**

SPSS software was used to assess the relationship between the total number of details provided for familiar and unique routes and performance on tests sensitive to hippocampal and
frontal/executive function. I also assessed the correlation between performance on the test of schematic spatial memory and tests sensitive to hippocampal and frontal/executive function.

**Results**

Mean performance on tests sensitive to hippocampal and frontal/executive function, and schematic spatial memory is reported in Table 3.1.

The mean number of details provided in each detail category for both familiar and unique walking routes is reported in Figure 3.1. Significantly more details were reported for familiar than unique routes (mean diff = 47.3, t(19) = 4.67, p <0 .001, two-tailed). It is important to note that the number of details provided for familiar routes did not correlate with the number of years of experience with the route (r = 0.29, p = 0.24), suggesting that familiarity alone cannot account for the variability in details recalled. However, the pattern of correlations between the number of details provided for familiar and unique routes and performance on the neuropsychological tests did not differ. As such, I will discuss the correlations with reference to the total details generated across both types of routes.

The total number of details provided was significantly correlated with all of the tests that were sensitive to hippocampal function (mean displacement on the table top task: r = -0.51, p = 0.01 (see Figure 3.2.); internal details on the AI: r = 0.63, p = 0.001; VPA I total score: r = 0.38; p = 0.04, one-tailed (see Table 3.2 for summary).

The total number of details provided was not significantly correlated with any of our measures of frontal/executive function (FAS: r = -0.32, p = 0.18; backwards digit span: r = 0.03, p = 0.91; WCST: r = -0.09, p = 0.73, two-tailed).

Accuracy on the test of schematic spatial memory was high for both easy (94.03%) and difficult (80.76%) questions. One participant had performance below chance and greater than
two standard deviations below the mean. This participant was excluded from the subsequent analyses for this particular task.

Performance on the easy questions from the test of schematic spatial memory was not significantly correlated with any of the measures sensitive to hippocampal function (mean displacement: $r = -0.16$, $p = 0.57$; internal details: $r = -0.12$, $p = 0.65$; VPA: $r = -0.30$, $p = 0.26$, two-tailed). The absence of a correlation between performance on the easy questions and tests sensitive to hippocampal function may be due to lack of variability in performance on the easy questions (SD = 9.67). Performance on the difficult questions showed greater variability (SD = 15.76), however even accuracy on the difficult questions was not correlated with any of the tests sensitive to hippocampal function (mean displacement: $r = 0.00$, $p = 0.99$ (see Figure 3.3); internal details: $r = -0.23$, $p = 0.40$; VPA: $r = 0.19$, $p = 0.48$). In addition, performance on the difficult questions was not correlated with any measures sensitive to frontal function (FAS: $r = 0.25$, $p = 0.34$; backwards digit span: $r = -0.14$, $p = 0.59$; WCST: $r = 0.25$, $p = 0.34$).

**Discussion**

Experiment 2 demonstrated that the hippocampus is involved in the retrieval of episodic details associated with spatial memory. The results of this experiment extend those findings to show that it is the degree of detail of the retrieved memory that is crucially dependent on the hippocampus. It is important to note that the details provided were not only spatial in nature, but also included a large proportion of sensory details (sensory descriptions accounted for 31% of the total details for familiar routes, and 37% of the total details provided for unique routes). This suggests that the correlations between the details provided and tests sensitive to hippocampal function cannot be explained simply in terms of spatial function. It appears that the role of the hippocampus is not limited to the encoding and maintenance of spatial context, but may include
the encoding and maintenance of more general perceptual details that contribute to the overall vividness of the memory. The fact that the same pattern of correlations was observed for both familiar and unique routes (in spite of more details being provided for familiar routes) supports the idea that it is the degree of detail of a retrieved memory, rather than its age or degree of rehearsal, that determines hippocampal involvement.

Importantly, the number of details provided in the descriptions of both familiar and unique routes did not correlate with any of the neuropsychological tests of frontal/executive function (WCST, backwards digit span, FAS). This finding suggests that the significant correlations reported cannot be attributed to variability in frontal lobe function, or to a more general variability in cognitive function with age. Further, the absence of a correlation between the number of details and performance on the FAS test of phonemic fluency suggests that the significant correlations between tests of hippocampal function and the number of details provided for routes cannot be related to variability in verbal output.

The results of this experiment are partially consistent with those of Experiment 2, in showing that the hippocampus is differentially involved in episodic and spatial memory. That is, tests sensitive to hippocampal function were correlated with the number of details provided (episodic memory), but not with performance on a test of allocentric spatial memory. The finding that the number of details provided in the spatial interview was most strongly correlated with the number of internal details on the AI, a measure of episodic memory function, further supports the idea that the hippocampus is differentially involved in these two types of memory.

However, the total number of details provided in the spatial interview was also correlated with performance on the table top task, a test of spatial memory. This suggests that although the hippocampus may be differentially involved in episodic and spatial memory, these two functions
may interact. Consistent with this idea, Experiment 2 reported a bilateral region in the middle of
the hippocampus that was recruited by both episodic and spatial memory conditions. The fact
that this region is in the middle of the hippocampus, between the clusters that respond
preferentially to either episodic or spatial memory retrieval, makes it ideally situated to integrate
these two forms of information. One possibility is that the spatial context provides a framework
for representing non-spatial perceptual details, as suggested by proponents of Cognitive Map
Theory (Nadel & Hardt, 2004) and implied in Hassabis et al.’s proposal that the hippocampus is
necessary for scene construction.

The finding that performance on the test of allocentric landmark knowledge (both easy
and difficult questions) was not correlated with any measures of hippocampal function is
inconsistent with the results of Experiment 2, in which both easy and difficult allocentric
questions engaged the hippocampus to some extent. However, the easy allocentric questions
activated a cluster in the middle of the hippocampus that was recruited by both spatial and
episodic memory conditions. As discussed above, it is likely that this region of the hippocampus
is engaged for reasons peripheral to the recollection of spatial information per se, such as the
integration of spatial and perceptual details in the service of scene construction. Further, the
results of Experiment 1 suggest that such coarse representations of the environment may be
supported by extra-hippocampal regions. Therefore, the lack of correlation between performance
on the easy allocentric questions and tests of hippocampal function may be reconciled with the
results of Experiments 1 and 2.

The lack of correlation between performance on the difficult allocentric questions and
tests of hippocampal function is more problematic, given that these questions uniquely activated
a posterior region of the right hippocampus in Experiment 2. One way to reconcile these
discrepant findings is to consider that activation in the posterior right hippocampus was negatively correlated with the number of years participants had lived in Toronto. This suggests that with extensive experience in an environment, even fine-grained representations of its spatial layout may come to be supported by extra-hippocampal regions. In Experiment 2, the participant with the most experience in Toronto had lived there for 34 years. However, in the current experiment all participants had lived in Toronto for over 40 years. One possibility is that with such extensive experience in the city, even fine-grained spatial details have become independent of the hippocampus, which is consistent with the trend shown in Experiment 2. Another possibility is that the older adult participants in this experiment used different (less hippocampally-dependent) strategies to complete the task than the younger adults in the previous experiments. Therefore some of the discrepant findings may be related to age in general. A related possibility is that given unlimited time to answer the allocentric spatial questions in the current experiment, participants may have engaged in alternative strategies such as imagining walking between the two landmarks. To the extent that the hippocampal involvement observed during the difficult questions in Experiment 2 depends on the use of an allocentric representation, such alternative strategies would lessen the observed correlation between performance and measures of hippocampal function.
Table 3.1

Mean performance on battery of neuropsychological tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>___________________________________________________________________________</td>
<td>__________</td>
</tr>
<tr>
<td>Hippocampal Tests</td>
<td></td>
</tr>
<tr>
<td>Table top spatial test:</td>
<td></td>
</tr>
<tr>
<td>Items recalled (maximum = 10)</td>
<td>6.85 (1.42)</td>
</tr>
<tr>
<td>Mean displacement (cm)</td>
<td>5.52 (1.52)</td>
</tr>
<tr>
<td>VPAI (Recall total score; maximum = 32)</td>
<td>19.40 (9.33)</td>
</tr>
<tr>
<td>Autobiographical Interview:</td>
<td></td>
</tr>
<tr>
<td>Total Internal details</td>
<td>45.61 (21.34)</td>
</tr>
<tr>
<td>Total External details</td>
<td>22.28 (16.39)</td>
</tr>
<tr>
<td>Frontal/Executive Function Tests</td>
<td></td>
</tr>
<tr>
<td>WCST (Perseverative errors)</td>
<td>8.37 (5.75)</td>
</tr>
<tr>
<td>Phonemic Fluency (FAS total score)</td>
<td>45.25 (12.56)</td>
</tr>
<tr>
<td>Digit Span Backwards (total score)</td>
<td>8.10 (2.10)</td>
</tr>
<tr>
<td>Schematic Spatial Memory Test</td>
<td></td>
</tr>
<tr>
<td>Accuracy (Easy questions)</td>
<td>90.27 (18.14)</td>
</tr>
<tr>
<td>Accuracy (Difficult questions)</td>
<td>77.78 (19.61)</td>
</tr>
</tbody>
</table>

*Note.* Standard deviations are given in parentheses.
Table 3.2

Correlations between neuropsychological tests and total details from spatial interview and accuracy on landmark test (difficult questions)

<table>
<thead>
<tr>
<th>Test</th>
<th>Total details</th>
<th>Landmark test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hippocampal Tests</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Table top spatial test (mean displacement)</td>
<td>-0.51**</td>
<td>0.01</td>
</tr>
<tr>
<td>VPAI</td>
<td>0.38*</td>
<td>-0.04</td>
</tr>
<tr>
<td>Autobiographical Interview (internal details)</td>
<td>0.63**</td>
<td>-0.14</td>
</tr>
<tr>
<td><strong>Frontal/Executive Function Tests</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WCST (Perseverative errors)</td>
<td>-0.07</td>
<td>-0.07</td>
</tr>
<tr>
<td>Phonemic Fluency (FAS total score)</td>
<td>-0.32</td>
<td>0.25</td>
</tr>
<tr>
<td>Digit Span Backwards (total score)</td>
<td>0.03</td>
<td>-0.10</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.01, one-tailed
Figure 3.1. The mean number of details provided for each detail category for both familiar and unique route descriptions.
Figure 3.2. The correlation between the total number of details given for familiar and unique routes and mean displacement (cm) on the table top test of spatial location.
Figure 3.3. The correlation between accuracy on the test of Toronto landmark knowledge (difficult questions) and mean displacement (cm) on the table top test of spatial location.
**General Discussion**

In this section, I will summarize the main findings of this thesis by discussing first the role of the hippocampus in long-term memory, and then contributions from other brain regions. I will then relate these findings to theories of hippocampal function and hippocampal-neocortical interaction. Although the findings are partially consistent with several competing theories, I will argue that they are most consistent with an account of hippocampal function based on Multiple Trace Theory and scene construction. I will conclude this section with a discussion of the limitations of the experiments presented in this thesis and questions for further research.

**Main Findings**

I will outline the main findings of this thesis before discussing them in detail below:

1. At least some spatial representations can become independent of the hippocampus with time and experience in an environment.

2. Hippocampally-mediated spatial representations differ from those supported by extra-hippocampal structures in at least two ways:
   a. They contain more fine-grained spatial details.
   b. They contain more episodic details.

3. The hippocampus is differentially involved in spatial and episodic memory:
   a. There is functional differentiation within the hippocampus (spatial and episodic memory recruit different regions of the hippocampus).
   b. The time course of hippocampal involvement is different for spatial and episodic memory.

4. The extra-hippocampal brain regions that are involved in long-term spatial memory are influenced by task demands.
Can spatial memories become independent of the hippocampus?

The first main finding of this thesis is that it is possible for at least some spatial memories that are initially dependent on the hippocampus to become independent of it with time and experience in an environment. This conclusion is supported by the results from Experiment 1: The hippocampus was recruited during mental navigation tasks when participants were new to and unfamiliar with the city (Toronto) that they were navigating in, but not after they had become familiar with the city by living in it for at least a year.

How do spatial representations mediated by the hippocampus differ from those mediated by extra-hippocampal structures?

The second main finding of this thesis is that spatial representations that are dependent on the hippocampus are fundamentally different from those that are mediated by extra-hippocampal structures. As spatial memories become independent of the hippocampus they lose the episodic details associated with them. What remains is a coarse schematic representation that is sufficient to support basic navigation (such as that required for the mental navigation tasks in Experiment 1). Such coarse schematic representations can become independent of the hippocampus within a year of familiarisation in a new environment (Experiment 1).

However, navigation in a familiar environment may still require the hippocampus when a fine-grained allocentric representation is needed. This conclusion is supported by the results of Experiment 2, showing additional hippocampal involvement for the difficult allocentric task. Therefore, hippocampally-mediated spatial representations may contain more fine-grained details, and be more strongly rooted in an allocentric frame of reference than representations supported by extra-hippocampal regions.
That being said, the results demonstrate that even such fine-grained allocentric representations can become increasingly less dependent on the hippocampus as experience in an environment increases. In Experiment 2, hippocampal involvement in the difficult allocentric task was negatively correlated with the number of years participants had lived in Toronto. This suggests that with enough experience, fine-grained spatial information may be incorporated into an extra-hippocampal representation of the environment. The participants in Experiment 3 had far more extensive experience with Toronto than those in Experiment 2. There was no correlation between performance on either the difficult or easy allocentric questions by these more experienced participants and tests sensitive to hippocampal function. Therefore, Experiment 3 extends the results of Experiment 2 to show that with even more experience in an environment, fine-grained spatial details can become independent of the hippocampus.

Another important finding relates to the role of the hippocampus in episodic memories associated with a familiar environment. The results presented here demonstrate that the hippocampus is continually involved in the retrieval of episodic details associated with a familiar environment. This is true regardless of one’s degree of experience with that environment, or the recency of the episodic details being retrieved. This conclusion is supported by the finding that unique regions of the hippocampus were recruited when participants were required to compare two familiar landmarks based on episodic information (Experiment 2). Further, activation during this episodic task did not correlate with the number of years participants had lived in Toronto or with the recency of the recalled events. Experiment 3 expanded on this finding to show a strong correlation between the number of retrieved episodic details associated with a spatial memory and hippocampal function. Importantly, these details were not only spatial in nature, but included
many perceptual descriptions. Therefore, hippocampally-mediated spatial representations may also contain more episodic details than those that are supported by extra-hippocampal structures.

The finding that retrieval of episodic details recruits the hippocampus may help to account for at least some of the discrepant neuroimaging findings with regards to hippocampal involvement in long-term spatial memory. If the task used to test spatial memory can be performed easily, participants may engage in elaborative processing, recalling details that are associated with the environment, but not essential for task performance. Such elaborative processing would recruit the hippocampus, but for reasons incidental to the retrieval of spatial memories per se. Experiment 2 supports this suggestion with the finding that the easy allocentric task activated the hippocampus, although successful performance could be supported by a coarse representation of the environment. Participants answered these questions faster than those of the other tasks, allowing more time for them to engage in elaborative processing. Also consistent with this idea, hippocampal activation during the easy allocentric task was in the context of other brain regions commonly implicated in scene construction, and self-projection (e.g. retrosplenial / posterior cingulate cortex, medial frontal lobes).

**Is the hippocampus equally involved in spatial and episodic memory?**

To summarize, the results of this thesis demonstrate that the requirement for fine-grained allocentric spatial details, and the requirement for episodic details can recruit the hippocampus even in a familiar environment. The third main finding of this thesis is that the hippocampus is differentially involved in these two forms of mnemonic information.

First, there is evidence for functional differentiation within the hippocampus. Retrieval of fine-grained spatial details recruits a posterior region of the right hippocampus, while the retrieval of episodic details recruits the anterior portion of the right hippocampus and a region
that extends along the rostrocaudal axis on the left (Experiment 2). Second, the time course of hippocampal involvement differs for spatial and episodic information. Spatial information can become independent of the hippocampus with time (Experiment 1). Even fine-grained representations can become less dependent (Experiment 2) and possibly independent (Experiment 3) of the hippocampus with enough experience in an environment. In contrast, the hippocampus is continually required for the retrieval of episodic details regardless of one’s familiarity with the environment, or the age of the episodic memory (Experiments 2 and 3).

One way to bridge these findings comes from the idea that scene construction is a crucial function of the hippocampus (discussed in further detail below). Briefly, the hippocampus may be necessary to integrate episodic details into a spatial context, creating a coherent and vivid mental scene. The layout of an environment may be represented schematically outside the hippocampus, and this representation may support basic navigation. With extensive experience, this extra-hippocampal representation may become increasingly complex. However, in order to recall an environment or an event associated with that environment in vivid detail, the hippocampus is always required.

**Extra-hippocampal brain regions involved in long-term spatial memory.**

The last main finding of this thesis is that the extra-hippocampal brain regions required to support long-term spatial memory are influenced by the demands of the spatial memory task being used. Experiment 1 demonstrated that basic mental navigation in a familiar environment can be supported by a set of brain regions including the posterior parahippocampal gyrus, lingual gyrus, superior temporal gyrus, caudate, inferior frontal gyrus, posterior cingulate / retrosplenial cortex, and precuneus. Together, these brain regions may support a coarse schematic representation of a familiar environment. Consistent with this idea, the parahippocampal gyrus is
thought to support the geometrical representation of spatial layouts (Epstein, 2008). The lingual gyrus is thought to be important for the identification of landmarks in a familiar environment (Takahasi & Kawamura, 2002), and lesions to this area impair the ability to use familiar landmarks in the service of navigation (Aguirre & D’Esposito, 1999; Rosenbaum et al, 2005). Activity in the superior temporal gyrus may reflect retrieval of semantic information (see Binder, Desai, Graves, & Conant, 2009). Caudate activity during spatial memory tasks has been related to the use of non-spatial, stimulus-response based navigation strategies (Etchamendy & Bohbot, 2007; Iaria et al., 2003; McDonald & White, 1994; Packard & McGaugh, 1996). The inferior frontal gyrus is required to select amongst competing representations in memory (Thompson-Schill, D’Esposito, Aguirre, & Farrah, 1997). The posterior cingulate is thought to mediate transitions between egocentric and allocentric representations (Maguire, 2001b) and the precuneus may support inspection of mental imagery in the service of navigation (Fletcher et al., 1995).

Some of these regions that were active during mental navigation in a familiar environment in Experiment 1 were also active during all three tasks (spatial and episodic memory) in Experiment 2. Activity in the lingual gyrus and superior temporal gyrus differentiated the three memory conditions from the control, providing further support that these regions support spatial memory in a familiar environment. However, some brain regions that were implicated in Experiment 2 were not active in Experiment 1. These include the angular gyrus, and superior occipital gyrus. These differences in activation likely reflect differences in task demands between the two experiments. For example, the angular gyrus is often implicated in episodic memory tasks and is postulated to reflect the capture of attention by a retrieved memory (see Cabeza et al., 2008; Ciaramelli et al., 2008; Hutchinson et al., 2009 for this and
other theories of recruitment of this region in memory tasks). The tasks in Experiment 2 likely promoted the recollection of more detailed memories than those in Experiment 1. That is, the episodic and difficult allocentric tasks required episodic and fine-grained spatial details respectively, and the easy allocentric task may have promoted elaborative processing, which likely involved episodic details. The retrieval of such details may have posed additional demands on attention, which could explain the differences in angular gyrus activation between the two experiments.

Experiment 2 also revealed brain regions that differentiate between the retrieval of episodic details and fine-grained spatial details. The episodic task was associated with increased activity in several of the regions described above (e.g. posterior cingulate, angular gyrus), and also the middle frontal gyrus, middle temporal gyrus, and the inferior parietal lobule. These regions may work in concert with the hippocampus to support the vivid recollection of a scene or event. For example, the middle frontal gyrus is often implicated in episodic retrieval and is thought to be important for the autobiographical (self-relevant) component of memory (Addis et al, 2007). The inferior parietal lobule activation is thought to reflect attention to the mnemonic output from the medial temporal lobes (Cabeza et al., 2004). The difficult allocentric condition was associated with increased activity in the right precuneus 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 supramarginal gyrus activation may reflect the need for increased spatial attention (Chambers et al., 2004), while the superior frontal gyrus may reflect increased working memory processes (Courtney et al., 1998).
Taken together, the results of Experiments 1 and 2 suggest that task demands are an important determinant of the extra-hippocampal brain regions that are involved in long-term spatial memory retrieval. When the task can be accomplished with reference to a coarse schematic representation, the posterior parahippocampal gyrus, lingual gyrus, and superior temporal gyrus can support performance. These regions can work independently of the hippocampus, when the environment is familiar. When the task requires inspection of a fine-grained spatial representation, the precuneus and supramarginal gyrus will be recruited. The posterior hippocampus may also be required, depending on one’s degree of experience with the environment. When the task requires the retrieval of episodic details, or allows for elaboration and the construction of a vivid and coherent scene, the posterior cingulate, angular gyrus, and medial frontal lobes will be recruited along with the hippocampus.

**Theoretical Considerations**

The main findings of this thesis have important implications for theories of hippocampal function and hippocampal-neocortical interaction. In the following section I will describe how these findings are partially consistent with several current theories, but offer the strongest support for an account of hippocampal function based on Multiple Trace Theory and scene construction. Please see Table 4.1 for a summary of the main findings and how they interact with the major theoretical accounts.

**Multiple Trace Theory.**

Multiple Trace Theory (MTT) proposes that the hippocampus is continually involved in the maintenance and retrieval of episodic memory, while semantic memory can become consolidated in the neocortex (Nadel & Moscovitch, 1997; Nadel, Samsonovich, Ryan, & Moscovitch, 2000). More recent formulations of MTT have proposed that the distinction
between episodic and semantic memory has its analogue in spatial memory (Moscovitch et al., 2005). Coarse, schematic representations that retain only major landmarks and the relations between them are considered analogous to semantic memory. These representations are sufficient to support navigation and can become consolidated in the neocortex. In contrast, detailed representations of space that support the vivid re-experience of an environment are considered analogous to episodic memory and are expected to be continually dependent on the hippocampus.

The findings of this thesis are broadly consistent with MTT. First, the finding that coarse schematic spatial representations can become independent of the hippocampus is consistent with the prediction that semantic-like spatial memories can become consolidated in the neocortex. Second, the finding that episodic details associated with a familiar environment are continually dependent on the hippocampus supports the prediction that the hippocampus is continually required for episodic memory (in general, but also for episodic memories associated with a particular spatial environment).

The finding that the hippocampus is more involved in fine-grained spatial representations than coarse schematic ones poses a challenge for MTT. This theory may attempt to explain this finding by proposing that fine-grained spatial details represent an episodic form of spatial memory, while coarse representations represent a semantic form of spatial memory. However, the present findings suggest that fine-grained spatial representations actually contain properties of both episodic and semantic memory: like episodic memory, they recruit the hippocampus even in a familiar environment, but like semantic memory they become less dependent on the hippocampus with time. MTT is also unable to account for the finding of functional
differentiation within the hippocampus, as it does not make any specific predictions regarding differences in function along the anterior-posterior axis.

**Scene Construction.**

The main findings of this thesis are also partially consistent with an account of hippocampal function that posits scene construction as an essential role. According to such an account the hippocampus is required to integrate retrieved information into a coherent spatial context (i.e. scene construction) (Hassabis & Maguire, 2007). The process of scene construction requires the retrieval of both spatial and episodic details. This account, therefore, is consistent with the finding that the hippocampus is implicated in both spatial and episodic memory. The strongest support for this hypothesis is found in Experiment 2, where a region in the middle of the hippocampus is equally engaged by spatial and episodic memory tasks. This region is located between a posterior region that is preferentially engaged in the retrieval of fine-grained spatial details and an anterior region that is preferentially involve in the retrieval of episodic details associated with a familiar environment. This region is therefore well-situated to integrate these two forms of detail into a coherent scene.

**Other Theories.**

Cognitive Map Theory (CMT) is an influential theory of hippocampal function which posits that the hippocampus is necessary for allocentric representations of space throughout the lifetime of a memory (O’Keefe & Nadel, 1978). The findings of this thesis are partially consistent with CMT, in demonstrating that the hippocampus is in fact involved in fine-grained allocentric representations of space. However, the results presented here have also demonstrated that the role of the hippocampus in such representations decreases as one gains experience with an environment. This is problematic for CMT. Further, this thesis demonstrates that although the
hippocampus may be important for spatial memory (at least for some time), this is not its only function. The hippocampus is also important in retrieving episodic details associated with an environment. Further, many of these details are not spatial, but describe perceptual information that is likely to be unnecessary for supporting navigation.

Relational theories of hippocampal function postulate that the hippocampus is necessary to bind disparate elements (e.g. landmarks) of a scene together according to the relations between them (Eichenbaum & Cohen, 2001). According to relational accounts, spatial memory is considered to be a specific example of the hippocampus’ more general role in relational processing. Episodic memory is also thought to require relational processing as one must bind the details of an event into a coherent representation. The finding that all three spatial memory tasks activated the hippocampus in Experiment 2 is consistent with relational theories, as all tasks require some degree of relational processing. One can also argue, that detailed episodic representations necessarily contain more elements and will therefore require more relational processing, resulting in greater hippocampal activation. The finding that the episodic condition uniquely activated a region that extended along the length of the left hippocampus (Experiment 2) is also consistent with this idea.

The finding that the hippocampus is recruited to a greater extent for fine-grained compared to coarse representations is problematic for relational theories. Both of these representations contain an equal number of elements; all that differs is the scale of representation. Therefore, coarse and fine-grained representations should make equal demands on relational processing, and activate the hippocampus equally. Another challenge for relational theories is the finding that the hippocampus plays a time-limited role in (at least some forms of) spatial memory. If memory for the spatial layout of an environment necessarily involves
relational processing, there is no reason why it should involve less relational processing over time.

Another influential theory of hippocampal function is Standard Consolidation Theory (SCT), which posits that all forms of declarative memory, including spatial memory, become independent of the hippocampus with time. According to this account, the neural substrate of the memory changes, but the nature of the representation remains the same. The findings of this thesis are partially consistent with SCT in demonstrating that spatial memories can become independent of the hippocampus with time. However, the results of this thesis also demonstrate that the hippocampus is continually required to retrieve episodic details associated with a familiar environment. The finding that time course of hippocampal involvement differs for spatial and episodic memory is problematic for SCT.

In sum, the findings of this thesis are partially consistent with several theories of hippocampal function, yet no single theory is able to account for all of the results presented. An MTT-based account is favoured because its distinction between highly detailed (episodic-like) and coarse schematic representations (semantic-like) offers the greatest explanatory power. The distinction between detailed and schematic representations may be an important factor in understanding the role of the hippocampus in long-term spatial memory. MTT is the one theory of hippocampal function that predicts that the hippocampus may be important for some forms of long-term spatial memory, but not others. However, this account still leaves some questions unanswered for future research; these questions are discussed below.

**Future Directions**

Future research may build on the findings of this thesis by examining what factors influence the rate at which spatial representations become independent of the hippocampus. For
example, the perspective from which an environment is learned (e.g. studying a map vs. wayfinding) is likely to influence the representation that is formed, and thus the brain regions required to support memory for that environment (see Ghaem et al, 1997; Mellet et al., 2000 for discussion). The degree of interaction with an environment is another important element of learning that was not tested. For example, Experiment 1 demonstrated that it is possible for a spatial representation to become independent of the hippocampus within a year. Future research may assess the relationship between the amount of exposure to the environment and the rate of consolidation.

Another unanswered question is how the complexity of the environment influences hippocampal involvement in spatial memory. Spiers & Maguire (2007) have suggested that at least some of the variability in reported hippocampal activation may be due to significant differences between the layout of Toronto and London, two cities commonly tested in studies of long-term spatial memory. A city with an irregular layout of roads and landmarks, such as London, would be difficult to represent schematically, and may always require a detailed and fine-grained representation. Such fine-grained representations were shown to require the hippocampus for a longer period of time than coarse representations (Experiment 2). Therefore the idea that memory for a complex environment may be more hippocampally dependent is consistent with the results of this thesis. Future research may test this prediction directly by comparing brain regions involved in memory for two environments of varying complexity in the same subjects.

Future research may also examine how experience with an environment and the requirement for fine-grained representations interact to predict hippocampal involvement in spatial memory. One hypothesis to be tested is whether more fine-grained details can be
incorporated into a schematic neocortical representation with extensive experience in an
environment. Such a finding would suggest that a more complex environment, or one with an
irregular layout, would require more time and experience for such consolidation to occur. A
related issue is how one’s interaction with the environment affects the rate of consolidation – can
increased experience with navigation result in more details being represented outside the
hippocampus at a faster rate?

Another question for future research is how to characterize spatial representations that are
supported by extra-hippocampal structures. I have provided evidence in favour of the notion that
such representations are sparse and schematic in nature, retaining only major landmarks required
for navigation and the relations between them. However, it is difficult to test this hypothesis
directly without a study of patients with hippocampal lesions. It is likely that in healthy adults,
hippocampally-dependent and hippocampally-independent spatial representations interact with
each other. Healthy adults, like the participants in these studies, may benefit from episodic
details that are ostensibly peripheral to the navigation tasks. In fact, evidence for such an
interaction between hippocampal and neocortical representations can be found in the episodic
and semantic memory literature. For example, healthy adults make faster and more accurate
fame judgments (a semantic task) about public figures who are associated with an episodic
memory (e.g. memory for the details of where you were when you learned of Princess Diana’s
death). Therefore, it is difficult to precisely characterize the nature of spatial representations that
are supported by extra-hippocampal structures, as it is always possible that some characteristics
are due to contributions from hippocampally-dependent memories.

The experiments presented here assessed the role of the hippocampus in long-term spatial
memory by means of neuroimaging or correlating tests sensitive to hippocampal function with
various aspects of spatial memory retrieval. Although both methods provide converging evidence that the hippocampus is crucial for fine-grained spatial representations (at least for some time) and episodic details, neither method is sufficient to prove that the hippocampus plays a necessary role. Future studies of patients with hippocampal lesions may help to characterize the types of spatial representation for which the hippocampus is necessary.
Table 4.1
How the main findings interact with current theories of hippocampal function

<table>
<thead>
<tr>
<th></th>
<th>MTT</th>
<th>SC</th>
<th>CMT</th>
<th>RMT</th>
<th>SCT</th>
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</thead>
<tbody>
<tr>
<td>Some spatial memories can become independent of the hippocampus with time.</td>
<td>P</td>
<td>X</td>
<td>X</td>
<td>Y</td>
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<tr>
<td>The hippocampus is important for fine-grained spatial representations.</td>
<td>Y</td>
<td>Y</td>
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<tr>
<td>The hippocampus is important for episodic details associated with a familiar environment.</td>
<td>Y</td>
<td>Y</td>
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<tr>
<td>Spatial details recruit the posterior and episodic details recruit the anterior hippocampus.</td>
<td>P</td>
<td>P</td>
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<tr>
<td>The hippocampus is continually required for episodic details associated with an environment.</td>
<td>Y</td>
<td>Y</td>
<td>X</td>
<td>Y</td>
<td>X</td>
</tr>
</tbody>
</table>

Abbreviations: MTT = Multiple Trace Theory; SC = scene construction; CMT = Cognitive Map Theory; RMT = Relational Memory Theory; SCT = Standard Consolidation Theory; P = partial support; Y = consistent with this theory; X = inconsistent with this theory
References


Burgess, N., Maguire, E.A., & O’Keefe, J. (2002). The human hippocampus and spatial and


Etchamendy, N., & Bohbot, V.D. (2007). Spontaneous navigational strategies and


rats of a spatial task with preoperative versus postoperative training. *Journal of Comparative Physiology and Psychology*, 92, 1119-1127.


Maguire, E.A., Gadian, D.G., Johnsrule, I.S., Good, C.D., Ashburner, J., Frackowiak, R.S.J.,


Niki, K., & Luo, J. (2002). An fMRI study on the time-limited role of the medial temporal


Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A., & Shulman,


Appendix A

Experiment 1: Questionnaire Assessing Familiarity with Toronto Landmarks

On a scale from 1 to 5, please indicate how familiar you are with the LOCATION of each of the following Toronto landmarks.

1 = unfamiliar; 5 = very familiar (i.e., visit or pass by at least 2-3 times per week)

<table>
<thead>
<tr>
<th>Landmarks</th>
<th>unfamiliar</th>
<th>2</th>
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<td>Air Canada Centre</td>
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<td>Art Gallery of Ontario</td>
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<td>Atrium-on-Bay</td>
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<td>Bata Shoe Museum</td>
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<td>CBC Broadcast Centre</td>
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<td>Clarke Institute (CAMH)</td>
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<td>CN Tower</td>
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<td>College Park</td>
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<td>Four Seasons Hotel (Yorkville)</td>
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### Appendix B

**Experiment 2: List of landmark pairs**

<table>
<thead>
<tr>
<th>First Landmark</th>
<th>Second Landmark</th>
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<tbody>
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<td>Bata Shoe Museum</td>
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<td>Hart House</td>
</tr>
<tr>
<td>Air Canada Centre</td>
<td>Eaton Centre</td>
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<tr>
<td>Bata Shoe Museum</td>
<td>Casa Loma</td>
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<tr>
<td>Bata Shoe Museum</td>
<td>CN Tower</td>
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<tr>
<td>Bata Shoe Museum</td>
<td>The Hospital for Sick Children</td>
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<tr>
<td>Casa Loma</td>
<td>Rogers Centre</td>
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<tr>
<td>Casa Loma</td>
<td>The Hospital for Sick Children</td>
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<td>CN Tower</td>
<td>Honest Ed's</td>
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<tr>
<td>CN Tower</td>
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<td>Hart House</td>
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<td>Honest Ed's</td>
<td>Mount Sinai Hospital</td>
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Appendix C

Experiment 3: Instructions for the spatial interview

Familiar Route

I am going to ask you some questions about a short walking route that is very familiar to you. Before we begin, please take some time to think of a route that you walk several times a week and have been doing so for at least the last year. It is best if you can choose a route that lasts about 10 minutes, but if your route is longer, you can choose a shorter 10 minute segment to describe. You can choose any route you wish; our interest is not in the route itself, but in how you describe it. For your comfort, it is best that you choose a route that you are comfortable discussing with me in detail.

Part 1: Basic directions

We’ll start by having you give me the most basic directions necessary to follow the route. I’d like you to restrict your description to the direction you walk (e.g. North, South, straight, left) and the major turning points where you change directions. It is not necessary to describe any buildings or landmarks along the way. I will ask you for a more detailed description shortly. I will be typing as you speak. I may have to interrupt you occasionally to ask you to repeat some words, but please try to speak as naturally as possible.

Part 2: Detailed description

Now I’d like you to select 2 or 3 blocks (or an equivalent segment) of your route to describe in further detail. Please choose the segment that you remember most vividly. Your goal is to paint as vivid a picture as possible. Assume that I have no prior knowledge of this route. Here are some examples of details you may include in your description:

- Buildings, landmarks, streets, places, large-scale structures that you pass.
We are more concerned with descriptive details than with proper names (although you may still use proper names to refer to buildings etc.). Provide as many details as you can about the physical appearance; no detail is too small. Keep in mind that I’m trying to visualize the route that you describe, so it is important that you tell me not only what things look like, but also where they are located in relation to each other and yourself.

- **Occurrences, behaviours, habits, routines**

If there is anything you commonly see or do along this route please describe this as well (e.g. “There are usually people sitting at this corner.” “I usually buy a coffee here.”). At this point, I’m only interested in common or regular occurrences. I will be asking you about specific/unique events next.

- **Uncertainty**

Please speak as naturally as you can. Do not feel the need to filter out details that you are not completely certain about. Please be candid with the experimenter about the quality or the accuracy of your memory.

**Unique Route**

Now I’d like you to think of a unique route, one that you may have walked only once or twice, preferably recently. We’ll follow the same sequence as the previous section so I’ll start by having you give me basic directions and then I’ll ask you for a more detailed description.