# INVESTIGATING SPATIAL MEMORY AND NAVIGATION IN DEVELOPMENTAL AMNESIA: EVIDENCE FROM A GOOGLE STREET VIEW PARADIGM, MENTAL NAVIGATION TASKS, AND ROUTE DESCRIPTIONS

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**Abstract**

This dissertation examined the integrity of spatial representations of extensively travelled environments in developmental amnesia, thereby elucidating the role of the hippocampus in forming and retrieving spatial memories that enable flexible navigation. Previous research using mental navigation tasks found that developmental amnesic case H.C., an individual with atypical hippocampal development, could accurately estimate distance and direction between landmarks, but her representation of her environment was fragmented, inflexible, and lacked detail (Rosenbaum, Cassidy, & Herdman, 2015). Study 1 of this dissertation examined H.C.'s spatial memory of her home environment using an ecologically valid virtual reality paradigm based on Google Street View. H.C. and control participants virtually navigated routes of varying familiarity within their home environment. To examine whether flexible navigation requires the hippocampus, participants also navigated familiar routes that had been mirror-reversed. H.C. performed similarly to control participants on all route conditions, suggesting that spatial learning of frequently travelled environments *can* occur despite compromised hippocampal system function. H.C.'s unexpected ability to successfully navigate mirror-reversed routes might reflect the accumulation of spatial knowledge of her environment over the 6 years since she was first tested with mental navigation tasks. As such, Study 2 investigated how spatial representations of extensively travelled environments change over time in developmental amnesia by re-testing H.C. on mental navigation tasks 8 years later. H.C. continued to draw sketch maps that lacked cohesiveness and detail and had difficulty sequencing landmarks and generating detours on a blocked route task, suggesting that her overall representation of the environment did not improve over 8 years. Study 3 thoroughly examined the integrity of H.C.'s detailed representation of the environment using a route description task. H.C. accurately described perceptual features of landmarks along a known route, but provided inaccurate information regarding the spatial relations of landmarks, resulting in a fragmented mental representation of the route. Taken together, these results contribute meaningfully to our current understanding of the integrity of spatial representations of extensively travelled environments in developmental amnesia. Non-spatial factors that could influence performance on navigation and spatial memory tasks are discussed, as is the impact of these results on theories of hippocampal function.

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# CHAPTER 1

## General Introduction

Spatial memory of newly encountered and well-known environments is critical for navigation in everyday life. To navigate, animals and humans must be able to remember the location of distant goals and orient themselves in relation to those goals (Hartley, Lever, Burgess, & O'Keefe, 2014). The hippocampus plays a necessary role in the formation of new allocentric spatial memories of the relations among landmarks contained within an environment, as indicated by findings in animals (Morris, Garrud, Rawlins & O'Keefe, 1982) and humans (Ekstrom et al., 2003; Maguire, Nannery, & Spiers, 2006; Rosenbaum et al., 2000). By contrast, recent research suggests that some aspects of remote spatial memory for familiar environments learned long ago can be spared following hippocampal damage or degeneration. Conclusions of spared remote spatial memory are largely based on tasks that rely on mental navigation of the environment, but immersive, real-time travel within environments may be necessary to detect deficits in individuals with hippocampal damage (Spiers & Maguire, 2007). In this dissertation, I will examine the integrity of spatial representations of environments traversed over many years in an individual with developmental hippocampal amnesia using mental navigation tasks and a novel paradigm that allows for first-person virtualized navigation of real-world cities using Google Street View. This dissertation research makes use of recent technological advances to address three main research questions:

1) What is the status of spatial memory representations of large-scale environments learned over many years in a person in developmental amnesia?

2) Is the hippocampus needed for flexible navigation, to reconfigure or remap familiar routes in the service of navigation?

3) Are detailed representations of well-known large-scale environments affected in developmental amnesia, as they are in individuals with adult-onset hippocampal amnesia?

Before providing an overview of the studies conducted to address these three questions, I briefly review the literature on the function of the hippocampus and how it is believed to play a necessary role in allocentric spatial memory. I then discuss findings that contradict conventional wisdom: individuals with adult-onset hippocampal pathology show preserved memory for places learned long ago, indicating that not all types of allocentric spatial memory representations depend on the hippocampus. Next, I discuss evidence of spatial learning in developmental amnesia and the role of the hippocampus in flexible navigation. Finally, I speak to the tools that are most commonly used to investigate spatial memory and introduce a novel paradigm based on Google Street View.

**Mnemonic Function of the Hippocampus**

Scoville and Milner's (1957) characterization of the amnesic case H.M., a man who underwent bilateral medial temporal lobe resection that resulted in severe anterograde amnesia, sparked renewed interest in the multiple memory systems view and how the medial temporal lobes play a role in some forms of memory but not others. H.M. was able to learn how to trace a star while only seeing an inverted reflection of his hand through a mirror (Milner, 1962). While he acquired this visuomotor skill, he had no conscious recollection of ever engaging in this task (Milner, 1962), suggesting that non-declarative procedural memory is dissociable from declarative (consciously accessible) forms of memory (Cohen & Squire, 1980). Research since H.M. has demonstrated other divisions in memory. The amnesic case K.C., who sustained extensive medial temporal lobe damage following a motor vehicle accident, was incapable of recollecting any personally experienced events, but had preserved general knowledge of the world and himself (Rosenbaum et al., 2005), supporting Tulving's (2002) proposed distinction between episodic (memories of specific events confined to a particular time and place) and semantic memory (memory for facts or general knowledge). There is growing evidence that the hippocampus is always necessary to support episodic memory and some forms of semantic learning and memory (Blumenthal et al., 2017; Eichenbaum & Cohen, 2001; Nadel & Moscovitch, 1997; O'Keefe & Nadel, 1978; Rosenbaum et al., 2008; Vargha-Khadem et al., 1997).

**Evidence that the Hippocampus is Specialized for Allocentric Spatial Memory**

Behavioural evidence from animal lesion studies implicating the hippocampus in allocentric spatial learning is plentiful (e.g. Morris, Garrud, Rawlins, & O'Keefe, 1982; Murray, Davidson, Gaffan, Olton, & Suomi, 1989; Olton, Becker, & Handelmann, 1979; see Good, 2002, and O'Keefe & Nadel, 1978 for reviews). Seminal evidence of the importance of the hippocampus for spatial memory acquisition and retention comes from O'Keefe and Dostrovsky's (1971) discovery of place cells in the rodent hippocampus, which show a low firing rate when the animal is travelling through an environment until an animal is within that cell's “place field”, a specific constrained region within the environment that induces increased firing. Place cell activity does not depend on the animal’s orientation. Hartley and colleagues (2014) describe place cells as the “building blocks of spatial representation,” giving rise to a cognitive map.

The discovery of place cells led to O’Keefe and Nadel’s (1978) Cognitive Map Theory (CMT), which posits that the hippocampus supports mental representations of the spatial relations among landmarks/cues that are map-like (with an Euclidean metric), flexible and view-independent. Such a representation is also referred to in the literature as an allocentric representation. Environments can also be learned via stimulus-response learning or habit learning, where self-referenced (egocentric) sequences of turns are used to form mental representations of the environment.  Navigation within an environment necessarily involves an egocentric representation, as one’s position within the environment must be updated. Such representations do not require the hippocampus (and instead rely on the caudate nucleus (Dahmani & Bohbot, 2014)), but they lack the flexibility required to navigate barriers (Eichenbaum, 2017; O’Keefe & Nadel, 1978). Successful navigation often involves the ability to switch between and integrate allocentric and egocentric spatial representations, which is believed to require the posterior cingulate cortex and the retrosplenial cortex (Columbo et al., 2017).

In 2005, Hafting, Fyhn, Molden, Moser, & Moser identified grid cells, which appear to be involved in path integration (estimating direction and distance using self-motion signals), in the hippocampal formation (specifically the medial entorhinal cortex, and pre- and parasubiculum; Boccara et al., 2010). Importantly, place cells (Ekstrom et al., 2003) and grid cells (Doeller, Barry, & Burgess, 2010; Jacobs et al., 2013) have also been found in humans.

Other cells involved in spatial cognition have also been found in the hippocampal formation (which includes the hippocampus itself and adjacent cortical areas with which it has connections, including the entorhinal cortex, subiculum, presubiculum, and parasubiculum). Head direction cells (Taube, Muller, & Ranck, 1990) have been found in the entorhinal cortex and dorsal presubiculum, as well as outside of the hippocampal formation, in the retrosplenial cortex and the anterior dorsal thalamic nucleus (Hartley et al., 2014). Head direction cells show increased firing when an animal is facing in the cells' "preferred" direction, which corresponds to a compass direction (Hartley et al., 2014), and are believed to provide directional information to place cells.

Boundary cells show increased firing when an animal approaches a constrained region near the edges of an environment, and have been found to influence place cell firing (Hartley et al., 2014). Although boundary cells have not been found in the hippocampus itself, they have been identified in all other regions of the hippocampal formation (Hartley et al., 2014). This highlights that external sensory information about environmental geometry can influence cognitive mapping (Hartley et al., 2014).

Studies of spatial memory and navigation in humans also implicate the hippocampus. Neuroimaging studies have shown increased hippocampal activation when healthy controls navigated complex virtual environments that they had learned prior to scanning (Maguire, Frackowiak, & Frith, 1996) and when taxi drivers recalled complex routes around London (Maguire, Frackowiak, & Frith, 1997). Studies of patients with hippocampal lesions provide further evidence that the hippocampus plays a critical role in learning new spatial layouts and routes. The amnesic case H.M. was unable to learn or show improvement on a visually guided maze-learning task (Milner, 1965). Similarly, the amnesic case K.C. had difficulty on a tabletop test of spatial memory (Rosenbaum et al., 2000). The inability to acquire new spatial information has also been seen for larger-scale environments in multiple amnesic cases. K.C. was unable to learn to navigate an 8-step route within a university building after extensive training or recall the floor plan of a library where he had worked for two years following the onset of his amnesia (Rosenbaum et al., 2000). When asked to navigate between landmarks within the neighbourhood that he moved to after the onset of his amnesia and lived in at the time of testing, amnesic case E.P., who sustained substantial bilateral damage to the hippocampus and surrounding structures, was unable to provide a response (Teng & Squire, 1999). While there is evidence that the hippocampus is not solely responsible for spatial navigation, it is clear that it plays a critical role in forming new spatial memories. In contrast, its role in retrieving spatial memories for environments learned long ago is less clear.

**Preserved Schematic Representations of Remote Environments in Adult-Onset Amnesia**

To examine the role of the hippocampus in retrieving spatial memories for environments learned long ago, Rosenbaum and colleagues (2000) compared the performance of K.C. and healthy control participants on mental navigation tasks designed to assess remote spatial memory for direction, distance, routes, and landmark appearance. This required that a mental representation of the remotely learned environment was recalled and used to solve verbal or paper-and-pencil tasks. These tasks were used to test K.C.'s memory for the environment in which he grew up and lived most of his life, learned prior to the onset of his amnesia. K.C.'s ability to estimate distance and direction from one landmark to another was intact, and he could draw the general layout of the environment in a sketch map. Results suggest that K.C. retained a representation of his home environment that was sufficient for navigation, despite extensive hippocampal and medial temporal lobe damage.

Gathering further evidence that remote spatial memories can exist independent of the hippocampus, Herdman, Calarco, Moscovitch, Hirshhorn, and Rosenbaum (2015) tested adult-onset amnesic cases D.G. and D.A. on mental navigation tasks specific to their home environments. Similar to K.C., D.G. and D.A. were able to draw sketch maps of their well-known environments that maintained the overall configuration, and provide estimates of distance and direction comparable to those provided by healthy controls on a vector-mapping task. Further support for the preservation of remote spatial memories in cases of hippocampal damage come from work with patient E.P., who showed intact performance on tests of topographical memory (Teng & Squire, 1999), and T.T., a former London taxi driver with bilateral hippocampal damage who could navigate main artery routes in a virtual reality simulation of central London, England (Maguire et al., 2006).

## Impaired Detailed Representations of Remote Environments in Adult-Onset Amnesia

Although it has been shown that several individuals with damage to the hippocampus are able to navigate in familiar environments learned long ago, there is evidence that they may experience spatial memories differently than controls, as representations of detailed features appear to be lost in some individuals. For example, the sketch maps of cases K.C., D.G., and D.A. contained fewer streets and landmarks compared to control participants' sketch maps, although landmarks and street segments that were included were accurately placed (Herdman et al., 2015; Rosenbaum et al., 2000). The amnesic cases also performed worse than controls on a landmark recognition task (Herdman et al., 2015; Rosenbaum et al., 2000). Furthermore, K.C., D.G., and D.A. each showed impoverished descriptions of familiar routes, suggesting that the hippocampus is required for vivid re-experiencing of a route (Herdman et al., 2015). Impoverished detailed representations are suggested in Maguire and colleagues' (2006) report of the case T.T., who could rely on main artery roads to reach a destination, but had difficulty navigating along non-artery (minor) roads. Taken together, adult-onset amnesic individuals show intact schematic mental representations of well-known, remotely learned environments, sufficient for navigation, but impoverished detailed representations of the same environments.

**Spatial Memory Development in Developmental Amnesia**

The study of developmental amnesic cases provides additional valuable information about hippocampal contributions to spatial memory, as it allows one to examine whether spatial memory develops normally in an individual with an atypically developed hippocampal system and absence of episodic memory. By examining spatial memory in an individual with developmental amnesia we can determine whether patterns of impairment and preservation are consistent with that seen in adult-onset amnesia. If not, it may be that the development of remote spatial memory is more vulnerable to early-onset hippocampal damage, or, alternatively, greater neural plasticity and tendency for functional reorganization may result in relatively more preservation (Manning, 2008; Rosenbaum et al., 2011).

Studies with individuals with developmental amnesia who have early-onset hippocampal abnormalities lend further evidence that the hippocampus is required to learn new environments. For example, Vargha-Khadem and colleagues (1997) found that three developmental amnesic cases were impaired in learning object-place associations and had difficulty remembering a route around the testing room. King, Burgess, Hartley, Vargha-Khadem, and O’Keefe (2002) reported that developmental amnesic case Jon was severely impaired in identifying the location of various objects within a virtual town square when tested from a shifted viewpoint, where successful identification would require the object location be defined relative to the environment (allocentric) rather than relative to the body (egocentric).

His ability to identify landmark locations was markedly better when tested from the same-viewpoint, where a hippocampal-independent egocentric framework could have been used, but he began to show a deficit when ten or more object locations had to be remembered (King et al., 2002).

Gardiner, Brandt, Baddeley, Vargha-Khadem, and Mishkin (2008) have shown that individuals with developmental amnesia have the ability to acquire semantic knowledge, albeit very slowly and over an extended period of time. As schematic spatial representations have been proposed as analogous to semantic memory (Winocur & Moscovitch, 2011), the following question arose: Can spatial learning ever occur in an individual with atypical hippocampal system development and the absence of episodic memory? Perhaps with extensive experience and time travelling within an environment, individuals with developmental amnesia can form spatial representations that resemble semantic memories that are sufficient for navigation. In Vargha-Khadem and colleagues seminal study published in 1997, caregivers of three cases of developmental amnesia reported that they were unable to reliably find their way in familiar surroundings. While this would suggest that spatial learning does not occur, even in highly frequented environments, this was not formally tested. On the contrary, family members of developmental amnesic H.C. reported that she is able to navigate within the environment she has lived in since birth when she is free from distractions (Rosenbaum et al., 2015), which led to the systematic testing of H.C. on mental navigation tasks.

In many ways, our work with developmental amnesic H.C. using mental navigation tasks shows a similar pattern to that seen with adult-onset amnesia cases. She shows intact performance compared to demographically-matched controls on tasks assessing distance and direction, including proximity judgments, distance judgments, and vector mapping (see Figure

1.1 for a sample of a vector mapping trial). Taken together, this suggests that she has been able to form a schematic representation of her home environment.

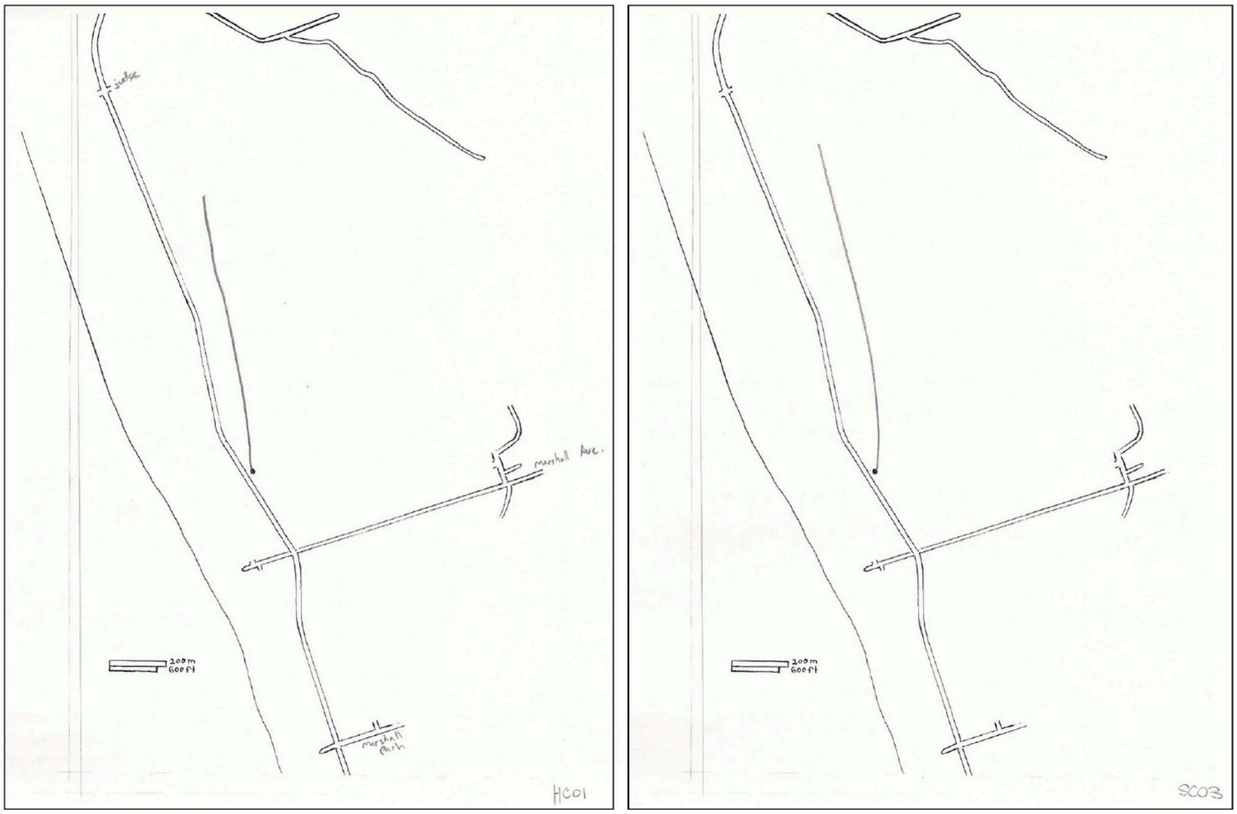


*Figure 1.1.* Sample of a vector mapping trial, reproduced without changes from Rosenbaum, Cassidy, & Herdman (2015). A vector (representing estimated direction and distance) from a marked landmark to an unmarked landmark was drawn by H.C. (left) and a control (right) on a map that outlines a frequently travelled environment. Link to Creative Commons attribution license: https://creativecommons.org/licenses/by/4.0/legalcode

She had difficulty, however, accurately sequencing more than two landmarks that were close in proximity to one another along a route and producing detailed spatial features on sketch maps (see Figures 1.2 and 1.3). She produced approximately one third the number of details (landmarks and street segments) on her sketch maps compared to controls. Such results hint towards an impoverished representation of her home environment that lacks detail and richness.

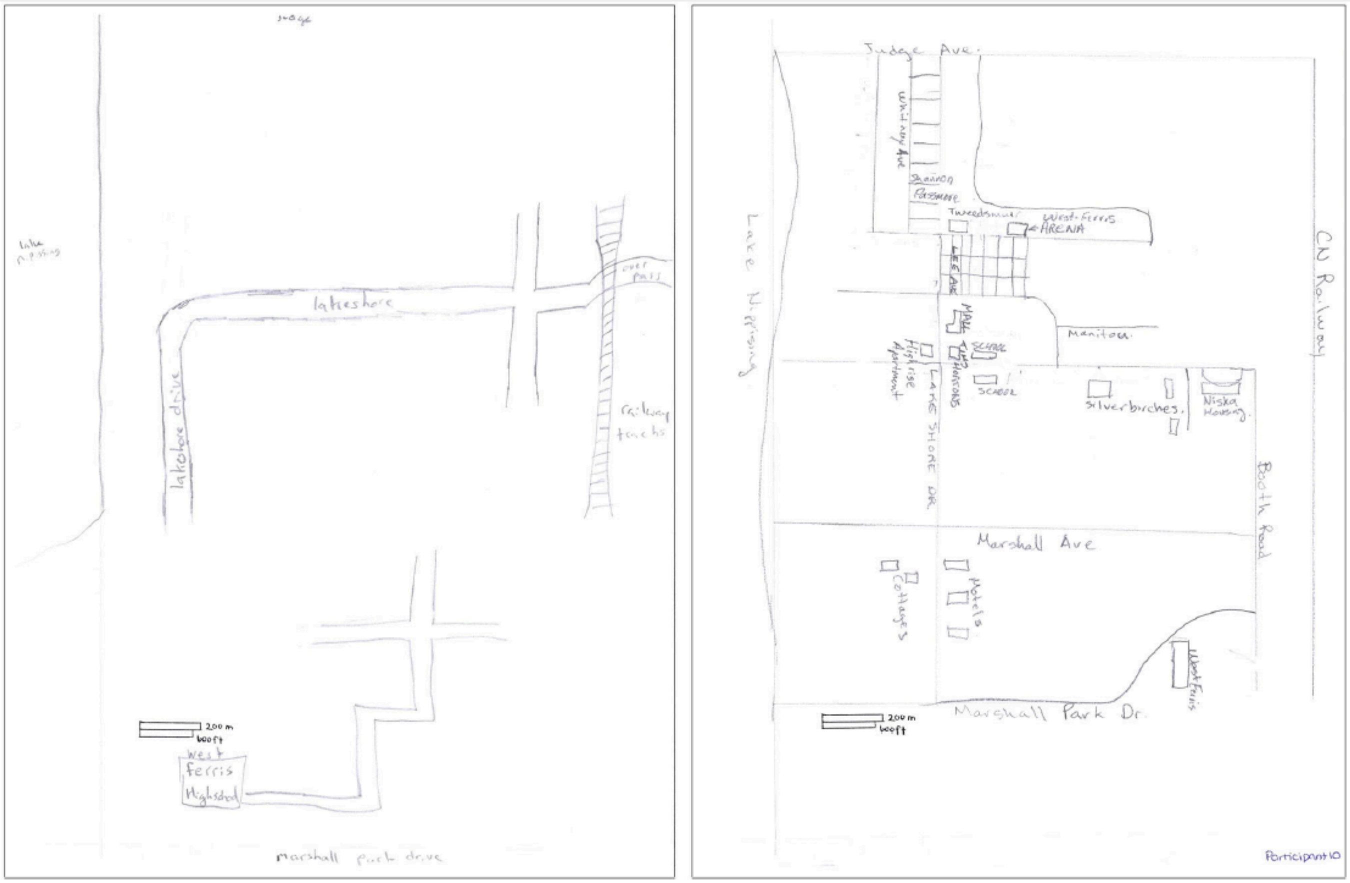


*Figure 1.2.* Sketch maps of H.C.'s childhood environment as drawn by H.C. (left) and a control participant in 2010 (right). Reproduced from Rosenbaum, Cassidy, & Herdman (2015), unchanged. Link to Creative Commons attribution license: https://creativecommons.org/licenses/by/4.0/legalcode

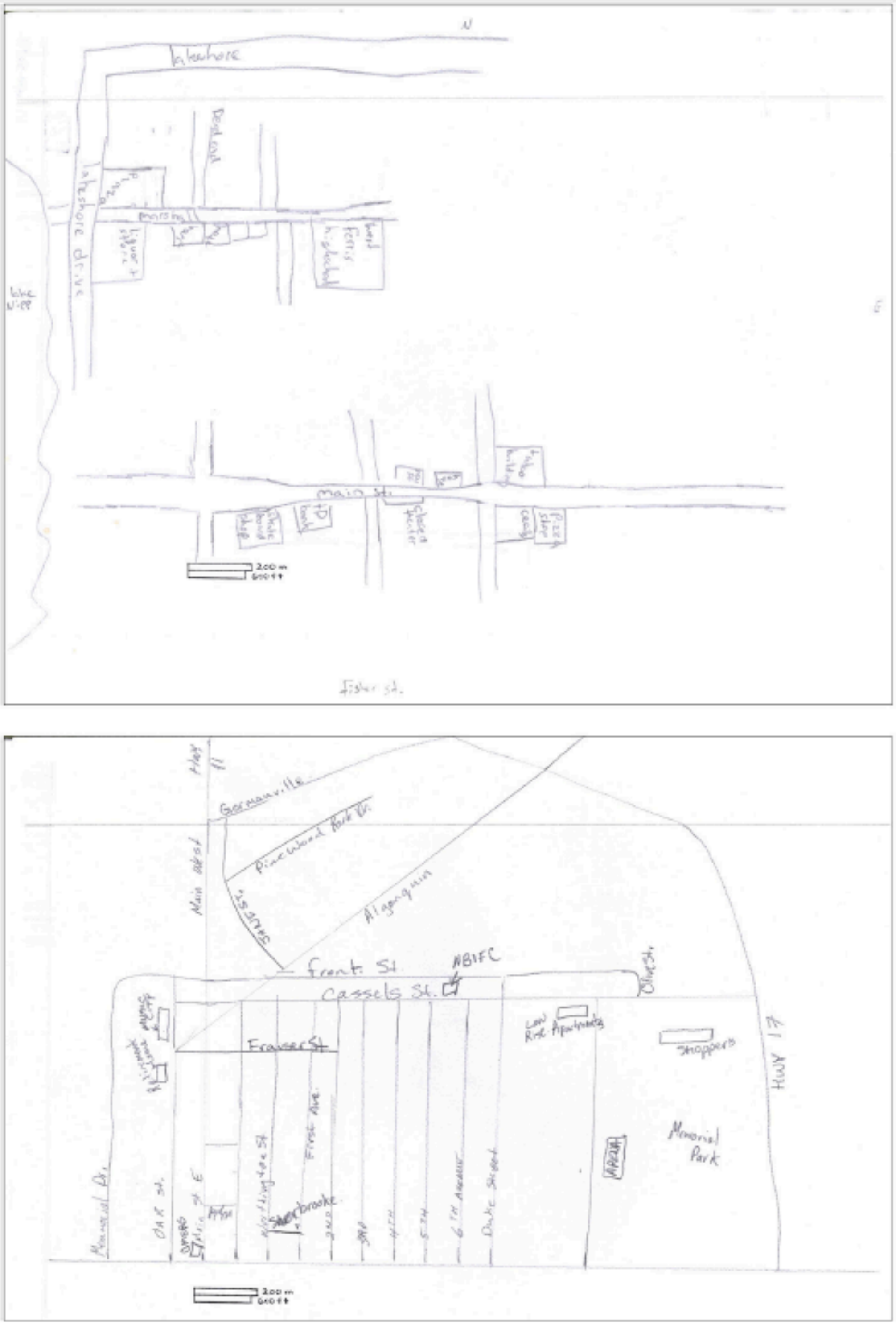


*Figure 1.3.* Sketch maps of a downtown city environment adjacent to H.C.'s childhood neighbourhood as drawn by H.C. (top) and a control participant (bottom) in 2010. Reproduced from Rosenbaum, Cassidy, & Herdman (2015), unchanged. Link to Creative Commons attribution license: https://creativecommons.org/licenses/by/4.0/legalcode

**Role of the Hippocampus in Flexible Navigation**

Successful navigation towards a goal that is not within plain sight can be achieved with different wayfinding strategies (Eichenbaum, 2017). Franz and Mallot (2000) found that goals could be reached by recognizing a landmark, moving towards it, recognizing another landmark, approaching it, and so on. Such recognition-triggered responses can be combined to form a route. Routes can overlap and intersect, which allows for topological navigation; however, navigation lacks flexibility, as it can only occur along paths that have been travelled before (Eichenbaum, 2017). Using allocentric survey navigation, a cognitive map allows novel routes within a well-known environment to be navigated flexibly, that is, using paths that have never been travelled but can be inferred from known relations between landmarks (Eichenbaum, 2017).

The Cognitive Map Theory (CMT) postulates that allocentric spatial representations of environments (view-independent knowledge of spatial relations among landmarks) are stored within the hippocampus, and that such representations permit flexible navigation (O'Keefe & Nadel, 1978). As O'Keefe and Nadel did not differentiate between recent and remote cognitive maps, it is unclear whether or not they believed that cognitive maps for remotely learned environments could exist without support from the hippocampus. Evidence of intact performance on many mental navigation tasks in adult-onset and developmental amnesia suggests that map-like knowledge of well-known environments can exist independent of the hippocampus.

To further test the limits of the CMT, one might question whether these intact map-like representations of environments learned long ago are sufficient for flexible navigation. One way to investigate this is with a blocked route task, where participants must deviate from their typical route to make their way to a specified destination. Amnesic case K. C. was able to provide directions for the most efficient route between two landmarks when the most direct route was blocked, which implies that the hippocampus may not be required for the flexible implementation of allocentric representations (Rosenbaum et al., 2000). Similarly, amnesic case E.P. was able to provide directions between well-known landmarks for the environment he grew up in and resided in for 28 years, even when the main street was blocked (Teng & Squire, 1999). One issue in interpreting these findings, however, is that the environments and routes within them are very well-known, so that even lesser-known detours do not require the same level of flexibility as would detours within newly learned environments. Testing someone with developmental amnesia shows that new spatial learning, even if extensive, may be inflexible when hippocampal integrity is compromised. Developmental amnesic case H.C. was also able to navigate between two landmarks using a detour, but she failed to use the most efficient route, suggestive of inflexible use of spatial representations (Rosenbaum et al., 2015). It appeared as though H.C. relied on well-known streets on the blocked route task, which suggests that she could have navigated using overlapping routes, exhibiting topological navigation rather than a map-like, survey navigation (Eichenbaum, 2017). Furthermore, H.C.'s configuration of space on the sketch maps seemed to be fragmented. In her sketch maps (Figure 1.2 and 1.3), she was able to represent distinct areas within the environment, but could not integrate them into a cohesive whole. Overall, H.C. was believed to have a coarse schematic representation of space that lacked coherence and thus could not be used flexibly (Rosenbaum et al., 2015).

Analogous to what is seen in humans with hippocampal lesions, rats with hippocampal lesions were able to navigate successfully in a complex "village" environment that was learned prior to hippocampal damage (Winocur, Moscovitch, Fogel, Rosenbaum, & Sekeres, 2005;

Winocur, Moscovitch, Rosenbaum, & Sekeres, 2010). When faced with a blocked route, however, rats with hippocampal lesions made more errors and took longer to find the goal destination (Winocur et al., 2010), in line with findings in developmental amnesic H.C. When the location of the goal destination was reconfigured within the environment, rats with hippocampal lesions had difficulty remapping and integrating this new information with preserved spatial memory of the familiar complex village (Winocur et al., 2005). Remapping requires learning new spatial relations, a skill well documented to be reliant on the hippocampus.

It remains inconclusive whether spatial representations that exist outside of the hippocampus can be flexibly used in humans. Attempts to mimic the level of disorientation created by reconfiguring major spatial cues in Winocur and colleagues' (2005) animal study in humans have been limited by the inability to reconfigure real-world environments that are well-known to participants.

## Tools Used to Investigate Spatial Memory

Virtual reality technology has become a popular tool to investigate spatial navigation, especially in studies investigating new spatial learning, because one can measure navigational aptitude within dynamic environments that were created specifically for the study and are free from distractions or changing cues. The use of virtually rendered environments is not, however, conducive to studying memory of real-world environments, particularly those that were learned long ago. As such, much research has relied on mental navigation tasks, as described above, to evaluate one's ability to remember and navigate environments learned long ago. While these measures have proven sensitive, they may not fully capture the experience of real-world navigation and additional important information could be gained by examining more immersive navigation in the real world (Maguire et al., 2006; Spiers & Maguire, 2007). In situ navigation is an option when investigating remote spatial memory, but this can be time-consuming, and mobility and physical fatigue issues can present considerable challenges. Attempts to employ virtual reality paradigms in the study of remote spatial memory have been made. Maguire and colleagues (2006; Spiers & Maguire, 2007, 2008) created a virtual reality rendering of London using video game software. Unfortunately, it is time-consuming and difficult to create virtual environments of real-world places that are not overly stylized. A recent software suite that capitalizes on Google Street View may remedy these problems by providing a platform that allows for virtual navigation of real-world environments using panoramics from actual environments, instead of a virtual-reality rendering. In a recent application, Patai and colleagues (2017) successfully used this software to investigate the brain regions involved during navigation of recently learned or highly familiar environments. The Google Street View software was also used in Brunec and colleagues' (2018) study, which found that the human hippocampus supports an anterior-to-posterior gradient of coarse-to-fine spatiotemporal representations. This Google Street View software is a promising new tool with which to investigate spatial memory.

## Overview of Studies

The above review suggests that spatial representations of extensively travelled environments can form in H.C., an individual with developmental amnesia. Similar to adult-onset amnesic patients, H.C.'s representation of her home environment seems to be coarse and lacking in detail. Contrary to what is seen in adult-onset amnesic cases, H.C.'s representation of space seems to lack coherence and thus likely cannot be used as flexibly. These findings, however, are based on mental navigation tasks, and immersive navigation (that combines visual cues with the sense of dynamic motion through the environment) may be more ecologically valid and necessary to detect additional difficulties. In this dissertation, I examined the integrity of spatial representations of an extensively travelled environment in H.C., a young woman with developmental amnesia, using a novel Google Street View platform that allows virtual reality navigation of real-world environments, mental navigation tasks, and a route-description task.

The first study sought to determine whether H.C. could virtually navigate routes of varying familiarity within her extensively experienced home environment. If this is the case, it would provide further evidence that an individual with atypical hippocampal development can form spatial representations of frequently travelled environments (Question 1) and that these representations are sufficient for virtual navigation. It also would be in line with adult-onset amnesic cases' intact performance on mental navigation tasks assessing distance and direction, and lend support to the theory that spatial representations of environments learned long ago can exist independent of the hippocampus. Difficulty travelling familiar routes within her home environment, however, would suggest that any representations of space that she may have formed (as documented in Rosenbaum et al., 2015) are not sufficient for virtual navigation.

By varying the level of familiarity with routes within well-known environments, we can examine whether intact performance is due to familiarity with a specific route, which can be learned by habit, or access to a cognitive map or schematic representation of space that allows for flexible navigation. An fMRI study by Hartley, Maguire, Spiers, and Burgess (2003) identified that the hippocampi were not activated when travelling well-worn, familiar routes, but instead the right caudate nucleus was activated. On paths less travelled, analogous to our less familiar routes, the hippocampus did appear to be activated, perhaps because such navigation requires a flexible representation of space, achieved with a cognitive map or schematic representation of the environment. If H.C. is able to virtually navigate less familiar routes, it provides evidence that a cognitive map, or a coherent schematic, gist-like representation of space, can exist outside of the hippocampus.

To push the envelope even further, we also examined whether the hippocampus is needed to reconfigure or remap familiar routes in the service of navigation (Question 2). H.C. and healthy controls were asked to navigate familiar routes within a well-known environment that had been purposefully altered to cause disorientation using the Google Street View paradigm. During these trials, participants' familiar routes were mirrored, so what was normally seen on the participants' right was seen on the left, and vice versa.

To foreshadow the results, H.C. performed better than expected on the less familiar and mirrored routes given prior evidence of inflexible, incoherent spatial representations of her home environment. One possible explanation for her intact performance is that because she was tested on the Google Street View task 6 years after completing the mental navigation tasks, her intact performance across all Google Street View route conditions reflects improved spatial memory due to additional experience navigating within her home environment and more time spent actively navigating while driving. To investigate this possibility, the second study in this dissertation reports on results from the more recent re-administration of some of the mental navigation tasks.

The third study focuses on the integrity of H.C.'s detailed representation of her home environment. Although neural plasticity may help individuals with developmental amnesia compensate and reorganize functions of the hippocampus within other areas of the brain, H.C. provided fewer details on her sketch maps (Figures 1.2 and 1.3) and had greater difficulty sequencing landmarks in close proximity to one another along a route when tested on mental navigation tasks, compared to controls (Rosenbaum et al., 2015). This hinted at a less detailed representation of her home environment. In the third study, H.C. and healthy control participants were asked to describe a familiar walking route in as much detail as possible. H.C.'s route description was transcribed and analyzed for the number of entities, spatial references, and sensory descriptions, and compared to that of healthy controls. In doing so, we gain a better understanding of whether representations of environments are lacking in richness of detail in developmental amnesia, even when the hippocampus is partially intact and there is greater potential for neural reorganization.

To summarize, prior research using mental navigation tasks to test adult-onset amnesic cases has revealed that schematic, map-like representations of environments learned prior to the onset of amnesia can exist independent of the hippocampus. The hippocampus, however, appears to be needed for representing detailed features of environments learned in the remote past that enable a sense of re-experiencing (Rosenbaum et al., 2000; Herdman et al., 2015) and for learning novel spatial relations (Maguire et al., 2006). A similar pattern was found in the developmental amnesic case H.C. using mental navigation tasks, but with a few exceptions. While H.C. had access to a spatial representation of her extensively travelled home environment that seemed to lack detail, her performance indicated a lack of cohesiveness between spatial features that was not see in adult-onset amnesic cases (Rosenbaum et al., 2015).

In this dissertation, a dynamic, immersive, virtual-reality Google Street View paradigm was used to test the extent of intact and impaired spatial memory by examining H.C.'s ability to virtually navigate within her home environment, thereby confirming whether or not spatial representations that are sufficient for navigation can form in developmental amnesia and whether the hippocampus is required for flexible navigation of extensively experienced environments (Study 1). In Study 2, we explored how representations of frequently travelled environments may change in developmental amnesia over the course of 8 years by re-testing H.C. on mental navigation tasks. A route description task (Study 3) was used to examine H.C.'s ability to richly recall a very familiar walking route, providing insight into whether the hippocampus is required for accessing a detailed representation of extensively travelled environments in developmental amnesia. These experiments have the potential to inform theories of hippocampal function and spatial memory, and improve our understanding of the nature of new spatial learning over extended periods of time in the absence of a typically functioning hippocampal system and episodic memory.

# CHAPTER 2

## Study 1: Intact Virtual Reality Navigation in Developmental Amnesia

Findings from studies with adult-onset amnesic cases suggest that schematic, gist-like representations of environments learned long ago can exist outside of the hippocampus (Rosenbaum et al., 2000; Herdman et al., 2015). While it may be that schematic representations of well-known environments do not rely on the hippocampus after years of experience, the creation of the representations themselves would have at one time relied on the hippocampus, as it has long been understood that the hippocampus is needed for forming new spatial memories (Barrash, 1998, Maguire et al., 2006). These findings led to the development of the Trace Transformation Theory (Winocur & Moscovitch, 2011), which states that an initial representation of a new environment preserves spatial features and perceptual details and is dependent on the hippocampus. With time and experience navigating within the environment, one can abstract the salient features of the environment that are important for navigation and form a schematic, gist-like representation of the environment. It remains unclear, however, whether such representations can form with extensive experience in the absence of a fully functional hippocampal system and without the full support of episodic memory, as in the case of developmental amnesia.

Developmental amnesia presents a unique opportunity to examine whether spatial representations can form in an individual who has impaired episodic memory as a result of atypical development of the hippocampal memory system. Episodic memory is well documented to be impaired in developmental amnesia, and cursory evidence from Vargha-

Khadem and colleagues (1997) suggest that spatial memory may also be compromised. Episodic memory and spatial memory appear to be intricately linked to one another. Indeed, encoding and retrieving a personal event involves the integration of rich temporal and spatial contexts (Good, 2002). Retrieval of episodic memories seems to rely, at least in part, on the spatial contexts in which they occurred. When one recalls an episodic memory, they often conjure up where it occurred, and events with spatial context are remembered more vividly and described in greater detail than those lacking such context (Robin, Wynn, & Moscovitch, 2016). The hippocampus has also been found to be important in forming “what-where” associations in rats (Day, Langston, & Morris, 2003; Gilbert & Kesner, 2002, 2003; Rajji, Chapman, Eichenbaum, & Greene, 2006) and monkeys (Gaffan, 1994). Spatial contexts seem to provide a basis for episodic memories to unfold, but are episodic details as important in forming spatial memories?

There is evidence that learning can occur in the absence of episodic memory. Semantic learning has been found to occur in adult-onset amnesia (Hayman, Macdonald, & Tulving, 1993; Verfaellie, Koseff, & Alexander, 2000) and developmental amnesia (Gardiner et al., 2008) over an extended period of time. Given this evidence and the proposed parallel between semantic memory and schematic representations of space (Winocur & Moscovitch, 2011), it may be possible that schematic spatial memories can form with extensive repeated exposure. Brooks and colleagues (1999) taught an adult-onset amnesic patient to navigate simple routes using a computer-generated environment that was based on the patient’s hospital rehabilitation unit. After several weeks of training, the patient was able to navigate the routes in situ, demonstrating that new routes can be learned in individuals with severe hippocampal damage after repeated exposure. Reports also suggest that amnesic case H.M. was able to draw the floor plan of the house that he lived in after the onset of his amnesia, perhaps due to significant, ongoing exposure (Corkin, 2002). Such human evidence is consistent with Winocur and colleagues (2010) findings that rats could form coarse representations of space after hippocampal lesions, although the formation of such representations required extensive training. H.C.'s previously reported intact performance on mental navigation tasks that estimate distance and direction suggests that learning can also occur for a larger-scale environment, even in the context of an abnormally developed hippocampal system and episodic memory impairment (Rosenbaum et al., 2015).

Unlike adult-onset amnesic patients, however, H.C. had difficulty on the blocked route task, which required her to provide an alternate route between two landmarks because the most efficient route was blocked (Rosenbaum et al., 2015). H.C. was able to provide an alternate route, but her directions were inefficient compared to controls. This, along with fragmented sketch maps, suggests a representation of space that lacks cohesion and likely cannot be used as flexibly. To our knowledge, such inflexibility in remote spatial memory representations has not been formally documented in adult-onset amnesic cases. This suggests that flexible representations that allow individuals to navigate to the same destination via different means may be more vulnerable to early-onset hippocampal damage.

While mental navigation tasks enable investigation of spatial memory of remotely learned environments, they rely solely on mental representations of environments. If one is able to accurately estimate distance and direction between landmarks, you might speculate that their mental representation of their home environment would be sufficient for real-world navigation, but this cannot be stated with certainty. A crucial next step is to test the limits of intact performance on mental navigation tasks using realistic, immersive virtual reality tests. Previous testing with mental navigation tasks also hinted that H.C. had access only to a coarse, schematic representation of her home environment that lacked cohesion and was inflexible (Rosenbaum et al., 2015). Using an immersive virtual reality paradigm, we can investigate whether the representations that H.C. has formed are sufficient for navigating familiar routes, as well as flexible enough to enable navigation of routes purposefully designed to cause disorientation. The Google Street View paradigm offers the additional benefit above conventional virtual reality paradigms of being able to test navigation within real-world, remotely learned environments.

The aim of Study 1 was to validate and extend findings of intact, but inflexible, schematic representations of space in developmental amnesia based on mental navigation of well-known environments using Google Street View as a platform to create a more dynamic, immersive real-world paradigm. Working with developmental amnesic H.C., the present study investigated the role of the hippocampus in navigating familiar and less familiar routes, as well as reorienting oneself in an environment following disorientation. This study sheds light on the development of spatial memories in the context of an abnormal hippocampal system and impaired episodic memory. As H.C. showed intact performance on mental navigation tasks assessing distance and direction, we expected that she would perform as well as age- and education-matched controls in navigating familiar routes within her home environment.

As previously mentioned, Hartley and colleagues (2003) found that healthy adults activated the right caudate nucleus, rather than the hippocampus, when navigating frequently travelled ("well-worn") routes, but that the hippocampus came online again when navigating paths less frequently travelled. Our less familiar route condition allows us to examine whether the hippocampus is needed to recall a representation of one's home environment that is interconnected and therefore flexible enough to enable successful navigation between two known landmarks that they have never purposefully travelled between before. As learning new information in developmental amnesia seems to require much exposure and repetition, we expected that H.C. would have difficulty navigating between familiar landmarks in the less familiar route condition.

This study also aimed to examine whether spatial representations that exist outside of the hippocampus are cohesive and flexible in humans or whether flexible use of the representations would require the hippocampus. Although rats reared in a complex village environment retained a representation of the environment after hippocampal lesions, when the goal destination was reconfigured in the environment, they were unable to successfully navigate to the goal destination because they could not learn new spatial relationships between the familiar external environment and the village maze (Winocur et al., 2005). In a follow-up study, Winocur and colleagues (2010) found that rats with hippocampal lesions had greater difficulty on a blocked route task, taking more time and making more errors than non-lesioned control rats before reaching the goal destination. Taken together, findings from these rodent studies suggest that representations of environments learned prior to hippocampal damage are less cohesive and less flexible than in non-lesioned animals.

One way to induce flexibility is to capitalize on the Google Street View technology to reconfigure real-world environments that are well-known to participants, by mirroring the environment, so that what is normally seen on the left is now seen on the right, and vice versa. Based on previous research implicating the hippocampus in reorienting or remapping the environment (see Latuske, Kornienko, Kohler, & Allen, 2018 for a review), we anticipated that this modification would reinstate the hippocampus. Given that previous research suggests that H.C. has an inflexible representation of space, we expected that H.C.'s performance on the mirrored route condition would be worse than her performance on familiar and less familiar conditions. Although we expected that both H.C. and control participants would show worse performance on the mirrored and less familiar conditions relative to the familiar condition, given the link between the hippocampus and flexible representations of space, we anticipated that H.C.'s performance would be even worse than that of control participants.

## Methods

### Participants

H.C. is right-handed woman who was 28 years old at the time of testing. H.C. reportedly suffered a hypoxic episode soon after she was born prematurely, at the gestational age of 32 weeks (Hurley, Maguire, & Vargha-Khadem, 2011). Her memory difficulties first became apparent around the age of four, before entering school (Hurley et al., 2011). She successfully graduated from a mainstream high school, and completed one year of technical college and one year of culinary school. She has 14 years of formal education, and worked as a cashier at a local retail store at the time of testing. H.C. obtained a driver's license when she was 17 years old, and had 12 years of driving experience within the city she grew up in and currently resides. She reports normal eyesight and hearing.

Results from detailed neuropsychological testing revealed impaired episodic memory and learning, in the context of average general intelligence and intact performance on tasks assessing other, non-mnemonic cognitive domains (see Table 1 for a summary of relevant findings from neuropsychological testing; Rosenbaum et al., 2011).  This pattern of performance has remained relatively consistent since age 11 (Hurley et al, 2011).

**Table 1. H.C.'s Neuropsychological Profile**

| Test | Raw Score | Normed Score | | Label |
|---|---|---|---|---|
| **Intellectual function and academic attainment** | | | | |
| WASI | | | | |
| Verbal IQ | 104 | *Percentile* | 61 | Average |
| Performance IQ | 106 | *Percentile* | 66 | Average |
| Full scale IQ | 106 | *Percentile* | 66 | Average |
| AM-NART | | | | |
| Total correct | 27 | *Standard score* | 101.28 | Average |
| WAIS-III | | | | |
| Arithmetic | 10 | *Scaled Score* | 8 | Low Average-Average |
| Information | 19 | *Scaled Score* | 12 | Average-High Average |
| **Language** | | | | |
| Boston Naming Test[1] | 58 | *Percentile* | 77-79 | High Average |
| Semantic fluency (animals) | 32 | *Percentile* | >90 | Superior |
| Phonemic fluency (FAS)[2] | 53 | *Percentile* | 70-80 | Average-High Average |
| WASI | | | | |
| Vocabulary | 58 | *T-Score* | 55 | Average |
| **Anterograde Memory** | | | | |
| WMS-III | | | | |
| Logical Memory I | 27 | *Scaled Score* | 4 | Borderline-Mildly Impaired |
| Logical Memory II | 3 | *Scaled Score* | 1 | Moderately Impaired |
| California Verbal Learning Test-II | | | | |
| Total Trials 1-5 | 44 | *T-Score* | 38 | Low Average |
| Short Delay Free Recall | 0 | *Z-Score* | -4 | Severely Impaired |
| Short Delay Cued Recall | 5 | *Z-Score* | -3.5 | Severely Impaired |
| Long Delay Free Recall | 3 | *Z-Score* | -3 | Severely Impaired |
| Long Delay Cued Recall | 4 | *Z-Score* | -3.5 | Severely Impaired |
| Recognition | 13 | *Z-Score* | -2 | Borderline- Mildly Impaired |
| Rey Osterrieth Complex Figure[3] | | | | |
| Immediate Recall | 4 | *T-Score* | <20 | Severely Impaired |
| Delayed Recall | 3 | *T-Score* | <20 | Severely Impaired |
| Delayed Recognition | 17 | *T-Score* | 22 | Moderately Impaired |
| **Processing Speed** | | | | |
| WAIS-III | | | | |
| Digit Symbol | 96 | *Scaled Score* | 13 | High Average |
| Symbol Search | 45 | *Scaled Score* | 14 | High Average-Superior |
| **Visuospatial Function** | | | | |
| Judgment of Line Orientation | 24 | *Percentile* | 56 | Average |
| Benton Facial Recognition | 45 | *Percentile* | 33-59 | Average |

| | | | | |
|---|---|---|---|---|
| Rey Osterrieth Complex Figure | | | | |
| Copy[3] | 33 | *Percentile* | >16 | Within Normal Limits |
| WASI | | | | |
| Block Design | 52 | *T-Score* | 54 | Average |
| **Attention & Executive Function** | | | | |
| Stroop[4] | | | | |
| Word full (seconds) | 45 | *Z-score* | 3.65 | Very Superior |
| Color full (seconds) | 48 | *Z-score* | -0.03 | Average |
| Interference full (seconds) | 80 | *Z-score* | -0.57 | Average |
| Trail Making Test [1] | | | | |
| Trails A (seconds) | 34 | *Z-score* | 0.69 | High Average |
| Trails B (seconds) | 55 | *Z-score* | -0.23 | Average |
| WASI | | | | |
| Matrix Reasoning | 29 | *T-Score* | 55 | Average |
| Similarities | 35 | *T-Score* | 50 | Average |
| WAIS-III | | | | |
| Digit Span Forward | 10 | | - | |
| Digit Span Backward | 5 | | - | |
| Digit Span Total | 15 | *Scaled Score* | 8 | Low Average-Average |
| Wisconsin Card Sorting Task | | | | |
| Categories[5] | 10 | *T-Score* | 57 | High Average |

*Note. AM-NART, American National Adult Reading Test; WASI, Wechsler Abbreviated Scale of Intelligence; WAIS-III, Wechsler Adult Intelligence Scale-III. Additional neuropsychological test results reported in Hurley et al. (2011), Rosenbaum et al. (2011), Rosenbaum et al. (2015) and Rabin et al. (2012). [1]Spreen and Strauss (1998), [2]Tombaugh et al. (1999), [3]Meyers and Meyers (1996), [4]in-house unpublished normative data, [5]Heaton et al. (1993).*

Developmental amnesic case H.C. shows intact personal and general semantic memory, but episodic memory impairment on tests of public and personal event memory (Rosenbaum et al., 2011). Her performance on a lab-based test of recognition memory that required participants to report whether each of 100 words was new or presented 10 minutes prior was impaired compared to healthy controls, with impairment found for words that she identified as remembering explicitly and words that were familiar, but not explicitly remembered (Rosenbaum et al., 2011).

While H.C.'s overall brain volume does not differ significantly from that of demographically matched controls, she shows a volume reduction of 29.5% and 31.2% in the left and right hippocampi, respectively (Olsen et al., 2013). Olsen and colleagues' (2013) manual segmentation of the hippocampi and surrounding medial temporal lobe cortices revealed that, in comparison to controls, H.C. showed significant anterior hippocampal volume reduction bilaterally, significant volume reduction in the posterior segment of the right hippocampus, and marginal reduction in the posterior segment of the left hippocampus. Further segmentation of the body of the hippocampi identified significant reduction in the $CA_1$ and subiculum bilaterally (Olsen et al., 2013). H.C.'s right dentate gyrus, $CA_2$ and $CA_3$ subregion was marginally smaller than controls, and significantly smaller on the left (Olsen et al., 2013). The volume of H.C.'s entorhinal cortex and perirhinal cortex did not differ significantly from controls, however left parahippocampal volume was marginally increased in H.C. (Olsen et al., 2013).

In addition to being smaller, H.C.'s hippocampi have been found to be oriented vertically and appear globular in shape, suggestive of disruption very early in gestation (Rosenbaum et al., 2014). Other neuroanatomical abnormalities include bilateral atrophy of the fornix, agenesis of the mammillary bodies, and bilateral atrophy of the anterior thalamic nuclei, all of which suggest a congenital basis for her memory impairment (see Figure 2.1; Rosenbaum et al., 2014).

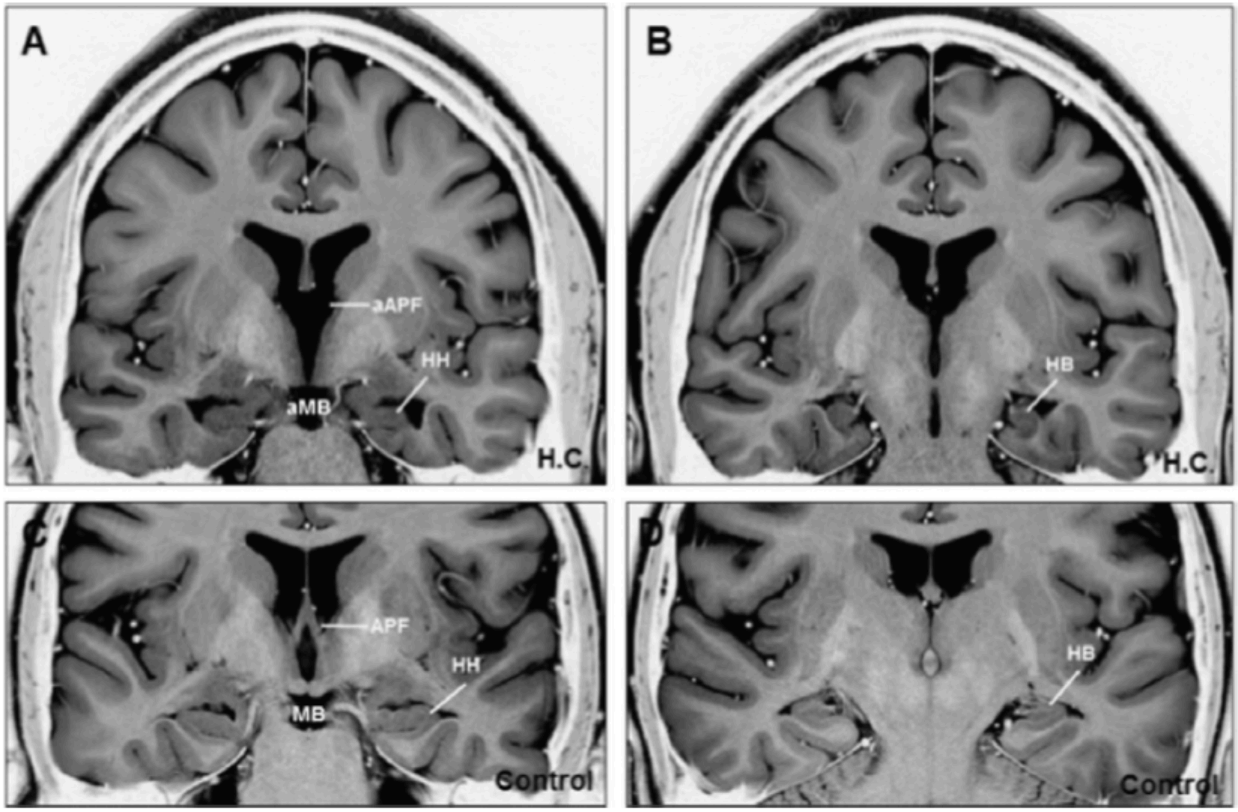


*Figure 2.1*. H.C.'s neuroimaging reproduced from Rosenbaum et al. (2014), unchanged. Figures A (H.C.) and C (control) show inverted coronal T2 images perpendicular to the hippocampus through the hippocampal head (HH). Note H.C. shows poor digitization of the HH, absence of the anterior pillar of fornix (aAPF), and absence of the mammillary bodies (aMB) compared to a control. Figures B (H.C.) and D (control) show inverted coronal T2 images through the anterior hippocampal body (HB). Note H.C. shows rounded HB compared to a control. Link to Creative Commons attribution license: https://creativecommons.org/licenses/by/4.0/legalcode

Twenty-three healthy control participants (16 women), who subjectively reported that they were free of neurological and psychiatric illness and had normal or corrected-to-normal hearing and vision, were matched in age (*M* = 28.43 years, *SD* = 4.55) and education (*M* = 16.26 years, *SD* = 2.07) to amnesic case H.C. One of these controls was H.C.'s younger sister, J.C. (26 years old, 15 years of education), who lived 23 years in the same environment as H.C. She moved to Toronto approximately one year prior to testing, but makes frequent trips back to her home environment. We also tested H.C.'s husband, J.D. (31 years old, 14 years of education), who has lived in the same city as H.C. his entire life. H.C.'s sister and husband were collectively termed "neighbourhood controls", given their familiarity with H.C.'s home neighbourhood. This study was approved by the ethics boards at York University and Baycrest Hospital. All participants gave informed written consent and were provided with monetary compensation for their time.

**Stimuli & Apparatus**

In this study, we used a Google Street View software package (designed by Dr. J. Ozubko), which includes an image downloader (gdownload), navigation paradigm (Google Street View paradigm), and route building (Gnav Route Builder). Using the gdownload software, which was written in MATLAB v7.5.0.342 and used the PsychToolbox v3.0.10, thousands of panoramic photos from real world environments were downloaded for use in the navigation paradigm. The Google Street View paradigm, also reliant on MATLAB and PsychToolbox, fulfills the Merriam-Webster dictionary definition of virtual reality[1], as it allows participants to view the virtual environment on a desktop computer monitor and navigate within the environment using keyboard controls. Keyboard controls were selected over a joystick due to limitations with

[1] Early simulated virtual reality environments were often highly stylized and constrained by technology, but advancements such as high-resolution displays and increased portability of virtual reality tools have made it easier to use virtual reality in research settings. Alongside this exponential growth, however, has come debate about what exactly constitutes virtual reality. The Merriam-Webster dictionary (2019) defines it as "an artificial environment which is experienced through sensory stimuli (such as sights and sounds) provided by a computer and in which one's actions partially determine what happens in the environment". Others have argued that in addition to interactive features (visual responses on the display in reaction to physical behaviours), virtual reality tools should evoke a sense of immersion and sense of presence.

the software system. Participants used the up button on the computer to navigate forward through the environment, and the left and right buttons to rotate their first-person view 10 degrees to the right or left. They could turn a full 360 degrees at any point. Although a sense of presence and immersion would have been increased by matching vestibular and proprioceptive cues to visual cues (e.g., by capitalizing on technology that allows one to navigate the environment by walking on a treadmill), given the relative novelty of the Google Street View paradigm and budget limitations, such considerations were outside the scope of the current project. We anticipate, however, that the Google Street View paradigm could be integrated with such technology in the future.

Familiar routes were generated using the Gnav Route Builder which allows participants to work with the experimenter to map out routes using Google maps. These participant-specific routes were then loaded into the Google Street View paradigm, allowing us to obtain outcome measures, described below, such as distance to goal location, that require the location of the end destination.

**Procedure**

Participants were tested in two separate sessions. In the first session, they filled out a Navigation Strategies questionnaire (Brunec et al., 2018), which classifies participants who tend to use a map-based navigation strategy into a “Mapping” group, and those who tend to use a scene-based strategy into a “Non-Mapping” group. Individuals in the “Mapping” group endorsed statements indicating that they picture a map when planning a route, find it easy to read and use maps, have difficulty picturing buildings along a familiar street in their minds eye, are able to take short cuts, and have a preference for providing directions in terms of map directions rather than landmarks. “Non-Mapping” individuals would more often endorse statements indicating that they picture scenes of what they would see along the way when planning a route, need to look around their surroundings when navigating, are able to very clearly picture buildings along a route, have difficulty reading and using maps, and have a preference for providing directions in terms of landmarks. This questionnaire was designed to examine whether people adopt a mapping/allocentric-based strategy when navigating or planning navigation, or whether they rely more on immersive, first-person views. It was used in the current study to characterize H.C.’s navigational strategy. It was also speculated that we might find differences in control participants’ who describe themselves as “Mapping” vs. “Non-Mapping” on the Google Street View task when navigating mirrored routes that are likely to require a coherent representation of the environment sufficient for flexible navigation.

Participants then worked with the experimenter to establish eight highly familiar routes within a well-known environment that they navigate on a regular basis. Since our interest is in remote spatial memory, the environments and routes were personalized and unique to each participant. The majority of controls navigated virtually within the Toronto or the Greater Toronto Area, as the remoteness of H.C’s home city limited recruitment of willing participants who had lived or continued to live in that city. H.C.’s sister, J.C., and husband, J.D., however, were tested on the exact same environment and, in fact, the majority of the same routes as H.C. As such, H.C.’s performance was compared to that of the full group of 23 healthy controls, and also examined more closely in direct relation to a subset of that group, her sister and husband (termed the neighbourhood controls), to ensure that potential differences in the environment did not drive results.

To ensure that participants' routes did not vary in complexity, routes were required to have at least three turns and be approximately 1.5 to 10 km in length. Participants were then asked to identify two landmarks of which they are familiar with the location, but have never purposefully travelled between, forming the basis of the required four less familiar routes. Participants were asked to identify neighbourhoods or cities with which they are unfamiliar so GPS follow-the-arrow control routes could be created in such environments.

During the second session, participants were asked to navigate routes using a novel computer paradigm that uses first-person images from Google Street View to allow participants to virtually walk through a real-world city with which they are very familiar. Developmental amnesic H.C. was asked to navigate her current environment in which she was born and raised.

Using this Google Street View paradigm, participants were asked to navigate four of the personalized highly familiar routes that they provided in the first session. They were also asked to navigate between four dyads of landmarks that they had never purposefully travelled between, but were aware of their locations (less familiar routes). While the start and end locations of the less familiar dyads were planned, the route itself was not planned out prior to navigation. Participants were reminded to navigate from one landmark to the next using at least three turns. Four of the highly familiar routes that participants provided during the first session were turned into mirrored routes so that what would normally be seen on the participants' right is now seen on the left, and vice versa (see Figure 2.2). This effectively disorients participants, requiring them to turn the opposite direction to which they are used to in order to navigate successfully along the route.


*Figure 2.2.* Example of conversion of a familiar route to a mirrored route, as seen from a survey and first-person view.

Participants were also asked to engage in four GPS follow-the-arrow control trials that provide a baseline of navigation when planning is not required (see Figure 2.3 for example). During this condition, they followed an arrow that directs them through an unfamiliar environment (established during Session 1). To ensure that participants were attending to the scenery as well as the arrow, they were asked to press a button every time they perceived that the scene had changed. Trials from all four conditions were randomly presented.


*Figure 2.3.* Example of a GPS follow-the-arrow control route.

**Analysis**

Information about whether the destination was successfully reached and parameters of navigational efficiency (number of pauses, speed of navigation, directness of travel, and number of errors) were collected for each trial and averaged for each condition. Calculation of these parameters involved collecting raw data output from the Google Street View paradigm, including the latitude and longitude of the participant at each “step” (button press) and the speed at which each step occurred. Speed could be deduced by calculating the distance between two steps divided by the duration of time between the last input (button press) and the current input. With this information, one could determine whether the participant was moving forward in a “steady” manner (5 steps in the same direction) or whether the participant stopped moving (i.e., paused). Pauses were defined as periods when individuals ceased stepping forward, looked to their left or right for any period of time, and then resumed travel in their original, pre-pause direction. During pauses, the participant could press buttons to shift their view left or right (i.e., look around), but if their view at the beginning of the pause shifted more than 60 degrees at the end of the pause, this was considered a purposeful turn, rather than a pause to look around, orient oneself, or plan navigation. The number of pauses in each trial were summed and averaged for each condition. Increased number of pauses is suggestive of more time spent reorienting or planning navigation.

Level of confidence in navigation during each condition was estimated by examining the speed of navigation, which was defined as the latency between button presses while navigating (with turns and pauses excluded). A higher average latency represents slower speed of travel, which is believed to represent less confidence in, or more cautious, travel.

The ratio of distance to target location informs how directly the participant was travelling towards the goal at any given step. Our final metric ranges from 0 to 1, with a 0 indicating direct travel towards the goal, and a 1 indicating travel in the opposite direction, directly away from the goal. Using the latitude and longitude of the destination and the participant's current location, the ratio of the distance to target location was calculated at each step to determine what proportion of the distance travelled by a step was in the direction of the goal. For example, if a participant pressed forward and took a step, travelling 10 meters forward, we then calculated how much closer the participant was to the goal after that step. If the participant was 8 meters closer to the goal, then the ratio of distance to target location was 0.8 for that step. Hence, this ratio could range from -1.0 (directly away from the goal) to +1.0 (directly towards the goal). Euclidean distance to goal calculated at each step taken within a trial (ignoring pauses and turns) was averaged, resulting in an average distance to goal for each trial. To make this metric amenable to statistical analysis, we subtracted 1 from the participant's mean ratio of distance to target location and then multiplied by -0.5. This linear transformation changed the scale, such that a 0 indicates travel directly towards the goal, whereas 1 indicates travel directly away from the goal. Looking at the average ratio of distance to target location for each step informs us as to how frequently the participant was moving towards the goal. This provides a metric of directness of travel, as participants who are taking efficient routes towards the goal should infrequently have high values for this ratio.

The number of errors for each trial was evaluated manually, with errors being defined as moving away from the goal location at any choice point or intersection. For illustrative purposes, Figure 2.4 provides an example of how errors were calculated. Figure 2.4 shows an example of a route taken by a participant with red circles indicating choice points where a decision could be made about the route. As can be seen, at most choice points, the participant was moving towards the destination, until the street labeled "H-Street". At the intersection of "F-Street" and "H-Street," the participant made an error (indicated with the orange X), choosing to continue along "F-Street" instead of turning onto "H-Street," which would have been a more efficient route; the participant effectively was moving away from the destination. At "A-Street," the participant made another error, as they continued to move away from the destination (rather than turning around to take a more efficient route). It was not considered an error at "B-Street" because at this point, the participant could reach the destination more efficiently by continuing forward, as they chose to do. Their choices past this street allowed continued efficient progression towards the goal location, until they reached the intersection of "H-Street" and "D-Street", where the participant made another error by turning left on "H-Street", away from the destination.

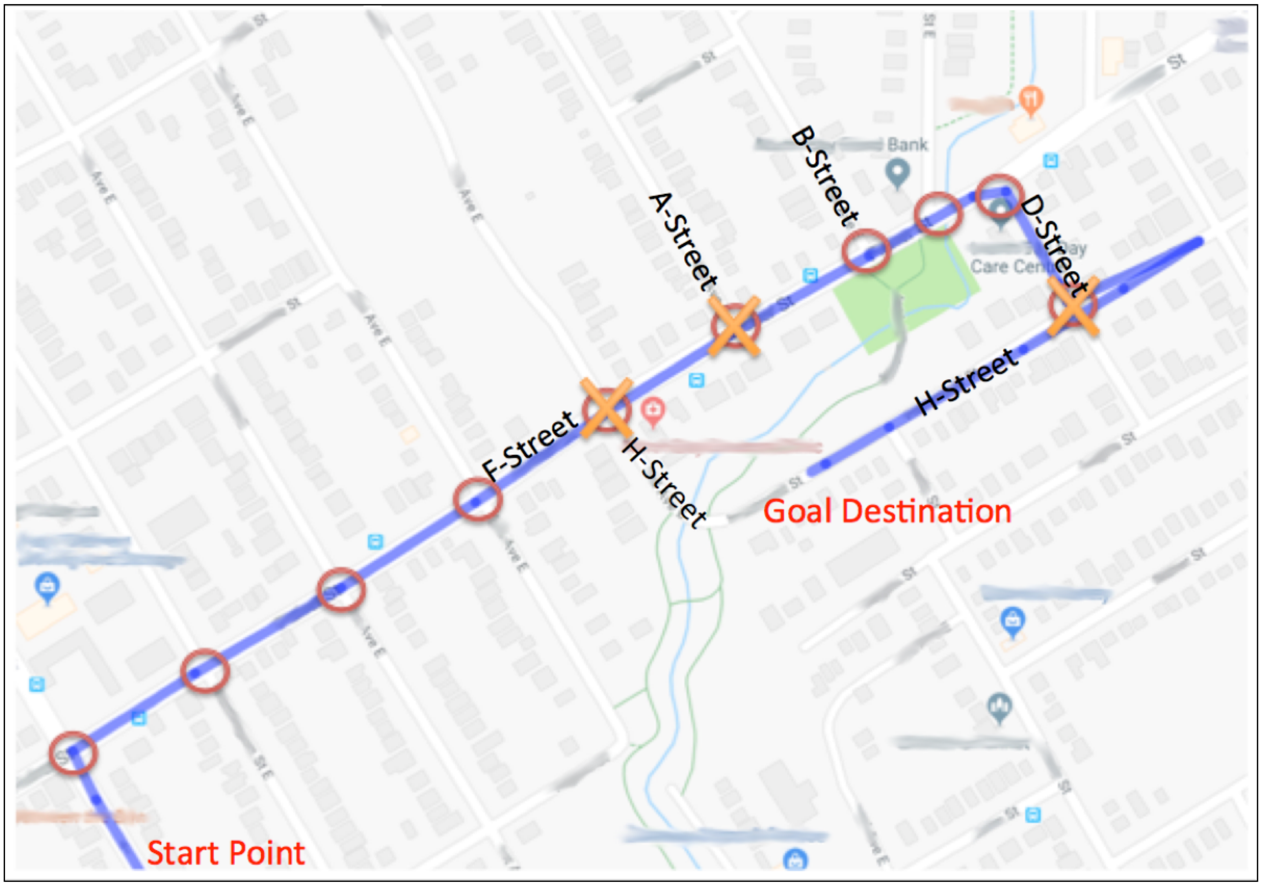


*Figure 2.4.* Illustration of error calculation. The blue line shows the path travelled by the participant while navigating between the (marked) start point and goal destination in a first-person view. Red circles represent choice points and orange Xs represent errors.

**Results**

H.C.'s performance on parameters of navigational efficiency (number of pauses, directness of travel, speed of navigation, and number of errors) was compared to that of age- and education-matched controls using Crawford and Garthwaite's (2002) modified t-test procedure, a conservative approach that allows comparison of single cases to control samples that are small to moderate in size. All analyses were tested at a significance level of $p < .05$. This procedure was also used to compare H.C.'s performance to that of the two controls that are familiar with her home environment.

Following a visual inspection of the distribution of the data, it was clear that the pauses and errors were not normally distributed. This is expected with count data and required a generalized linear model approach. As such, a Poisson regression with an exchangeable working correlation matrix was used to examine whether healthy controls' number of pauses and number of errors differed on familiar, less familiar, mirrored, and GPS control trials. Healthy controls' directness of travel and speed of navigation were analyzed using a Gamma regression with an exchangeable working correlation matrix. Again, given the non-normal distribution of the data, a classic parametric approach was deemed inappropriate. As our research questions were most concerned with performance on mirrored and less familiar routes compared to the familiar routes, significance testing between other dyads (e.g., GPS and mirror) was not completed to protect against Type I errors.

Finally, the Revised Standardized Difference Test (Crawford & Garthwaite, 2005) allowed us to examine whether H.C.'s performance on route conditions differed significantly from one another. All analyses were tested at a significance level of $p < .05$.

**Destination Reached**

Taken as a group, healthy controls were able to reach their target destinations on 98% of the familiar route trials, 90% of the less familiar routes, 86% of the mirrored routes, and 100% of the GPS follow-the-arrow control routes. H.C. was able to successfully navigate to 100% of the route destinations, in all route conditions.

**Number of Pauses**

As seen in Figure 2.5, healthy control participants had fewer pauses per trial for the GPS follow-the-arrow and familiar conditions compared to the more challenging mirrored and less familiar conditions. Compared to the familiar condition, the less familiar condition led to an additional 0.425 increase in the log of the number of pauses (*B* = 0.425, $\chi^2$ = 25.213, *p* < .001), meaning that the less familiar condition resulted in significantly more pauses than the familiar condition. Similarly, the mirrored condition resulted in an additional 0.188 increase in the log of number of pauses (*B* = 0.188, $\chi^2$ = 4.785, *p* = .029), and the GPS control condition led to a 0.403 decrease in the log of number of pauses (*B* = -0.403, $\chi^2$ = 14.790, *p* < .001) compared to the familiar condition.

Amnesic case H.C. showed a comparable number of pauses compared to healthy controls across familiar (*t* = 0.325, *p* = .748), less familiar (*t* = -0.489, *p* = .315), mirrored (*t* = 0.177, *p* = .430), and GPS control trials (*t* = -0.371, *p* = .714; Figure 2.5). This pattern did not deviate when H.C.'s performance was compared only to her sister and husband.

H.C.'s performance on the familiar route condition did not differ significantly from the mirrored (*t* = 0.249, *p* = .403), or less familiar route condition (*t* = 0.916, *p* = .185). H.C.'s number of pauses on the mirrored route also did not differ significantly from the less familiar route (*t* = 0.719, *p* = .240). The number of pauses on the GPS route did not differ significantly from the familiar (*t* = 0.702, *p* = .490), mirrored (*t* = 0.414, *p* = .341), or less familiar conditions (*t* = 0.133, *p* = .448; Figure 2.5).

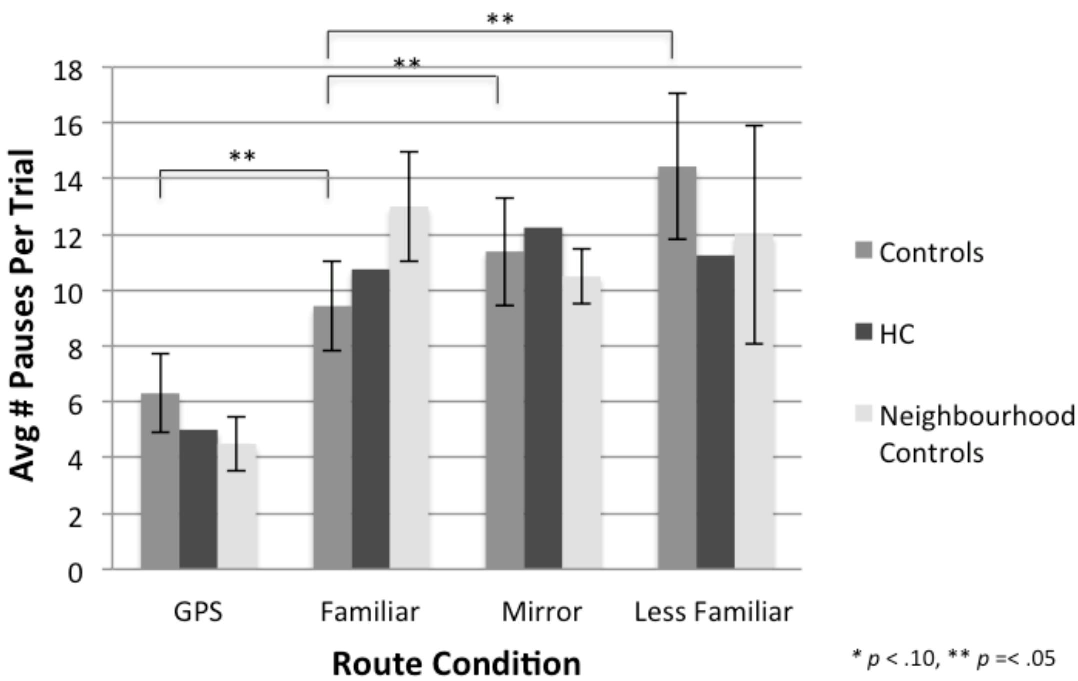


*Figure 2.5.* Average number of pauses across route conditions for 23 controls, developmental amnesic case H.C., and 2 neighbourhood controls with experience navigating H.C.'s home environment. Error bars represent a 95% confidence interval.

**Directness of Travel**

Compared to the familiar condition, control participants' less familiar condition led to an additional 0.189 increase in log of the distance to goal ratio ($B$ = 0.189, $\chi^2$ = 3.845, $p$ = .050; Figure 2.6), meaning that directness of travel was significantly worse for the less familiar condition than the familiar condition. Similarly, the mirrored condition resulted in a 0.364 increase in log of the distance to goal ratio ($B$ = 0.364, $\chi^2$ = 35.379, $p$ < .001), and the GPS control condition led to a 0.402 increase in the log of distance to goal ratio ($B$ = 0.402, $\chi^2$ = 36.776, $p$ < .001), all in comparison to the familiar condition.

H.C.'s performance on the distance to goal parameter was similar to that of healthy controls for the familiar ($t$ = -0.979, $p$ = .338), mirrored ($t$ = 0.734, $p$ = .235), less familiar ($t$ =

0.326, *p* = .374), and GPS routes (*t* = -0.392, *p* = .699; Figure 2.6). H.C.'s pattern of results was also similar to that of her 2 family members, except that her ratio of distance to goal was significantly higher on the mirrored condition (*t* = 11.304, *p* = .028), indicating less direct travel on mirrored routes compared to her family members.

Unlike controls, H.C.'s distance-to-goal ratio was significantly closer to zero on the familiar condition compared to the mirrored condition (*t* = 1.748, *p* = .047; Figure 2.6), indicating more direct travel toward the goal on the familiar routes. Although her distance to goal ratio for the familiar condition was numerically lower than the less familiar condition, this was not significant (*t* = 0.989, *p* = .167). H.C.'s distance-to-goal ratio did not differ significantly between the mirrored and less familiar conditions (*t* = 0.449, *p* = .329). Similarly, the distance to goal ratio for the GPS routes did not differ significantly from the familiar (*t* = 0.448, *p* = .659), mirrored (*t* = 0.863, *p* = .199), or less familiar conditions (*t* = 0.547, *p* = .295).

Control participants and H.C. both performed worse than expected on the GPS control route condition. Upon closer inspection, most individuals did not deviate substantially from the planned GPS route, so the higher ratio of distance-to-goal likely reflects the nature of the routes provided, rather than difficulty navigating the routes.

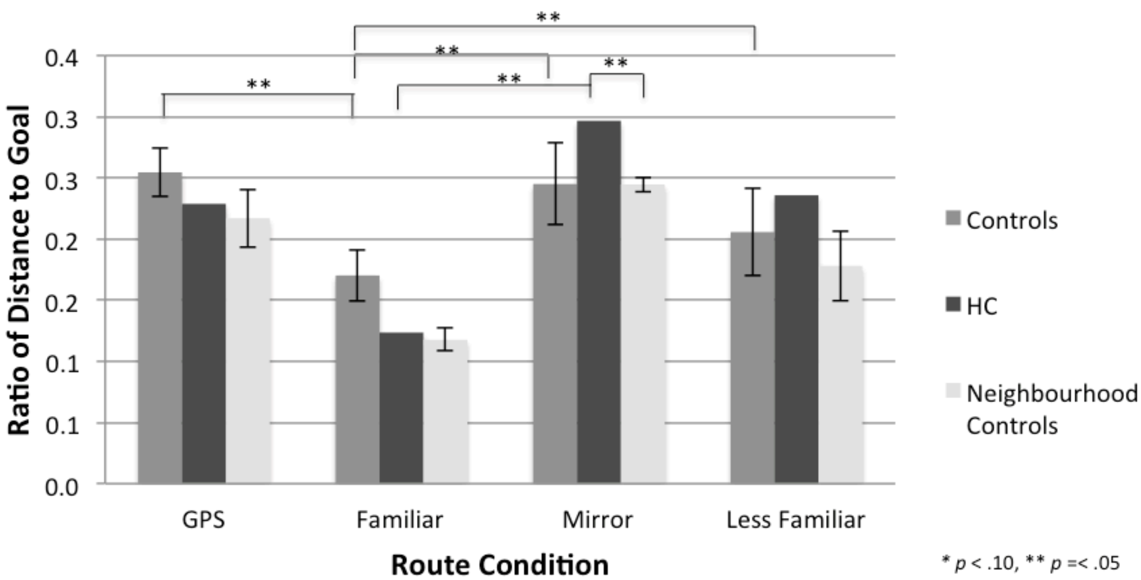


*Figure 2.6.* Directness of travel calculated using ratio of distance to goal across route conditions for 23 controls, developmental amnesic case H.C., and 2 neighbourhood controls with experience navigating H.C.'s home environment. Error bars represent a 95% confidence interval.

**Speed of Navigation**

Control participants' level of confidence in navigation was estimated by examining the average latency between button presses. Compared to the familiar condition, the less familiar condition led to a negligible 0.016 decrease in the log of reaction time ($B$ = -0.016, $\chi^2$ = 0.387, $p$ = .534; Figure 2.7), meaning that the average latency between button presses for the less familiar condition was not significantly different from the familiar condition. The mirrored condition, however, resulted in an increase of 0.108 ($B$ = 0.108, $\chi^2$ = 12.177, $p$ < .001). Thus, level of confidence in travel, as measured by the average latency between button presses, was significantly worse in the mirrored condition compared to the familiar condition. The GPS control condition led to a 0.056 increase ($B$ = 0.056, $\chi^2$ = 2.892, $p$ = .089).

H.C.'s reaction time was comparable to that of healthy controls when travelling along on familiar routes ($t$ = -0.544, $p$ = .592), less familiar routes ($t$ = -0.612, $p$ = .273), and mirrored routes ($t$ = -0.163, $p$ = .436; Figure 2.7). She was, however, significantly slower than healthy controls when travelling along the GPS control routes, which required the added task of pressing "s" when the scenery changed ($t$ = 3.10, $p$ = .005). Similar findings were obtained when H.C.'s performance was compared to her family members', except that her performance on the GPS condition was no longer significantly significant when compared just to her sister and husband ($t$ = 1.983, $p$ = .297).

Intra-individual analyses indicated that H.C.'s speed of navigation did not differ significantly across the familiar and less familiar conditions ($t$ = 0.074, $p$ = .471), or the familiar and mirrored conditions ($t$ = 0.518, $p$ = .305; Figure 2.7). There was no significant difference in H.C.'s speed of navigation between the less familiar and mirrored conditions (t = 0.431, $p$ = .336). H.C. was significantly slower, however, on the GPS condition compared to the familiar ($t$ = 4.603, $p$ < .001), less familiar ($t$ = 5.242, $p$ < .001), and mirrored conditions ($t$ = 3.675, $p$ < .001).

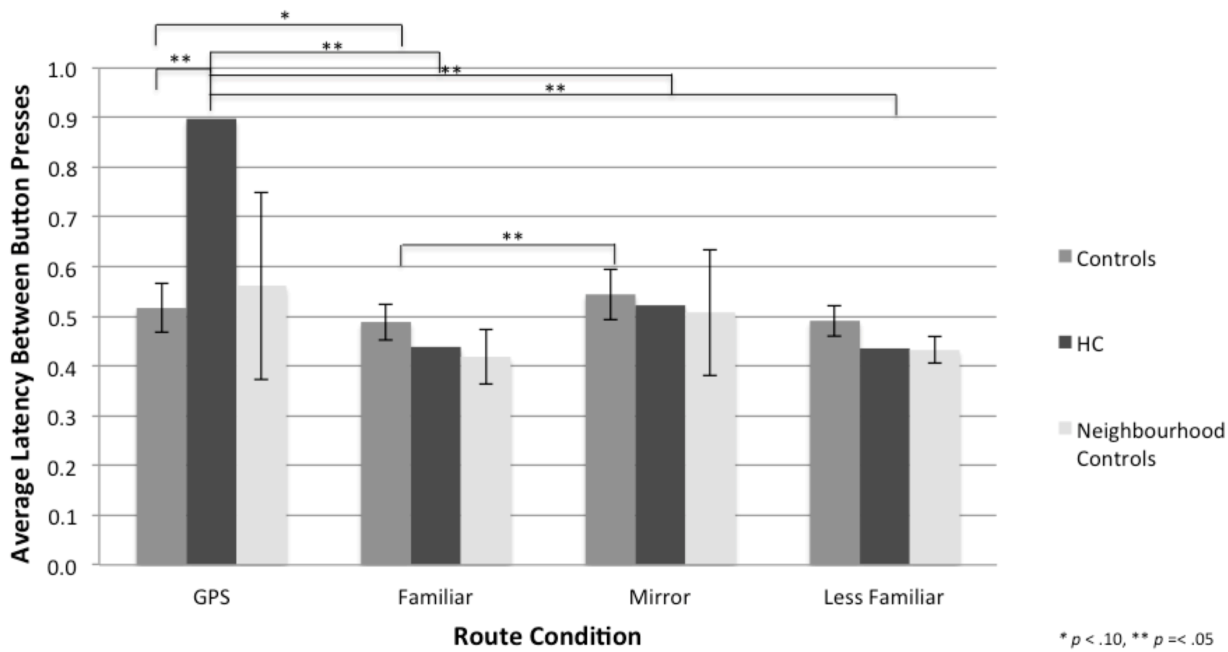


*Figure 2.7.* Level of confidence in navigation measured by average latency between button presses across route conditions for 23 controls, developmental amnesic case H.C., and 2 neighbourhood controls with experience navigating H.C.'s home environment. Error bars represent a 95% confidence interval.

**Progression Errors**

As progression errors were defined as moving away from the goal location at any choice point or intersection, they were not calculated for the GPS control route, as the route had been pre-planned by experimenters. As expected, controls' performance on the less familiar condition led to an additional 1.549 increase in the log of progression errors ($B$ = 1.549, $\chi^2$ = 13.578, $p$ < .001) and the mirrored condition resulted in an increase of 1.324 log of progression errors ($B$ = 1.324, $\chi^2$ = 31.017, $p$ < .001) compared to the familiar condition (Figure 2.8). Thus, the regression model would predict that significantly more errors are made on the less familiar and mirrored conditions than the familiar condition for control participants.

At turns or possible turning points, the number of errors H.C. made (movement away from goal location) was comparable to controls across the familiar ($t$ = -0.381, $p$ = .707), less familiar ($t$ = 0.068, $p$ = .473), and mirrored conditions ($t$ = 0.069, $p$ = .473; Figure 2.8). There were no significant differences between H.C. and her family members across conditions.

H.C. showed the expected trend of fewer errors on the familiar condition compared to the less familiar ($t$ = 0.305, $p$ = .382) and mirrored conditions ($t$ = 0.383, $p$ = .353), but this difference did not reach statistical significance. The number of errors she made on the mirrored and less familiar condition did not differ significantly ($t$ = 0.001, $p$ = .500).

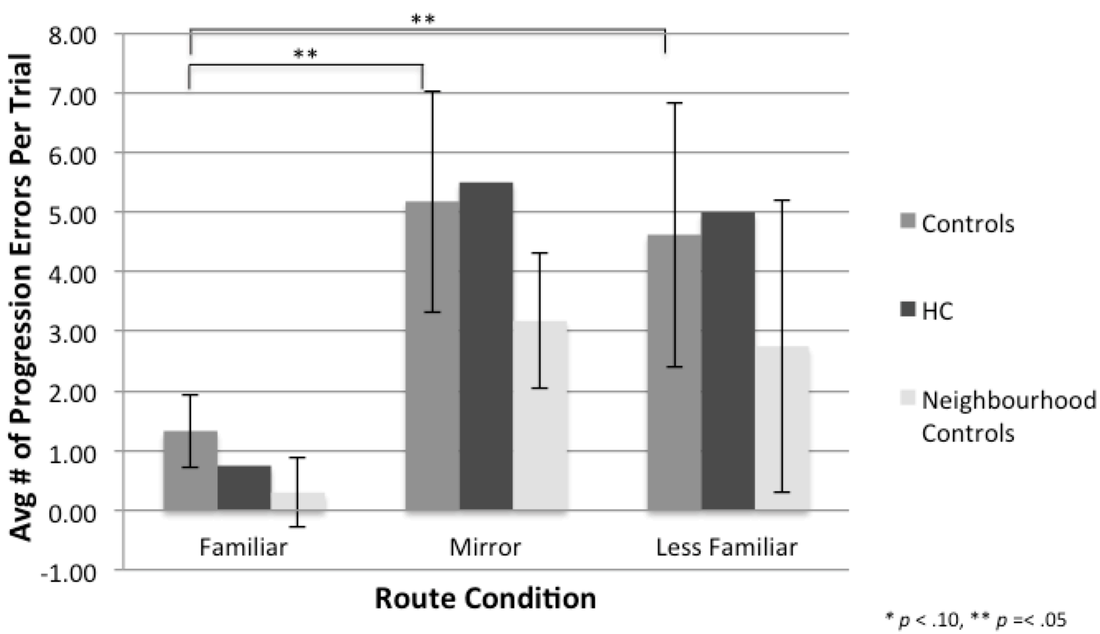


*Figure 2.8.* Average number of progression errors per trial across route conditions for controls, developmental amnesic case H.C., and 2 neighbourhood controls with experience navigating H.C.'s home environment. Error bars represent a 95% confidence interval.

**Navigation Strategies Questionnaire**

On the Navigation Strategies questionnaire, a higher, positive score on a scale of -14 to +14 means that the participant uses more of a mapping strategy, as opposed to a negative score, which suggests a non-mapping, scene-based strategy. Based on their self-report, fifteen of the twenty-three control participants were classified as using a mapping strategy. The average score for the mapping group was 6.07 ($SD$ = 2.58), and scores ranges from 2 to 9. Five control participants were classified as using a non-mapping strategy, including H.C.'s husband. Their average score was -4.4 ($SD$ = 2.41), with a range of scores between -1 to -7. Three participants earned a score of 0, including H.C.'s sister, which resulted in their not being classified as belonging to either a mapping or a non-mapping group. Performance did not differ by strategy group on number of pauses ($\chi^2$ = 0.290, $p$ = .865), reaction time ($\chi^2$ = 4.080, $p$ = .130), directness of travel ($\chi^2$ = 0.4.983, $p$ = .083), or progression errors ($\chi^2$ = 1.817, $p$ = .403). On the Navigation Strategies questionnaire, H.C.'s self-report resulted in a score of -5, which means she used a non-mapping strategy. When planning a route, she reported picturing scenes of what she would see along the way. She also reported picturing herself travel a route using a street-level view rather than a bird's eye view, and said that she would be more likely to give directions to a friend using landmarks rather than map directions. She said that she prefers to navigate using a list of directions rather than a map, and she reported often using landmarks to orient herself when navigating.

## Discussion

The purpose of this study was to substantiate findings that representations of environments travelled over many years can develop and be maintained outside of the hippocampus, and investigate whether these representations are sufficient for flexible navigation. Both amnesic case H.C. and healthy controls were asked to navigate very familiar routes, less familiar routes, mirrored routes and GPS-control routes. As expected, H.C. was able to navigate very familiar routes as well as healthy control participants, providing further evidence that representations of frequently travelled environments can form in an individual with atypical hippocampal development. While H.C. showed greater difficulty with the less familiar routes compared to the familiar routes, her performance did not differ from that of controls in the less familiar routes condition. H.C. performed similarly to controls on the GPS-control route condition across all navigational parameters, except speed of navigation, where she was significantly slower than the large sample of controls, but not the two controls familiar with her neighbourhood. This difference may reflect difficulties in task switching or working memory. H.C.'s directness of travel on the mirrored routes was significantly worse than that for the two controls familiar with her home environment, though she did not differ from the larger control sample.

H.C.'s ability to navigate very familiar routes shows that representations of frequently travelled environments can form despite an atypically functioning hippocampus. The nature of these representations, however, remains unclear. It may be that she has created a mental representation of her environment that is akin to a cognitive map, which can be used to navigate flexibly, and is traditionally believed to require the hippocampus. Given the frequency with which familiar routes are travelled, however, successful navigation of these routes also could have been achieved without the support of the hippocampus, using habit memory. The unfamiliar condition was designed to address this; if she was able to navigate between landmarks within her home environment that she had never purposefully travelled between before, we expected that her intact performance could not be fully be explained by habit. H.C.'s ability to navigate less familiar routes comparably to control participants suggests that she may have access to a representation of her home environment that is somewhat flexible in nature. It is important to note that H.C. worked with the experimenter to come up with landmark pairs between which she had never purposefully travelled. As such, it is possible that she underestimated the frequency with which she travelled between the landmarks, and that that the routes were sufficiently rehearsed to support performance.

The GPS control routes required participants to press the “s” button when they perceived that the scene had changed, ensuring that their focus was not solely on the arrow at the top of the screen that pointed towards the goal location. Subjectively, the experimenter noted that H.C. seemed to be more fixated on accurately documenting scene changes than healthy controls. She also appeared to have more difficulty switching between the two tasks (pressing “s” for scene change and pressing arrows to navigate), which suggests that her slower navigation on the GPS-control routes may be more related to a task-switching or working memory difficulty rather than a spatial deficit per se.

H.C.’s overall intact performance in the mirrored condition was somewhat surprising in the context of previous findings of inflexible representations of her home environment (Rosenbaum et al., 2015). It may be that navigating a mirrored environment may require a different type of flexibility than that needed when navigating a blocked route or remapping an environment. This possibility is discussed in detail below. Although H.C.’s mirrored route navigation was generally indistinguishable from the larger control group and she was able to reach all mirrored route destinations successfully, H.C. showed the greatest relative difficulty when directness of travel was taken into account, which is perhaps not surprising given past evidence that she was unable to provide the most efficient detour on a blocked route task

(Rosenbaum et al., 2015). It may be that directness of travel would be the most sensitive measure to capture differences in navigating in studies moving toward, and that H.C.'s performance on this measure would be much worse than controls when challenged to find the most direct detour on a blocked route task.

**How Might Spatial Representations of Environments Form Without a Typically Functioning Hippocampus and the Full Support of Episodic Memory?**

Using mental navigation tasks (Rosenbaum et al., 2015) and the immersive Google Street View virtual navigation paradigm employed in this study, we have demonstrated that spatial representations of frequently-travelled environments can form in H.C., an individual with atypical hippocampal system development, yet the nature of the representations and mechanism by which this occurs remains unclear. Previous research with adult-onset amnesic cases using mental navigation tasks provides evidence that the hippocampus is not required for retrieving a schematic, map-like representation of environments learned prior to the onset of their amnesia. These results are consistent with the Trace Transformation Theory, as the environments that are recalled were encoded pre-injury or illness, with a typically functioning hippocampus and intact episodic memory. Given that H.C. has never had a typically functioning hippocampus or episodic memory system, reconciling her intact performance assessing distance and direction on mental navigation tasks and navigating using the Google Street View paradigm is more difficult. The hippocampus is well known to be required for learning new environments, which has received support from studies of adult-onset amnesic cases, neuroimaging studies, and non-human animals. As previously discussed, developmental amnesic cases also are unable to form new spatial representations, at least after minimal exposure (King et al., 2002; Vargha-Khadem et al., 1997).

Perhaps H.C was able to learn the spatial layout of her home environment over many years, akin to how H.C. and other developmental amnesic cases have been able to gain semantic knowledge, with a substantial amount of repetition. As semantic memory is relatively preserved in individuals with selective hippocampal damage (Baddeley, Vargha-Khadem, & Mishkin, 2001; Vargha-Khadem et al., 1997; including H.C.: Rosenbaum et al., 2011), Gardiner and colleagues (2008) attempted to teach new semantic facts to developmental amnesic case, Jon, to gain a better understanding of the circumstances required for acquisition of semantic knowledge. They found that Jon had difficulty retaining facts during the acquisition trials and showed inter-trial forgetting, which they took as evidence that episodic memory facilitates the acquisition of semantic knowledge. He was, however, able to retain new semantic facts with substantial repetition. As Gardiner and colleagues demonstrated with developmental amnesic case Jon, semantic knowledge can be acquired without the full support of episodic memory, albeit with laborious training. Our results suggest that coarse knowledge of environments can also be acquired without the full support of episodic memory, with extensive exposure. In this way, the environment is "semanticized", where a schematic, gist-like representation may form that is sufficient for navigation. It would appear that H.C. has acquired a representation of her home environment that is sufficient for navigation, but it is unclear how long it took to form the representation or how substantially this representation may have changed over time. Future studies could aim to identify the minimum amount of time needed to create a spatial representation of an environment.

We cannot rule out the possibility that H.C.'s residual hippocampal tissue may be adequate for navigating within her home environment. While it is plausible that the remaining tissue in H.C.'s hippocampi is viable and sufficient for learning new spatial relations and developing representations of space sufficient for navigation, we view this as unlikely given that H.C's residual tissue does not support episodic memory. An experimental design similar to Gardiner and colleagues' (2008; described above) that charts the acquisition of spatial knowledge (rather than semantic knowledge) in developmental amnesia may provide insight into this possibility. If H.C. showed increased inter-trial forgetting and poor retention of spatial facts during acquisition trials, this could be interpreted as evidence that the residual hippocampal tissue is not functioning optimally, and that alternate explanations of acquisition, such as the "semanticization" of the environment, may provide a better explanation for the acquisition of spatial knowledge. Furthermore, fMRI could examine the role of the hippocampus during recollection of a spatial representation to determine which brain structures are active when navigating familiar environments.

It is clear that H.C. has been able to form a representation of her home environment over many years of travel, but we cannot state with certainty that this representation resembles a flexible, cognitive map, or is topological, where navigation is relational between points of interest but precise metric information is not used. It is possible that H.C. may have been able to navigate familiar routes within her home environment using a non-hippocampal dependent strategy, relying instead on the caudate nucleus that is involved in habit memory.

The fact that she was able to navigate between landmarks within her home environment that she had never purposefully travelled between before suggests that her intact performance may not fully be explained simply by habit, and that she could have relied on a cognitive map. Alternatively, H.C.'s successful navigation of the less familiar routes also could have been accomplished by extrapolating the relations between landmarks that she had never purposefully travelled between (e.g., A and C) using existing knowledge about spatial relations between overlapping landmark pairs (e.g., A-B and B-C). For example, H.C. said that she had never purposefully travelled between two specific restaurants, but she could have been familiar with the relationship between both restaurants and her in-laws' house, which she passed along her route. In this way, it seems that H.C.'s representation of her home environment can be used somewhat flexibly, as she is able to navigate between two landmarks that she reports she has never travelled between. However, it is possible that the nature of her representation may not be a cohesive cognitive map that allows for unlimited flexibility, but instead could be a topological representation formed by overlapping frequently travelled routes. Knowledge of overlapping routes could permit some flexible navigation, but only along known, overlapping routes. Travel along such well-learned routes may be habit-based, and thus successful navigation on the unfamiliar trials might require only habit memory and the knowledge that the two routes overlap. A route-based approach such as this is also consistent with H.C.'s self-reported "non-mapping" strategy.

**Flexible Navigation: Reconciling Discrepancies Between Mental Navigation Tasks and Virtual Reality**

H.C. previously drew sketch maps that had disjointed features, and, although she was able to navigate to a goal destination on a blocked route task, she was unable to do so using the most efficient route (Rosenbaum et al., 2015). Taken together, this hinted towards an inflexible and incoherent representation of her home environment. While H.C.'s intact performance on familiar routes in this study was in line with expectations, her ability to successfully navigate 100% of the mirrored routes similarly to controls was unexpected, as such routes were designed to cause disorientation and require flexibility to solve. Her ability to navigate the mirrored routes as well as healthy controls contradicts the mental navigation findings, and suggests that

H.C. does have access to a flexible representation of her home environment. What might explain H.C.'s intact performance on the mirrored routes?

As H.C. was tested on the mental navigation tasks in 2010, 6 years prior to her being tested on this study, her intact performance across all Google Street View route conditions could reflect an improvement in her spatial representation of her home environment. As described above, individuals with amnesia can acquire semantic knowledge (and, it would seem, coarse, gist-like spatial knowledge) over an extended period of time. Six years may have provided H.C. with a sufficient amount of exposure to form a more coherent representation of space that can be used flexibly. Within this time, she may have had more experience to areas that she was previously less familiar with, and with ample exposure, gist-like representations of those areas could have formed that would have enabled successful navigation on the less familiar routes. During the 6-year delay between testing, H.C. also may have travelled between well-known routes, which would encourage the formation of a cohesive representation of space. Indeed, within this period, H.C. moved from her childhood neighbourhood to an apartment and then to a house within the city core. When H.C. and her husband moved into their new house, they travelled routes between her workplace and her new home, and her apartment and her new home multiple times, so as to help H.C. better orient her new house within her familiar environment. Both H.C. and her husband felt that this exercise was useful. H.C. and her husband reported that H.C. is able to travel between her current house, which she's lived in for 3.5 years, and multiple other landmarks, including her childhood home, her place of work, the movie theatre, and various restaurants and stores. H.C. and her husband's subjective reports were corroborated with objective results from this study, as H.C. was successfully able to navigate between her new home and other landmarks successfully. This would suggest that she was able to either learn new routes within this three year period, and/or was able to successfully orient her new home within a previously-formed cognitive map, allowing her to navigate flexibly.  It is important to note that during these years, H.C. spent more time driving and actively engaging in her home environment, which has been associated with the development of an in-depth cognitive map that can be used for navigation (Maguire, Woollett, & Spiers, 2006). It may be that the years she spent driving were more influential and allowed for faster acquisition of spatial knowledge.

The nature of the tasks themselves also could have contributed to H.C.'s intact performance on the mirrored route condition. For the sketch map task, she was required to conjure up a representation of space, without any cues except for the names of the boundaries of the environment. H.C.'s inclusion of significantly fewer details on her sketch maps and difficulty accurately sequencing more than two landmarks that were close in proximity to one another along a route hinted towards an impoverished representation of her home environment that lacked in richness and detail. The Google Street View task, however, provides visual cues in the form of landmarks, roads, textures, and other environmental features that may support flexible navigation. It may also allow access to relational information among landmarks and the geometry of space that may make it easier to estimate traversed distance. It is possible that using an immersive virtual reality tool provides more details or cues that can be used to navigate, which H.C. has difficulty conjuring up in her mind's eye. It is uncertain whether a detailed representation of her home environment fails to exists, or whether she just has difficulty accessing it, however we view the former as more likely given the parallels drawn between episodic memory and detailed representations of space. As the provision of details in

Google Street View may have aided navigation, further examination of the integrity of detailed representations of H.C.'s home environment may further illuminate these results.

It is possible that, despite having difficulty on several of the mental navigation tasks, H.C. was able to navigate within the immersive virtual reality task because the visual input and immersion may lend itself to habit or procedural memory. In studies looking at skilled tool use, Fernandes, Park, & Almeida (2017) found that particular elements of the task (e.g., retrieving attributes of the tool and its function) required declarative memory, which relies on the medial temporal lobe, whereas skilled performance involving actual use of the novel complex tools is mediated in part by the motor procedural memory, which relies on the basal ganglia. It may be that successful performance on mental navigation tasks requires the hippocampus because the environment must be conjured up in the participants' minds eye, but with additional visual and motor cues, provided by the virtual reality task, hippocampal-independent habit memory is sufficient for successful navigation.

The discrepant mental navigation task and Google Street View paradigm results suggest that, although mental navigation tasks may be less ecologically valid, they may be more sensitive to deficits in spatial memory found in developmental amnesia than immersive virtual reality tasks, at least in the context of how they were used in this study. While this may be the case, it is also possible that subtle deficits could be identified using immersive virtual reality tasks that incorporate conditions that are more challenging than the mirrored condition. With ongoing technological advances, this becomes increasingly more feasible. For example, future work could test H.C. and healthy control participants on conditions where landmarks central to navigation are removed from Google Street View. This may be enough to disorient H.C. and further our understanding of well-travelled environments in developmental amnesia.

Although the mirrored condition was designed to elicit disorientation, similar to what was seen in Winocur and colleagues (2005) study with rats, it does not require remapping or reconfiguration in the traditional sense, which are known to be dependent on the hippocampus. While we can speculate about hippocampal involvement in such a condition, we cannot rule out the possibility that a non-hippocampal-dependent strategy can be used to successfully navigate the mirrored routes.

Reorientation is traditionally believed to involve re-establishing a sense of one's position within the environment (Vieites, Nazareth, Reeb-Sutherland, & Pruden, 2015) or recalibrating egocentric knowledge using allocentric knowledge (Sutton & Newcombe, 2014). As such allocentric knowledge has long been believed to be reliant on the hippocampus, we anticipated that the mirrored route would require the hippocampus. External cues can help one to regain their bearings when their internal sense of direction is disrupted (Keinath, Julian, Epstein, & Muzzio, 2017), as it is in the case of this study's mirrored route condition. Successful navigation of the mirrored route condition, however, may not entail traditional reorienting. Whereas traditional reorientation involves recalibrating your position within an unchanged environment, the mirrored condition involves navigating a changed (mirrored) environment. While the distance between landmarks remained consistent in the mirrored condition, the direction of travel flipped. An allocentric or map-like representation of the environment is not sufficient to reorient oneself because the environment is mirrored. The mirrored condition, however, can be solved by evoking a new rule: Turn the opposite direction from what you would normally turn. In this sense, successful navigation may require an allocentric or map-like representation of the home environment, that may be dependent on the hippocampus, as well as the knowledge of this new rule, which allows for one to adapt their typical egocentric frame of reference, that is, where one would normally turn left at a particular landmark, they will now turn right.

External changes that occur when alterations are made to an animals' surrounding or when it is moved to a different environment lead to the reorganization of the ensemble of place cells in the hippocampus that represent the position of the animal, termed "remapping" (Latuske et al., 2018). When "global remapping" occurs, the activity of a particular place cell that is observed in two different environments is not correlated and different ensembles of place cells result in different internal maps of the environment (Latuske et al., 2018). The mirrored condition in this study would not constitute global remapping, as many of the cues in the environment remained unchanged.  It may be more in line with "partial remapping", which occurs when only some of the local environment cues are changed that affect the geometry or context of the environment (i.e., the environment is not substantially different; Latuske et al., 2018). We are unaware, however, of studies that use mirrored environments to examine hippocampal remapping. There is evidence that well-known hippocampal maps can be flexible and withstand minor changes in distance between landmarks or cues (Fenton, Csizmadia, & Muller, 2000), but to our knowledge it is unknown whether they can withstand a reversal of direction, as seen in this study.

Given that the mirrored condition may represent some form of partial remapping and a successful strategy may combine a hippocampal-dependent, allocentric representation of the environment with knowledge that ones' movement within the environment will require turning the opposite direction compared to normal, we anticipated that the mirrored condition would require the hippocampus. That being said, if a schematic representation of space could exist outside of the hippocampus, then that representation plus the knowledge of the new rule may enable successful navigation, even in individuals with hippocampal compromise. Alternatively, since the mirrored routes were essentially familiar routes that were flipped, it is possible that these trials could be successfully solved using a hippocampal-independent, habit-based strategy together with acquisition of this new rule. In hindsight, the mirrored condition may not have been the best choice to explore H.C.'s ability to navigate flexibly within her home environment. Instead, a blocked-route task may be more appropriate to answer this question and should be explored in a future study.

**Limitations**

One of the major limitations of this Google Street View study is that movement through the environment was generated using computer keys, which reduces validity and generalizability, and is not optimal for perceiving the amplitude of turning movements (Chance, Gaunet, Beall, & Loomis, 1998). Furthermore, given that the virtual reality stimuli is created panoramic photos from Google Street View, they do not present stereoscopically and do not provide three-dimensional information that could be used to aid in the estimation of distance and direction. Navigation is complex and involves much more than just visual input. Vestibular, proprioceptive, auditory and somatosensory information is also processed and integrated during navigation (Ekstrom, Arnold, & Iaria, 2014). Although visual cues are thought to be most informative when processing large-scale space, proprioceptive information has been found to increase the accuracy of participants' visual perception of path length, even when the proprioceptive information was incongruent with visual cues (Sun, Campos, & Chan, 2004). While desktop virtual navigation of a real-world environment is more ecologically valid than mental navigation tasks, it fails to allow the participant to utilize and integrate information obtained outside of the visual domain; information that may assist participants during navigation of virtual reality environments. Due to budgetary constraints and because the Google Street View paradigm was novel when this study first began, this study did not incorporate more immersive technologies, such as larger visual displays, head tracking devices, kinetic movement sensors, or treadmills/bikes, that would have enabled participants to interact more naturally with the environment and increased ecological validity and generalizability. Large advances in technology have made testing participants on a more immersive paradigm more practical and economically feasible. Growth has been exponential. For example, Roupé, Bosch-Sijtsema, & Johansson (2013) recently capitalized on the XBOX 360 Kinect sensor system to create an interactive navigation interface for virtual reality that uses the human body. In future studies, we plan to work with collaborators in Computer Science and Visuomotor laboratories to build a more immersive and ecologically valid Google Street View paradigm. It will be important, however, to weigh the added demands on participants that arise when mobility is necessary to complete the task. Adding sensory-motor information requirements for walking during navigation can put elderly or brain-injured subjects in a double task situation, increasing cognitive demands and therefore reducing performance. Therefore, when future researchers create more ecologically valid tasks, they should carefully consider whether doing so increases cognitive demands, which might confound the results. An example of how increased demands can impact performance in cognitively compromised individuals can be found in this study, where H.C. seemed to have difficulty switching between navigating the GPS routes and pressing the “s” button to indicate a scene change. Individuals with neurological compromise may perform poorly not because of the navigation component, but due to difficulties with multitasking.

Unlike examining participant performance in new environments, testing participants on environments that are well known to them presents a unique challenge, as each participant required their own personalized routes within a well-known environment. Given our investigation was of environments traversed over many years, it was very difficult to use the same routes for multiple controls. We were fortunate that H.C.'s sister and husband had experience navigating many of her familiar routes, which allowed us to test H.C. and her family members on most of the same routes. Given the individualized nature of the task, another limitation of this study was that the length of time spent generating familiar routes with the participant (approximately 2-3 hours) and preparing the stimuli for each participant (approximately 5 hours) was substantial. The lengthy first session combined with a 4-5 hour second session, where participants were tested on personalized routes for all four route conditions, made this a particularly onerous study for participants and not conducive to working with populations that tire easily. While much can be gained from virtual navigation of a real world environment, methods in the future should be altered so as to reduce the burden on participants.

Given the personalized nature of the task, testing participants on familiar routes required that participants provided a verbal description of familiar routes, with an overhead map available for reference, during the first session. This had the potential to prime participants for navigation of the route in the subsequent session and it is possible that participants could have been relying on the description they gave or envisioning the overhead map when they navigated from a first-person view using Google Street View. This possibility was viewed as unlikely, as H.C. was tested 3 months after her first session and most participants were tested at least one month after the first session, based on their availability.

### Summary

To summarize, the first study of this dissertation used a virtual reality paradigm that allows for navigation of real-world environments, with Google Street View as a platform, to substantiate findings that spatial representations of extensively travelled environments can exist in a developmental amnesic case, H.C., who experienced atypical development of her hippocampal system and has impaired episodic memory. Importantly, H.C. was able to successfully navigate familiar routes that had been mirrored, a condition originally designed to require flexibility and reconfiguration or remapping of the familiar environment, potentially taxing hippocampal function. Overall, the results suggest that with extensive experience, representations of well-known environments may exist independent of the hippocampus and may be used flexibly. These results seem to be at odds with H.C.'s previous incoherent sketch maps and generation of inefficient detours on a blocked route task (Rosenbaum et al., 2015). One possibility, tested in Study 2, is that the 6 years between testing sessions that included active driving experience within the environment was sufficient for forming more flexible representations of H.C.'s home environment. Alternatively, it may be that immersive navigation provides the additional visual cues required for flexible navigation, which H.C. has difficulty conjuring up in her own mental representations, or that H.C. was able to navigate the mirrored routes using a hippocampal-independent habit-based strategy, combined with knowledge that she must act against her instincts and adapt their typical egocentric frame of reference.

# CHAPTER 3

## Study 2: Do representations of frequently travelled environments improve with time and experience in developmental amnesia?

In the previous experiment, I showed that developmental amnesic case H.C. was able to navigate familiar, less familiar, and mirrored routes in her home environment as well as 23 age- and education-matched healthy controls. These results held when her performance was compared only to her sister and husband, who shared knowledge of the same home environment and most of the same routes. Although H.C. was able to navigate to the goal destination on all conditions, she took less direct routes in the mirrored condition compared to her sister and husband, which is in line with previous findings on a blocked route mental navigation task (Rosenbaum et al., 2015). Nonetheless, it is still the case that H.C. was otherwise able to navigate similarly to controls on the mirrored route task, which was designed to elicit remapping or reorientation of the familiar environment and depend on hippocampal function. Several explanations for H.C.'s seemingly intact performance on the mirrored condition were described above, including: H.C.'s residual hippocampal tissue may have been sufficient for flexible navigation; H.C. did not need to conjure up a detailed representation of the environment as visual cues were provided during dynamic navigation, which may have improved her ability to navigate flexibly; the transformation involved in the mirrored condition may not have involved remapping and reconfiguration in the traditional sense, and therefore may not depend on the hippocampus; and with more time and exposure the representation of her home environment, perhaps learned in a similar way as semantic information, may have become more coherent and therefore more flexible. The latter possibility is explored in the current study.

Developmental amnesic cases show a pattern of impaired episodic memory in the context of intact semantic memory (Vargha-Khadem et al., 1997). Gardiner and colleagues (2008) demonstrated that developmental amnesic case Jon was able to learn some new semantic facts after three testing sessions that occurred in intervals of 6-8 weeks and consisted of 6 acquisition trials. While he required greater exposure to the study material than control participants and failed to recall more than 16 of 24 facts even with this additional exposure, he was nonetheless able to acquire new semantic knowledge (Gardiner et al., 2008). Our previous work with H.C. using mental navigation tasks (Rosenbaum et al., 2015) and the Google Street View paradigm described in the previous chapter demonstrated that representations of environments can form with extensive time and exposure, but the nature and extent of those representations is unknown. To date, no studies have formally examined whether spatial memories can be accrued in a comparable way to semantic facts, and, if this is possible, how much time and exposure would be required. Given that spatial representations require the integration of multiple pieces of information, one might predict that learning the layout of an environment would take substantially longer than learning a single fact. Designing a spatial memory study analogous to Gardiner and colleagues' study (2008) that takes into account the complexity involved in learning large-scale spatial memory would be time-consuming and challenging.

In this chapter, we report results from the re-testing of H.C. on mental navigation tasks 8 years after she was initially tested by Rosenbaum and colleagues (2015). Results from H.C.'s first testing session revealed that she was able to accurately identify landmarks and estimate distance and direction on vector mapping, distance judgments, and proximity judgment tasks, suggesting that over many years she formed a representation of her home environment

(Rosenbaum et al., 2015). This representation, however, seemed to be inflexible and lacking in detail, as evidenced by her impoverished and fragmented sketch maps, difficulty accurately placing and sequencing landmarks that are in close proximity to one another, and failure to provide the most efficient detour on a blocked route task (Rosenbaum et al., 2015).

While the current study cannot speak to exactly how much time and exposure is required for an individual with atypical hippocampal system development to *form* a representation of a large-scale environment, it will provide insight into whether such representations continue to improve with time. This study may also provide an understanding of why H.C.'s performance was largely indistinguishable from that of controls on the challenging mirrored route condition of the Google Street View paradigm reported in Chapter 2, which was administered 6 years after she was first tested on mental navigation tasks. There is evidence that H.C. can form spatial representations of environments that are coarse and inflexible, and it is likely that the formation of these representations of space required extensive exposure and/or time (Rosenbaum et al., 2015). As such, it would stand to reason that H.C.'s representation of her home environment would improve over the course of 6-8 years.

If improvement is seen, we can examine more closely what types of information about the environment change over time. For example, with additional time and exposure H.C. could have formed a more flexible representation of her home environment, which could explain the discrepancy between her intact Google Street View performance in 2016 and the incoherent sketch maps and poor performance sequencing landmarks demonstrated in 2010 (Rosenbaum et al., 2015). Conversely, one might predict that H.C.'s representation of her home environment may not gain flexibility as H.C. subjectively reported using a non-mapping strategy during navigation (see Chapter 2). It is also possible that over the course of many years, H.C.'s representation of space has come to include more detailed, perceptual information that may or may not be relevant to navigation. If this is the case, we may see more detail in her sketch maps. By re-testing H.C. on mental navigation tasks, we can examine whether frequent navigation over 8 years benefits spatial memory for large-scale environments in the face of hippocampal compromise and gain insight into the nature of such (if any) improvements.

To anticipate, we found that H.C.'s performance did not improve on any of the mental navigation tasks, and was qualitatively worse on the blocked route task. As a follow-up, the possibility that a retrieval deficit impeded performance was explored by re-testing H.C. on the landmark localization task while providing maps with increasing levels of support.

## Methods

### Participants

H.C. (previously described) was 30 years old when she participated in this study, which took place in April 2018, two years after the Google Street View study described in Chapter 2 of this dissertation, and 8 years after she was originally tested on mental navigation tasks (Rosenbaum et al., 2015). She received her driver's license at the age of 17. Soon after she was first tested on the mental navigation tasks in 2010, she moved to an apartment in the downtown city core. Although the primary impetus for this study was to examine differences between H.C.'s current and past performance on mental navigation tasks, for comparison purposes, we also compared H.C.'s performance to the previously reported results from the 6 controls that were tested in the original study (Rosenbaum et al., 2015; mean age = 26.5, *SD* = 12.34; mean education = 14, *SD* = 1.79). This study was approved by the ethics boards at York University and Baycrest Hospital. All participants provided informed written consent and were provided with monetary compensation for their time.

**Materials and Procedure**

H.C. was re-tested on a set of mental navigation tasks that has been used extensively in previous research to assess spatial memory for environments learned long ago (Herdman et al., 2015; Rosenbaum et al., 2015; Rosenbaum et al., 2000). H.C. was re-tested on tasks based on two environments that are each approximately 6 $km^2$ – the neighbourhood that she grew up in and resided in until 2010, and the adjacent downtown city core, where she has since lived. Due to time constraints, H.C. was tested on a subset of the original tasks. She was re-tested on those tasks on which she previously showed a deficit in order to address the question about improvement over time. Stimuli were kept consistent whenever possible. The tasks were completed in the following order:

**Sketch mapping.**

H.C. was asked to draw a detailed map of the neighbourhood that she grew up in as accurately as possible, including as many of the landmarks and streets as she could think of, on an 8.5 x 11-inch sheet of white paper that was marked only with imperial and metric scales. Prior to beginning, she was directed to attend to the scales and was provided with the names of the streets, railway tracks, or body of water that made up the northern, eastern, southern, and western boundaries of the environment. This process was repeated for the downtown city core environment that is adjacent to her childhood neighbourhood, and in which she has resided for the past 8 years.

The number of street segments and landmarks in her childhood neighbourhood and her current downtown neighbourhood were calculated based off a modified version of Blades (1990) sketch map information content (as used in Rosenbaum et al., 2015). Street segments were defined as segments of streets, roads, or transit passages that were attached on at least one end to a landmark or neighbouring street segment, and could be named or unnamed. Landmarks were functionally relevant and/or easily identifiable static structures. The number of landmarks and number of street segments were summed across both environments to create a "Landmark Total" and "Street Segments Total" score, which were then summed to create a "Details Total" score. The coherence of the overall configuration of each map was also noted.

***Landmark localization.***

For this task, H.C. was asked to mark the locations of ten landmarks within her childhood neighbourhood as accurately as possible on an 8.5 x 11-inch sheet of white paper that was marked with the streets that made up the boundaries of the environment and both imperial and metric scales. This process was repeated for the downtown city score environment. The same ten landmarks from each neighbourhood were used at Time 1 (2010) and Time 2 (2018).

Landmark localization error for each landmark was calculated as the absolute linear distance in kilometers between H.C.'s response and the actual placement of the landmark. A mean landmark localization error was calculated by averaging the error from each trial.

***Landmark sequencing.***

This task spanned both the downtown core environment and H.C.'s childhood neighbourhood. Consistent with the testing that occurred 6 years ago, H.C. was provided with randomly ordered photographs of well-known landmarks from both environments. In Rosenbaum et al. (2015), H.C. was tested on fifteen landmarks. In the current study, only thirteen of the fifteen photographs could be re-used as one location no longer existed (Blockbuster) and another (Mac's Convenience Store) had been relocated. A photograph of the new Mac's Convenience Store location was used instead. As such, H.C. was provided with fourteen photographs of well-known landmarks and asked to imagine travelling from North to

South and put the photographs in the order that they would be passed travelling along this route.

A landmark sequencing accuracy score was derived by calculating the total number of landmarks that were correctly sequenced with respect to at least one adjacent landmark and dividing this number by 14.

***Blocked routes.***

Given H.C.'s ability to virtually navigate mirror-reversed routes (as described in Chapter 2), whether her performance would improve on the blocked route task, another task that requires flexible navigation, was of particular interest. Unfortunately, many of the blocked routes used in the previous study could not be re-used in the current study as the landmarks no longer existed or had changed location. As such, only two blocked routes in this study were consistent with those used at Time 1. We also examined whether H.C. would be able to complete a blocked route task for some of the routes that she navigated in Google Street View, with the hopes that this might shed some light on whether the immersive nature of the task may impact the results. She was also asked to navigate between her workplace and home, avoiding a detour, as well as between her current home and her childhood home, where her parents still reside.

## Results

H.C.'s current performance on the navigation tasks (Time 2) was compared to her performance when last tested in 2010 (Time 1) using Crawford, Garthwaite, and Wood's (2010) C_CTC.exe program, which allows one to test the difference between the scores of two single cases, taking into account the standard deviation of a control sample (in this case, the 6 controls who participated in the original study (Rosenbaum et al., 2015)). While this test fails to account for the repeated measurement of H.C. on each task (as it assumes two separate cases), it seems to be the best single-case statistical test to address the question at hand.

H.C.'s current performance was also compared to the 6 controls' performance reported in Rosenbaum et al. (2015) using Crawford and Garthwaite's (2002) modified t-test procedure.

**Sketch Mapping**

H.C.'s sketch maps of her childhood environment and the city centre are found in Figures 3.1 and 3.2, respectively. Identifying landmark and street names have been replaced for confidentiality purposes. For comparison purposes, we direct the reader to reproductions of the sketch maps that H.C. and a representative control drew of the same environments when tested in 2010 (Figures 1.1. and 1.2; Rosenbaum et al., 2015). The graph in Figure 3.3 illustrates the number of landmarks, street segments, and total details that H.C. and controls included in both their childhood and city centre sketch maps at Time 1 and that H.C. included at Time 2, regardless of whether they were accurately placed. H.C.'s current sketch maps included 23 landmarks in total, compared to the 20 reported previously (Rosenbaum et al., 2015), which does not represent a significant difference ($t$ = -0.245, $p$ = .408). It is important to note that the landmarks that were included differed from Time 1 to Time 2. For example, H.C. failed to include her childhood home on the map at Time 1 but included it on her most recent test. Consistent with Time 1, H.C. included significantly fewer landmarks in her sketch maps compared to controls ($\mu$ = 44.833, $SD$ = 8.660; $t$ = -2.334, $p$ = .033).

H.C. drew 38 street segments on her sketch maps at Time 2, compared to 34 at Time 1, but this was not statistically significant ($t$ = -0.080, $p$ = .470). There was a trend towards fewer street segments included in H.C.'s sketch maps at Time 2 compared to those included in the sketch maps created by controls at Time 1 ($\mu$ = 106.167, $SD$ = 35.254; $t$ = -1.790, $p$ = .067).

The total number of details contained within H.C.'s sketch maps at Time 2 (61) did not differ significantly from those at Time 1 (54; $t$ = -0.140, $p$ = .447), and remained significantly fewer than those included by controls ($\mu$ = 151, *SD* = 32.254; $t$ = -2.364, $p$ = .032).

H.C. had difficulty scaling streets and landmarks within her sketch maps, a problem that was also seen in the sketch maps of control participants (Rosenbaum et al., 2015). She spent approximately five minutes planning out her drawing before beginning the sketch map of her childhood environment (Figure 3.1), often using her hands to help orient. She shared that she would begin by putting things where she "knows they are" and seeing if she "can connect them with the proper street." While she labelled the sides of the pages with the boundaries that were described to her prior to drawing, she did not actually draw the lake, intersection on the northern border, or the railroad tracks. Consistent with the sketch map drawn in 2010, H.C. oriented one of the main roads, Lakeshore, East to West, when in fact its correct orientation is North to South and it intersects with M-Drive. Along this street, she added in some street segments, but they were not grounded using a street name or nearby landmarks.

Similar to the sketch map drawn at Time 1 (Figure 1.1), H.C.'s sketch map of her childhood neighbourhood lacked cohesiveness. While she drew a street connecting the street bordering the bottom (southern) part of the page (M Street) to the street on which her parents' live (G Street), this street was not labelled. There is no road that directly connects the M and G streets, providing further evidence that H.C. may have difficulty integrating disparate elements of her environment. The streets placed to either side of her parents' street were flipped, such that the one on the right should have been on the left and vice versa. H.C. also drew her parents' street (G Street) as connecting to Lakeshore Drive, which, in actuality, run parallel to one another. H.C. said that while drawing her sketch maps, she was envisioning the area as if she were immersed in it. She may have been generating her sketch map based on what she might visualize along the way, but she had difficulty integrating separate areas. This is consistent with her plan to place landmarks and then try to connect them with a street. The paucity of detail in her sketch map of her childhood neighbourhood, however, limits the conclusions that can be made about her ability to integrate elements.

The sketch map that H.C. drew of the downtown city environment (Figure 3.2) included several more streets compared to that drawn in 2010 (see Figure 1.2), but several of those streets were not anchored to another street segment or landmark, and therefore did not fit the definition of a “street segment” as defined above and in our previous study (Rosenbaum et al., 2015). H.C. included Main Street, one of the busiest downtown streets, and several other street segments that run perpendicular to F Street, a street that she frequently takes when navigating to and from her current home. Interestingly, H.C. did not connect these streets to F Street, but instead left these streets as separate lines isolated in the centre of the page. She also failed to include several other streets that intersect with F Street. On a map, Third Avenue intersects with F Street and south of F Street, Third Avenue turns into the street on which H.C. lives (H Street). H.C. did not connect Third Street to F Street or H Street, and although she included her house as a landmark on the map, it was further west than it should have been given the position of Third Street. H.C. also included an unlabelled street connecting the northern tip of Third Street to F Street, which does not exist on an actual map.

H.C. accurately positioned the Burger World and mall landmarks relative to one another, and relative to F Street and H Street. It is notable that H.C. frequently travels a route between her home and the mall, where she works. The mall is located directly off a major highway, which H.C. included on the top right of her map but failed to position accurately relative to the mall.

She also included some street segments and landmarks (e.g., McDonald's and Montana's) below the highway that instead, are located north of the highway and therefore placed outside of the boundaries requested for this sketch map. H.C. drew a street segment with landmarks labelled "liquor store" and "grocery store" drawn to the right of it, when, in fact, they are located on the same road as the McDonald's and Montana's restaurants.

H.C. labelled a line on her sketch map as Lakeshore Drive, which also did not connect to any other elements in the sketch map. Lakeshore Drive is part of her childhood neighbourhood, and, in fact, turns into Main Street past an overpass that connects the two environments. Curiously, she placed this line parallel to Main Street. Like the map she drew in 2010, H.C. included other elements from her home neighbourhood in the downtown city core sketch map. On the far left of the page, it is evident that H.C. drew the street her parents live on, including their house, as well as a street that runs between her parents' street and Lakeshore Drive. While none of these streets belonged on the sketch map of the city centre, it is interesting to note that these erroneous elements were also flipped, such that her parents' street was oriented to the left of Lakeshore Drive, when it should be on the right.

Consistent with the sketch maps drawn in 2010 (see reproductions from Rosenbaum et al., 2015, in Figures 1.1 and 1.2), H.C.'s most recent sketch maps continued to show a paucity of landmarks and street segments compared to controls, and also lack cohesiveness.

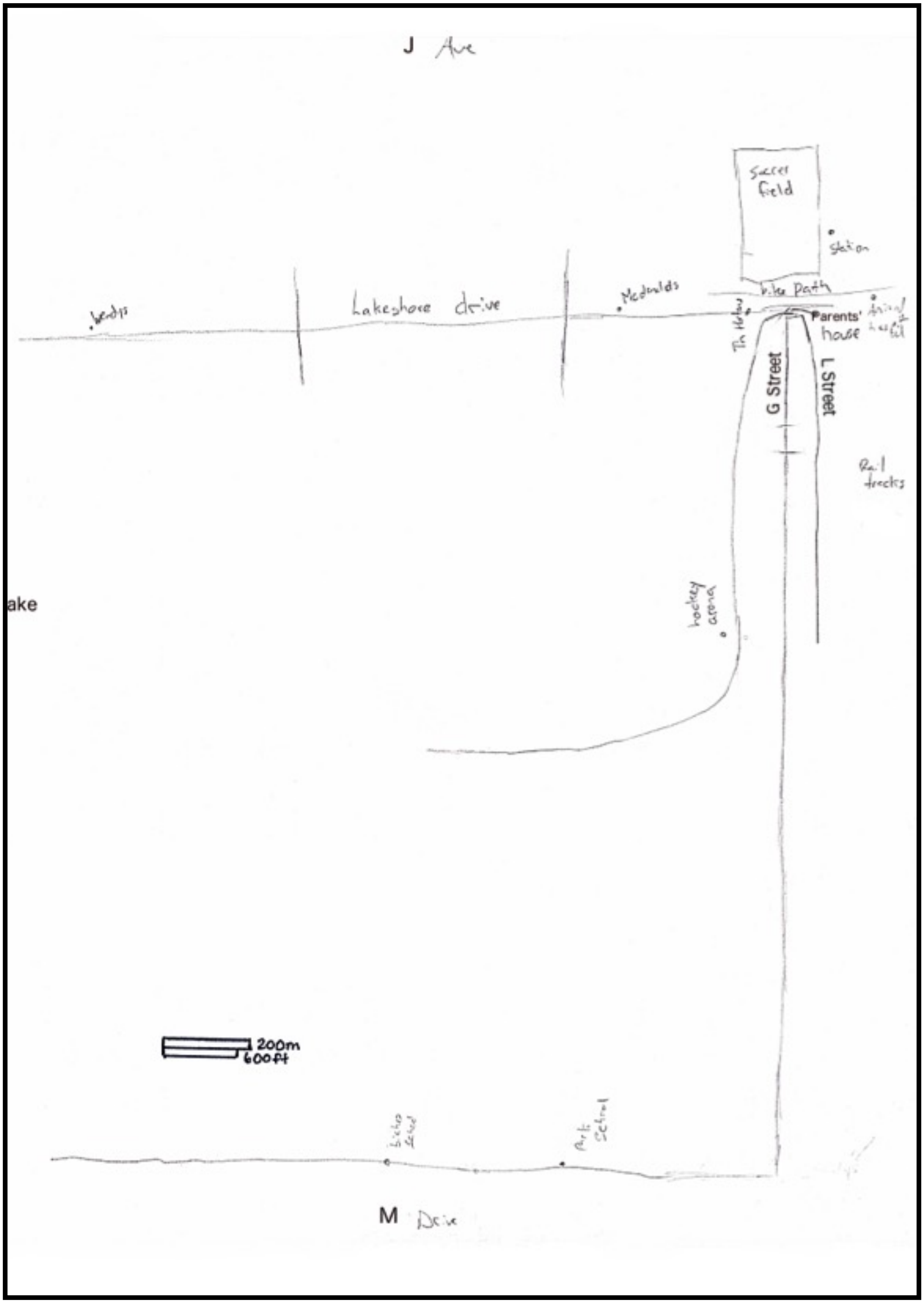


*Figure 3.1.* H.C.'s current sketch map of her childhood neighbourhood.

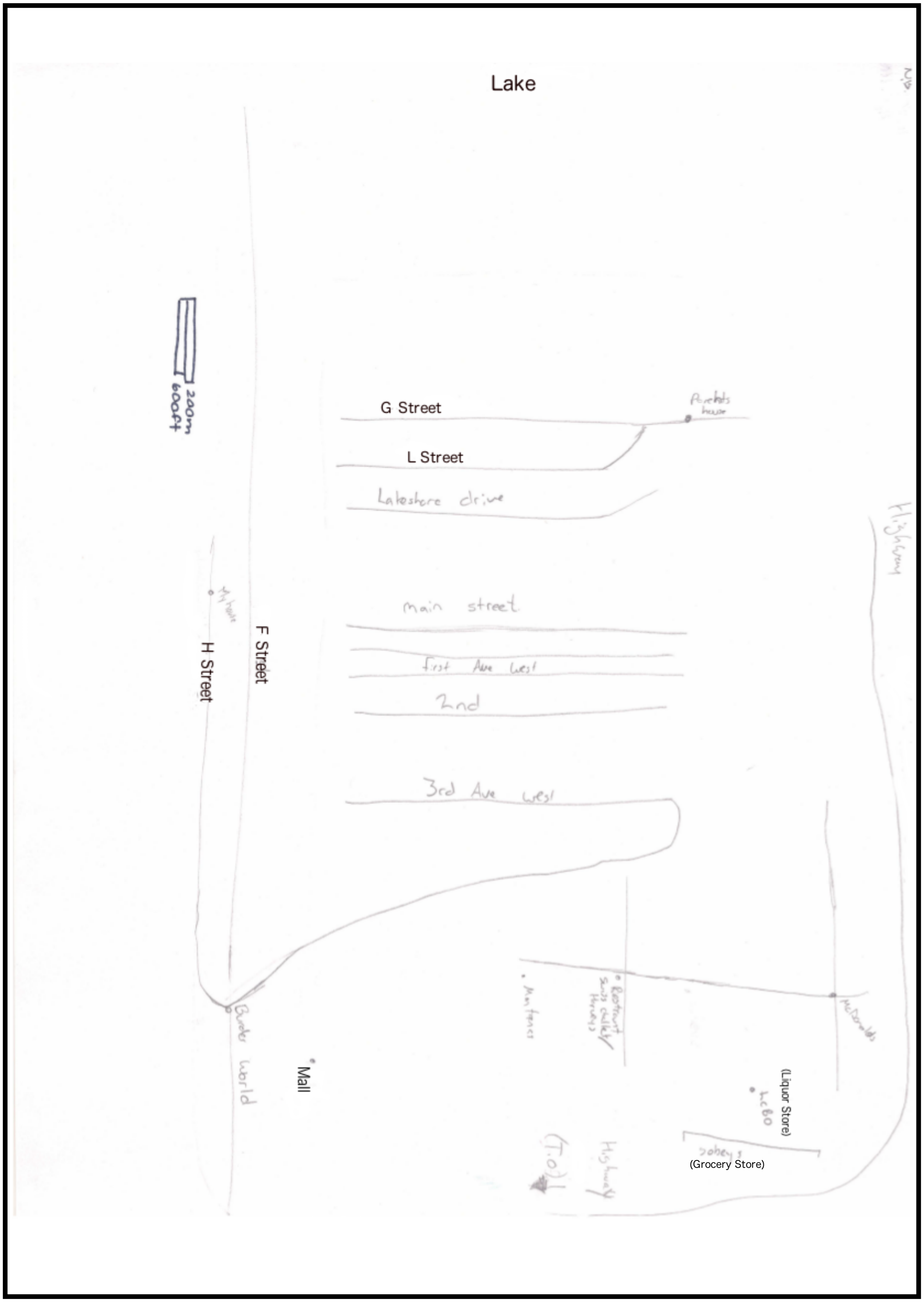


*Figure 3.2.* H.C.'s current sketch map of the downtown city core, where she currently resides.

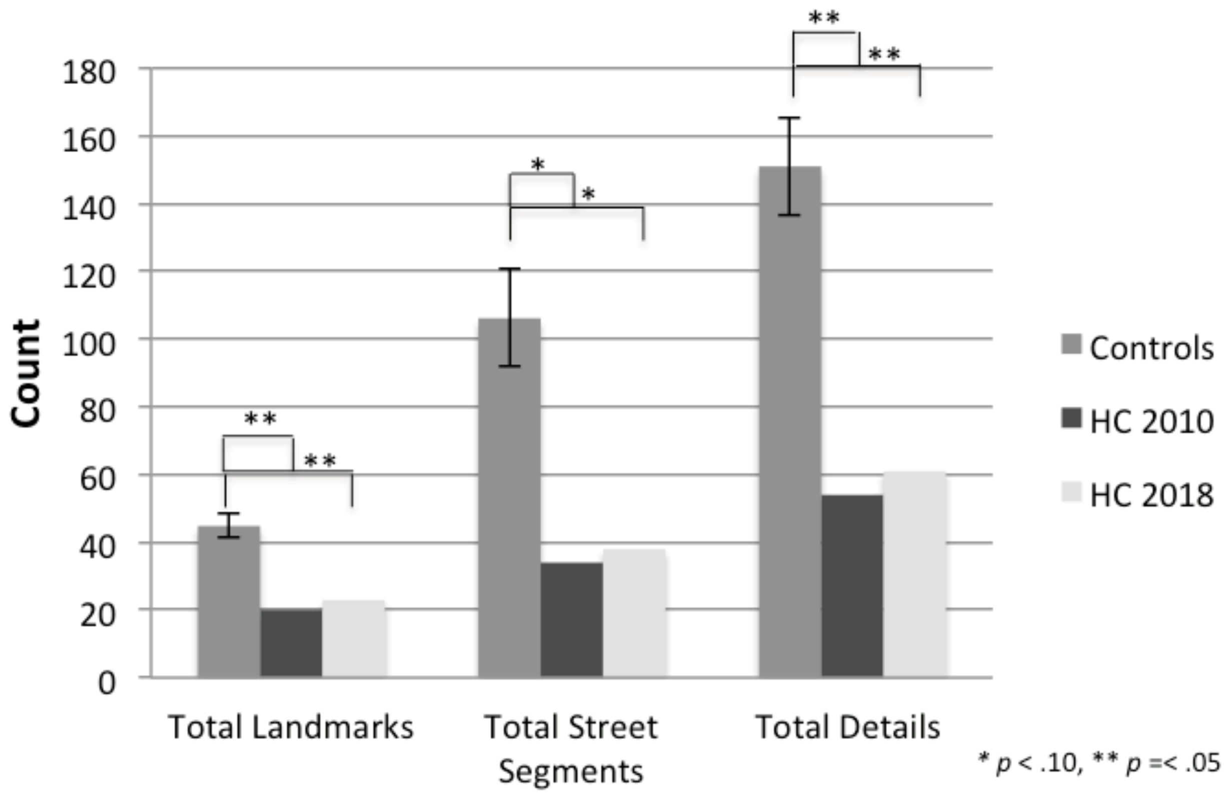


*Figure 3.3.* Number of landmarks, street segments and total details on sketch maps drawn by control participants in 2010, H.C. in 2010, and H.C. in 2018. Error bars represent standard error.

**Landmark Localization**

When provided with a sheet of paper containing only the outline of streets that border her childhood neighbourhood, H.C's ability to place well-known landmarks accurately on that page was similar to that demonstrated in 2010 (Rosenbaum et al., 2015). Her mean localization error for this neighbourhood on current testing was 0.279 km, which does not differ significantly from her mean localization error calculated in 2010 (0.370 km; $t = 0.894$, $p = .206$; see Figure 3.4). Her performance compared to controls (0.247 km ($SD$ = 0.072 km)) showed sufficient improvement such that her mean localization error was no longer representing a trend towards significance, as it had in 2010, but instead did not differ significantly ($t$ = 0.411, $p$ = .349). Notably, H.C. seemed to place most of the landmarks very close to the main street in her childhood neighbourhood, which may relate to her assertion that she was imagining walking down this street while deciding where to place the landmarks. Given this disclosure, it is especially interesting that she seemed to have difficulty placing the landmarks as a dot on the map in the correct sequence. In fact, she did not place any of the landmarks in the correct sequential relationship (North-South) to at least one neighbouring landmark on the childhood neighbourhood map.

When asked to place well-known landmarks accurately on a sheet of paper containing the outline of streets that border the downtown city centre neighbourhood, H.C.'s mean localization error (0.707km) remained significantly impaired compared to controls' (0.273 km ($SD$ = 0.118 km); $t$ = 3.405, $p$ = .010). Her mean localization error for the downtown neighbourhood on current testing did not differ significantly from her mean localization error calculated in 2010 (0.762 km; $t$ = 0.330, $p$ = .378). Her total mean localization error, calculated by combining error scores from her childhood environment and the city centre, was significantly impaired compared to controls' (0.260 km ($SD$ = 0.086 km); $t$ = 2.508, $p$ = .027), and did not differ significantly from her score at Time 1 (0.566km; $t$ = 0.600, $p$ = .287).

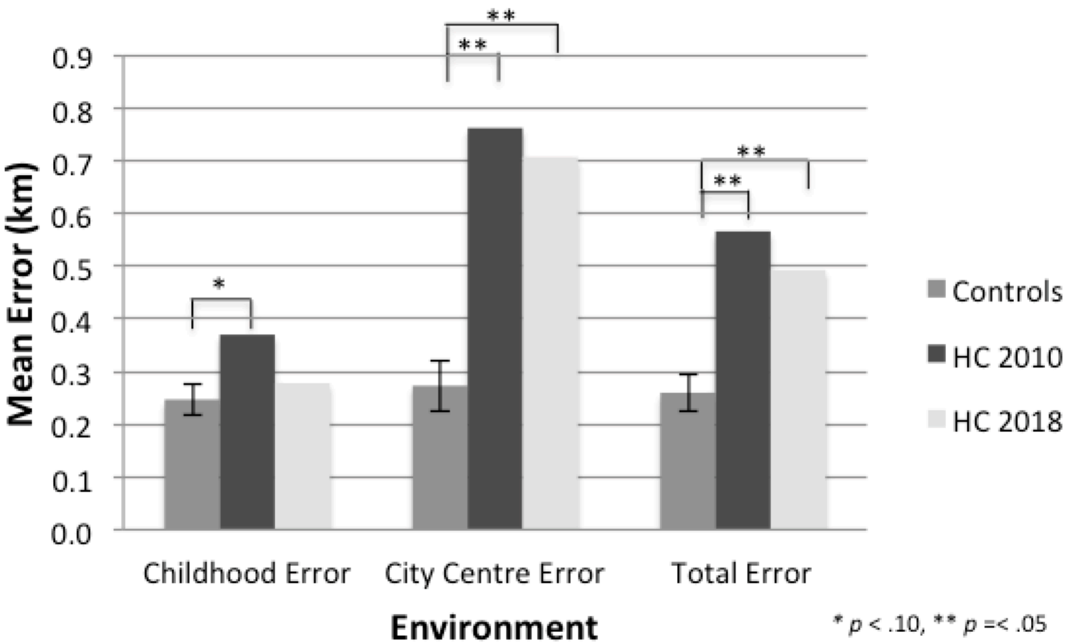


*Figure 3.4.* Mean localization error for H.C.'s childhood environment and the downtown city centre, where she currently resides, for control participants in 2010, H.C. in 2010, and H.C. in 2018. Error bars represent standard error.

**Landmark Sequencing**

On a formal task assessing landmark sequencing that required placing photographs of landmarks in the correct order, the results indicated a trend towards worse performance from Time 1 (0.800) to Time 2 (0.643; $t$ = 1.528, $p$ = .094; Figure 3.5). When recently tested, H.C. accurately sequenced fewer landmarks to at least one adjacent landmark compared to controls ($\mu$ = 0.933, $SD$ = 0.073; $t$ = -3.678, $p$ = .014). While H.C.'s performance on this task remained impaired, it is notable that she was able to accurately sequence more landmarks when asked to place photographs of landmarks in order, compared to when she was asked to place a dot on an outline of a map (described above).

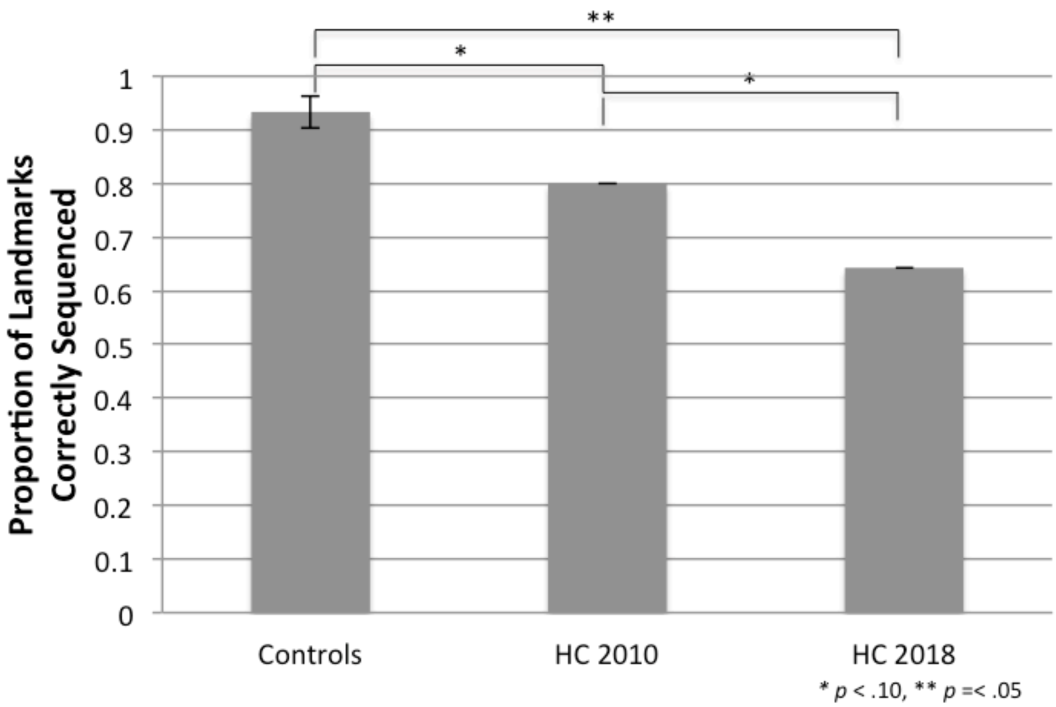


*Figure 3.5.* Proportion of correctly sequenced landmarks on the landmark sequencing task for control participants in 2010, H.C. in 2010, and H.C. in 2018. Error bar represents standard error.

**Blocked Routes**

As previously reported in Rosenbaum et al. (2015), H.C.'s ability to describe the most efficient detour between two landmarks when the most direct route was blocked was significantly impaired compared to controls (with one control outlier removed). As H.C. could only be tested on two of the original five routes, it was not prudent to compare her current performance to her past performance or controls' performance quantitatively. Her performance on six blocked routes is described qualitatively below.

**Route 1.**

When tested in 2010 on a blocked route between two restaurants, both familiar to H.C., she was able to provide accurate directions but did not take the most efficient route, resulting in a score of zero. When tested on the same route for this current study, she was unable to provide accurate directions. She did not use street names, instead giving directions such as, “From there go left for three intersections.” When the examiner tried to follow her directions on a map, it became apparent that H.C.’s directions were not fluid. For example, she described arriving at an area where the “road turns,” but no such turn could be found anywhere within the area. The examiner had the impression that H.C. was having difficulty keeping in mind the area that she just described and was navigating from, which led to very disjointed directions. As her initial directions were difficult to follow, H.C. was asked to describe the route again. This time she successfully described arriving at an overpass that was part of a longer route to the destination, but she did not continue, ultimately failing to reach the destination.

**Route 2.**

When asked in 2010 to navigate between the high school she attended and a pharmacy located in her childhood neighbourhood, whilst avoiding a main street, H.C. was able to reach the destination, but unable to do so in the most recent testing session. At one point, she instructed that one would take a right at a retirement residence and then continue “up 3 intersections,” where the pharmacy could be found on the right. However, the road does not, in fact, continue for three intersections and would have required returning to the blocked street. It is interesting to note that the pharmacy was located north, past 3 intersections, had she turned on the blocked street instead of at the retirement residence, which again suggests that she may have had difficulty keeping track of where she was on the route.

**Route 3.**

On another blocked route trial, H.C. was asked to navigate a very familiar route from her parents’ home to her current residence, avoiding a main street. In the Google Street View task

(Study 1), she was able to navigate a portion of this familiar route when there was no detour, even though the route was mirrored. When attempting this blocked route, H.C. stopped herself midway and asked to start over. On her second attempt, she was able to provide accurate directions from her parents' home into the city proper, and her directions were accurate until the end of the route. After giving directions to "go right" at a "big government building near a parking lot," she said to "Cross [street that was hypothetically blocked]," which would have been impossible as it was two blocks south and parallel to the street on which she imagined herself. It seems she missed heading South on one street, which, had she included it, would have resulted in successful navigation of the blocked route.

**Route 4.**

H.C. was able to successfully navigate a route from the cinema in her childhood neighbourhood to her parents' house on the Google Street View task (Study 1; familiar route) and the blocked route task, where she was required to avoid a main street. On this trial, she took the second-most efficient route given that the most direct route was blocked. When describing this route, she used key landmarks to signify the streets to turn onto (e.g., Elementary school, Catholic school, Gas Provider). It is notable that H.C. navigated using landmarks located along this route, whereas in the routes described above she provided minimal mention of landmarks and predominantly described how many intersections to cross before turning. It may be that using landmarks at choice points was a more useful strategy to keep track of her location than the number of streets passed when describing the route.

**Route 5.**

When navigating between her in-laws' home and her current home on Google Street View, H.C. was able to successfully reach the destination (familiar route). By contrast, when asked to navigate between the two landmarks in this grid-like environment, avoiding one of the streets she typically takes, H.C. had some difficulty. She described travelling straight down a street and turning left at City Hall. Notably, had H.C. continued straight, she could have taken a more direct route and would have reached a main street that intersects with the street on which she lives. H.C. described arriving at a set of lights where one "can't turn right". There were no intersections on the street with streetlights. Furthermore, navigation onto her own street would have required turning onto one of the main roads, which she did not mention when providing directions.

**Route 6.**

Finally, H.C. was asked to navigate between her place of work and current home, avoiding a major street. This was a slightly more challenging route, as the most direct pathway usually requires only one turn, whereas the most direct detour would require five turns. On her first attempt, H.C. used the blocked road. When asked to begin again, she successfully navigated part of the route but seemed to repeat a portion of the route multiple times. The first time she instructed that one should turn right at a particular house, and then seemingly returned to this same corner in her mind, directing one to turn right at the elementary school (which is beside the house). She gave directions that led away from this street but said at one point that it "puts you at the church on [home street]," which suggests that she again had returned a third time to the same street (without giving directions to navigate there). When navigating from the church on the street on which she resides, she also instructed the experimenter to go left "3 intersections," whereas one would only need to go past two.

## Discussion

The purpose of the study described in this chapter was to examine whether spatial representations of extensively travelled environments can improve over time in H.C., an individual who experienced atypical hippocampal development. Results from re-testing on mental navigation tasks suggest that H.C.'s impoverished and incoherent representation of her home environment has not changed significantly since she was tested 8 years ago. Her performance remains impaired on the sketch mapping, landmark localization, and landmark sequencing tasks, and her performance on the blocked route task was qualitatively worse.

### No Evidence of Substantially Improved Flexible, Map-like Representations of Space

In 2016, H.C. was able to successfully navigate very familiar and less familiar routes within her home environment on the Google Street View task, as well as the more challenging mirrored routes that were expected to require flexible navigation (described in Chapter 2). This raised the possibility that H.C.'s representation of her home environment became more coherent and flexible since she was first tested on mental navigation tasks in 2010. When initially tested, H.C. was able to represent distances and directions between familiar landmarks and describe accurate, albeit inefficient, detours on a blocked route task (Rosenbaum et al., 2015). Her fragmented sketch maps and inefficient detours suggested a coarse representation of her home environment that limited flexible navigation (Rosenbaum et al., 2015).

Although H.C.'s intact performance on the mirrored routes (Chapter 2) suggests that her representation of space may have become more flexible over time, results from re-administration of the mental navigation tasks for the current study suggest that H.C. continues to lack a coherent representation of her home environment, which one would expect would limit flexible navigation. For example, many elements of her sketch maps were disjointed and incorrectly oriented. She also was unable to provide accurate verbal directions on five of the six blocked route trials. This was worse than expected given that H.C. was able to provide verbal directions that were accurate, although inefficient, on the same task when tested 8 years prior (Rosenbaum et al., 2015). It was not possible to retest H.C. on all of the same routes used in the 2010 test session, but an effort was made to achieve a similar level of difficulty in both versions. Nonetheless, we cannot rule out the possibility that her decline in performance reflects trial difficulty. While H.C.'s poor performance on this task could be attributed to her having an incoherent and inflexible representation of her home environment, it is also possible that the verbal nature of the task could have impacted her performance, as she had to keep track of her position along the route in her mind's eye, without cues from an external source. While impairment on the blocked route task may appear to be discordant with H.C.'s intact ability to navigate mirrored routes, it is possible that the type of flexibility required to successfully navigate along mirrored routes differs from that required to navigate a blocked route (as proposed in Chapter 2). It is unclear whether H.C. would have fared better if asked to navigate a blocked route task in vivo or using Google Street view. Future studies examining H.C.'s performance on a dynamic, virtual reality, blocked route task would provide insight into whether H.C.'s difficulty on the blocked route task is due to an inflexible representation of space that lacks cohesion, the demands on working memory, or a mixture of the two.

H.C.'s lack of improvement on the mental navigation tasks suggests that representations of frequently travelled environments do not become more coherent or flexible in an individual with an atypical hippocampal system, even after 8 additional years of time and frequent exposure. This contradicts H.C.'s personal belief that her ability to navigate within her home environment has improved over time. It may be that 8 years is not enough time to observe substantial improvements. It seems highly unlikely, however, that we would not see even incremental improvement over nearly a decade of daily exposure. Perhaps features of an environment integral for navigation are more easily acquired, but since H.C. already has access to a coarse, schematic representation of her home environment that is sufficient for navigation, it is possible that additional spatial information that enables flexible navigation is acquired at a slower rate, or may not benefit at all from extended exposure.

Although H.C.'s performance on the mental navigation tasks administered to her did not improve, it is still possible that she acquired new spatial information. For example, she was able to learn the location of her apartment and, later, her new home within the city centre. Also, there is anecdotal evidence from actual navigation and objective evidence from Google Street View (Chapter 2) that she can travel successfully using these "new" landmarks. In an attempt to keep the tests as consistent as possible, these new landmarks were not included in the re-test of the landmark localization or landmark sequencing tasks. It is notable that H.C. included a few of these new landmarks on her sketch maps, but overall her sketch maps remained impoverished and did not change substantially in quality from 2010 to 2018. Some of these new landmarks were used in the blocked route task, and H.C. had difficulty navigating with these, although her difficulty on this task could have been confounded by other factors, as discussed in greater detail below.

It may be that the coarse representation of space acquired prior to 2010 did not improve, as it was sufficient for navigation, but that schematic information about areas with which H.C. was less familiar could be acquired with time. Perhaps it does not take much time or experience to learn new locations and basic relations between them, especially when they can be anchored to established knowledge. For example, H.C. learned the location of her new home by considering its location in the context of previously learned landmarks and by repeatedly travelling between her home and those landmarks. H.C.'s difficulty navigating blocked routes with these new landmarks, however, suggests that flexible use of these places may not be possible. The landmarks that H.C. learned during the past 8 years were also likely the most meaningful, as she lived in them. The speed at which new learning would occur, if at all, for landmarks that are not personally meaningful is unclear. Additional time and experience do not seem to benefit the flexible nature of a representation of a well-known environment in H.C. It appears, however, that additional landmarks can be integrated into the representation, which might still be viewed as schematic and sufficient for travelling between a start location and a goal, albeit in an inefficient way.

It is possible that H.C. navigates and learns novel routes using an egocentric framework, defining landmark locations in relation to body-centered coordinates, rather than to other landmarks. This is consistent with her self-report on the Navigation Strategies questionnaire, described in Chapter 2. An egocentric framework is not viewed as relying on the hippocampus, but instead the caudate nucleus (Bohbot, Lerch, Thorndycraft, Iaria, & Zijdenbos, 2007; Hartley et al., 2003; Iaria, Petrides, Dagher, Pike, & Bohbot, 2003; Marchette, Bakker, & Shelton, 2011). While the status of H.C.'s caudate nucleus remains to be determined, it is possible that H.C. has adopted an egocentric strategy over an allocentric strategy. Because an egocentric framework is less conducive for flexible navigation than an allocentric framework, H.C.'s ability to form a cognitive map and flexibly navigate environments may be limited.

**No Evidence of Improved Detailed Representations of Space**

Perhaps less surprising, H.C.'s sketch map remained impoverished and she continued to have difficulty accurately sequencing more than two landmarks that were close in proximity to one another, which suggests that she did not form a more detailed representation of her home environment, even after an additional 8 years of navigational experience. This is consistent with findings that adult-onset hippocampal amnesic patients have impoverished detailed representations of well-known environments that lack richness of detail (Rosenbaum et al., 2000; Herdman et al., 2015), and supports the Trace Transformation Theory, which posits that the fine, detailed, perceptual information about an environment will always rely on the hippocampus (Rosenbaum, Winocur & Moscovitch, 2001; Winocur & Moscovitch, 2011). It may be that fine-grained detailed features of an environment do not benefit from extended time and exposure in the same way that coarse spatial features do, as they are not as pertinent to navigation.

When completing the landmark localization task and landmark sequencing tasks, H.C. shared that she tried to envision the landmark and imagine what was surrounding it, rather than evoke a picture of a map of the environment in her mind. H.C. reports such a strategy yet she continues to have difficulty sequencing landmarks. This raises the possibility that H.C.'s ability to richly envision a route and think about additional context, possibly beyond the two landmarks that are being compared, is somewhat impaired. She may believe that she is envisioning the route while sequencing landmarks but she may have access to a less rich representation of space compared to controls, which affects her ability to sequence the landmarks. Interestingly, on a question on the Navigation Strategies questionnaire (Study 1) that asked about her ability to picture buildings along a familiar street, H.C. said she could picture the buildings "somewhat clearly". It is possible that H.C. may not have a detailed representation of space from which to draw information. The mental navigation tasks described in this study require the ability to conjure up a coherent spatial representation in imagery. On the other hand, the immersive nature of the virtual reality Google Street View paradigm eliminates the demand to retrieve or construct a detailed representation of space, and instead relies on recognizing landmarks or spatial features to navigate. The provision of this detail may have helped H.C. to navigate flexibly on the mirror-reversed routes described in Chapter 2. Chapter 4 further examines whether H.C. can conjure up a rich, detailed representation of her home environment that allows for a sense of re-experiencing. It is also possible that there are other factors contributing to the lack of detail on H.C.'s sketch maps and her difficulty sequencing and localizing landmarks that are in close proximity to one another.

## Additional Factors that May Affect Performance on Mental Navigation Tasks

### Strategic retrieval.

Re-administration of the mental navigation tasks revealed that H.C. likely has an incoherent representation of her home environment that is lacking in detail. She continued to draw impoverished sketch maps and have difficulty on navigation tasks that require fine-grained discrimination between landmarks. H.C. may not have a detailed representation of space from which to draw. It is also possible that H.C. has maintained in memory a representation of detailed information about environments, but a retrieval deficit makes it difficult for her to construct or conjure up such representations. Intensive cueing may be required to retrieve a rich, detailed representation of her home environment. Such visual cues were available to H.C. in the Google Street View task, described in Chapter 2, and may explain her intact performance flexibly navigating routes in the mirrored route condition. Similarly, in the current study, H.C. qualitatively performed better (although her performance was still significantly worse than controls) on the landmark sequencing task, where pictures of landmarks were provided and might have assisted her imagery, compared to the landmark localization task, where landmark locations that needed to be placed on the map were cued only verbally.

Perhaps H.C. also benefits from cues that are not as perceptually rich as those seen in the Google Street View paradigm or the pictures of landmarks in the landmark sequencing task. To further test the possibility that a retrieval deficit impeded performance, H.C. was re-tested on the landmark localization task for her childhood neighbourhood and retrieval demands were reduced by providing maps with increasing levels of support. In approximately one-hour intervals, H.C. was given maps that provided increasing support and instructed to place the landmarks without regard to where she placed them on previous trials. The first map had boundaries of the environment marked on the map, and she was required to place dots on the page indicating the locations of 10 specified, well-known landmarks. The second map was identical to the first, except that the map had three of the ten landmarks pre-marked on the page. The third map offered the most support, with all of the streets within the boundaries clearly marked. With increasing support, H.C. was able to improve her mean localization error score (absolute deviation in distance from the marked landmark to the actual location) from 0.364 km to 0.265 km to 0.213 km. Based on these results, it would seem that a retrieval deficit could, in part, explain H.C.'s impoverished sketch maps and difficulty on the landmark localization task.

When the placement of the dots (representing landmarks) relative to other placed landmarks was examined on these maps, we found variable performance in terms of landmark sequencing (see Table A.1 in the appendix). On the first map, which consisted only of the boundary streets, H.C. placed five of ten landmarks in the correct sequential relationship relative to at least one neighbouring landmark. When she was provided with increased support in the form of three of the ten landmarks pre-marked on the map, she was able to correctly sequence only two landmarks, which suggests that there may have been some interference. Finally, provided with a map that included all of the streets within the boundaries, H.C. was able to correctly sequence six of ten landmarks. The variability in the accuracy with which H.C. placed landmarks on the three maps with increasing support suggests that a retrieval deficit does not fully explain H.C.'s difficulty accurately sequencing landmarks.

**Relational memory.**

In both 2010 and 2018, H.C. had difficulty on those mental navigation tasks that involved 4+ landmarks, even when she did not have to hold information in mind but instead could refer to it visually. For example, when placing well-known landmarks in the landmark localization task, H.C. did not have to keep the locations of all landmarks in mind and, instead, could visually refer to landmarks that were previously placed (whether correctly or incorrectly). While her deficient performance in this regard could be due to increased susceptibility to interference, it could alternatively be due to a deficit in relational memory, or perhaps a combination of the two. H.C. seems to have difficulty representing and integrating individual spatial elements in relation to other elements. This possibility was suggested by Rosenbaum and colleagues (2015) to explain H.C.'s poor performance on the landmark sequencing task that approached significant impairment in 2010 and upon noticing the existence of "swap errors," where she would reverse the relative positions of landmarks along a route. We see a similar pattern when we more closely examine her most recent performance on the landmark sequencing task, where she correctly sequenced 9 of 14 landmarks relative to at least 1 adjacent landmark. Of the 5 landmarks that were incorrectly sequenced, 3 were swap errors between landmarks that were relatively close in distance. This pattern is also found when we look at the relative placement of landmarks on a map of H.C.'s childhood environment during the landmark localization task. While H.C.'s deviation in absolute distance did not differ significantly compared to that of controls, she placed landmarks on the map such that none of the landmarks were correctly sequenced relative to a neighbouring landmark. On this task, H.C. incorrectly swapped two pairs of landmarks. Further evidence of this comes from the follow-up landmark localization tasks, on which H.C. placed landmarks on maps with increasing visual aids. While these swap errors occurred consistently, even with the provision of additional cues as an aid to place the landmarks, swap errors do not account for every incorrectly placed landmark.

The frequency and persistence of swap errors in H.C. is reminiscent of that seen in adult-onset hippocampal amnesic cases. Swap errors on an object array were found to occur 40 times more often in adult-onset hippocampal amnesic patients compared to healthy controls, and multiple swap errors within a single trial were common in amnesic patients (Watson, Voss, Warren, Tranel, & Cohen, 2013). Watson and colleagues found that swap errors contributed to the localization error, as the absolute distance between the object's position at study versus the position as placed by the participant was significantly reduced when swap errors were removed from the analysis. This raises the possibility that the swap errors seen on H.C.'s maps could have inflated her localization error score. Watson and colleagues (2013) also consistently found swap errors on trials involving only a single pair of objects. On mental navigation tasks, H.C. seems to exhibit swap errors on tasks that involve the sequencing or placement of multiple landmarks, such as the landmark sequencing task or the landmark localization task. The paucity of details on H.C.'s sketch map make it difficult to identify swap errors, but there was evidence that she swapped the streets on either side of her parents' street. On mental navigation tasks that involved 3 or fewer landmarks, however, H.C.'s performance was intact (Rosenbaum et al., 2015). Swap errors would have been impossible with the vector mapping task, as participants were given the location of a landmark on a map and asked to draw a vector representing distance and direction to a named landmark. Nevertheless, it is curious that H.C. was able to select which of two landmarks was closet to a third reference landmark (proximity judgment task) as well as control participants, as such a task could be influenced by swap errors.

The evidence of swap errors provided in the current study is compatible with the proposition that the hippocampal system is required for relational processing (Eichenbaum et al., 2016; Eichenbaum & Cohen, 2001; Watson et al., 2013). Individuals with hippocampal amnesia have been found to show deficits in memory for spatial, temporal, and associative relations among items (see Konkel & Cohen, 2009, for a review).

There is also evidence of relational binding deficits outside of the spatial realm in developmental amnesic H.C. Olsen and colleagues (2015) tested H.C.'s ability to recognize faces studied from variable viewpoints. They found that H.C. was able to recognize faces she encoded from a fixed viewpoint, but significantly impaired compared to controls on recognizing faces studied from variable viewpoints, which led them to suggest that H.C. did not have access to flexible relational representations. This may parallel H.C.'s inflexible representation of her home environment. A deficit in relational processing would explain the incoherence seen in H.C.'s sketch maps and demonstrated during the blocked route task.

**Susceptibility to distraction & interference.**

That H.C. correctly placed only two landmarks on a map in the correct sequence when provided with additional support on the landmark localization task raises the possibility that additional stimuli might actually interfere with H.C.'s ability to accurately represent spatial information. When provided with a map that included all of the streets within a specified boundary, H.C. improved and was able to correctly place six of ten landmarks in the correct sequence relative to at least one neighbouring landmark. Unfortunately, we do not have a control group for the follow-up test that examined the benefits of additional support but one might speculate that accurately sequencing 60% of the landmarks would be significantly worse than controls, who accurately sequenced 93% of the landmarks on the actual landmark sequencing task described above that involved sequencing pictures of landmarks.

The mental navigation tasks on which H.C. performed poorly when first tested (2010), and again when tested more recently (2018), required placement or sequencing of 4 or more landmarks. Those mental navigation tasks on which H.C. was reported to show intact performance at Time 1 required manipulation or placement of 3 or fewer landmarks (Rosenbaum et al., 2015). For example, the vector mapping task required her to draw a line representing the relative distance and direction between a marked landmark and a second, unmarked landmark. On the proximity judgment task, she had to identify which of two landmarks was closest in distance to a third landmark. The distance judgment task required an estimation of absolute distance between just two landmarks. This suggests that H.C.'s performance may decline when an increasing number of landmarks or spatial features must be considered.

Of note, both H.C. and her husband reported that H.C. rarely gets lost in her home environment, unless she is distracted. Her husband provided an example of H.C. travelling to one location, but upon mention of another location during the course of a conversation, she began driving to the second location. He also mentioned that she forgets where she was going if she gets absorbed in music while driving. Distraction or interference may make it more difficult to represent and integrate elements or maintain a route in working memory. This may be especially true for H.C., who has an anterograde memory deficit; as information may not be transferring from working memory to long-term memory, it would be harder for her to recover from even a minor distraction. This should not come as a surprise as the fact that hippocampal lesions increase susceptibility to interference is well established in the animal literature (Douglas, 1967; Kimble, 1968; Winocur & Mills, 1969). As described in the next section, this is also in line with findings that H.C. was impaired on complex working memory tasks that included a distractor task, where attention was shifted away from the items to be remembered (Rose, Olsen, Craik, & Rosenbaum, 2012).

**Working memory.**

H.C.'s performance on mental navigation tasks seems to decline when an increasing number of landmarks or spatial features must be considered. This may be explained by an increased susceptibility to distraction and interference. Alternatively, H.C.'s poor performance could be explained by a deficit in a related construct, working memory, which involves maintaining and manipulating information in mind. It may be that maintaining 4 or more landmarks or spatial elements in mind may place too great a demand on H.C.'s working memory. H.C.'s difficulty with online processing of individual landmarks in relation to one another and recent performance on the blocked route task raised flags that she may have a working memory deficit. On most blocked routes, she had difficulty providing a fluid and accurate verbal description to the goal location, and she seemed to jump to particular parts of the route unexpectedly. She performed marginally better when her directions included notable landmarks rather than streets, which may speak to the use of a route-based navigation strategy rather than the use of a flexible cognitive map. These landmarks also may have made it easier for H.C. to keep track of her position along a route.

In the current study, H.C. was asked to provide detours for routes that were also used in the Google Street View task (Chapter 2). She was able to successfully navigate all routes on the Google Street View task, even when the route was mirrored, yet she was able to successfully navigate to only one goal destination on the blocked route task. It may be that solving a blocked route task is more challenging than navigating a mirrored route, as a mirrored route may be successfully navigated using a hippocampal-independent strategy (e.g., egocentric strategy). It is also possible, however, that the visual aids provided during dynamic virtual navigation place fewer demands on working memory compared to a blocked route task requiring the generation of a mental representation of space and verbal output.

Interest in the role of the medial temporal lobes in working memory has grown in the past few decades. Visual working memory deficits for faces, scenes, and abstract shapes and patterns (Holdstock, Shaw, & Aggleton, 1995; Olson, Moore, Stark, & Chatterjee, 2006; Owen, Sahakian, Semple, Polkey, & Robbins, 1995) and on complex tasks where elements must be bound together (Ezzyat & Olsen, 2008; Hannula, Tranel, & Cohen, 2006) have been documented in several cases and groups of adult-onset amnesic cases with medial temporal damage.

The possibility of working memory impairment in H.C. was unexpected as H.C. showed no evidence of a working memory deficit on neuropsychological testing (see Table 2.1). For example, her performance on the Digit Span was in the low average to average range. Perhaps there is a discrepancy because visual working memory tasks are more difficult than verbal working memory tasks, as there are fewer techniques that enable rehearsal (Ezzyat & Olson, 2008). Rose and colleagues (2012) tested H.C. on a delayed match-to-sample task for novel and familiar faces and words. They found that she was able to maintain familiar faces and words in mind for 1-8 seconds, but showed significantly impaired performance for novel faces, low-frequency words and non-words compared to controls. The authors took this as evidence that working memory for familiar stimuli can exist independent of the medial temporal lobe, but that the hippocampus is required for maintaining a novel stimulus in working memory. Rose and colleagues (2012) suggest that the demands to learn new relations among features are reduced when associations and representations already exist in semantic memory. Congruent results were found in neuroimaging studies, where the medial temporal lobe regions were found to be more active when maintaining novel information in working memory than familiar information (Ranganath & D'Esposito, 2001; Stern, Sherman, Kirchhoff, & Hasselmo, 2001). These results are discordant with the working memory difficulties seen on our tasks, which involve familiar stimuli. Perhaps task complexity plays a role; maintaining a famous face or word in mind is less challenging than maintaining elements from a complex visual representation of space. Yonelinas (2013) suggests that tests of working memory involve the hippocampus when items are complex or require fine discrimination. This may be why H.C.'s performance was intact on simple working memory tasks, such as the Digit Span. It is unclear whether H.C.'s difficulty on the mental navigation tasks is best explained by a strategic retrieval impairment, relational memory deficit, susceptibility to distraction, working memory deficit, or a combination of the above.

**Limitations**

One limitation of this study is that we did not have the opportunity to test H.C. on those mental navigation tasks that she had performed well on when first tested in 2010. We might have seen that her performance on these tasks improved beyond her intact ability in 2010 and results could perhaps speak to whether certain types of spatial information within an environment are more easily or efficiently learned. Similar to vector mapping, proximity judgment, and distance judgment tasks, the landmark localization and sketch mapping tasks assess one's ability to estimate distance and direction between landmarks. As such, it is conceivable that H.C.'s performance upon further testing on those tasks on which she was previously intact may have also remained consistent with her performance when tested the first time.

Another limitation of this study was that H.C.'s most recent scores on the mental navigation tasks were compared to the same controls who were tested in 2010. H.C.'s home environment is located in a remote part of Ontario, making it difficult to recruit individuals who are familiar with the environment. Therefore, the controls recruited for the original study varied in age, ranging from 16 to 50. As H.C. was 30 years old when re-tested on the mental navigation tasks, her age did not differ significantly from that of the controls ($t = 0.263$, $p = .803$), although it is important to be mindful that she was compared to a group with high variability in age.

We are unable to speak to how long it might take to form a representation of a familiar environment in an individual with an abnormal hippocampal system, as we did not attempt to have H.C. learn a new environment in this study. Nevertheless, it is clear that flexible and detailed representations of frequently travelled environments do not appear to emerge over an 8-year period of time in an individual with a compromised hippocampal system. In the future, H.C. could be formally tested on her knowledge of "new" spatial locations, learned since she was first tested in 2010, using mental navigation tasks to determine whether coarse information of such areas have formed. Better yet, she could be followed over an extended period of time to see how long it would take for her to form a representation of new landmarks or areas within her current environment, though it may be difficult to implement from a logistical standpoint (for a similar attempt, see Gardiner et al., 2008).

**Summary**

Building on results from the Google Street View study (Chapter 2), which showed that H.C.'s ability to navigate was intact and flexible when significant visual cues and an immersive environment were provided, the current study aimed to examine whether H.C.'s mental representation of that same environment improved and gained similar flexibility over the 8 years that elapsed since she was first tested on mental navigation tasks. Results from sketch mapping, landmark localization, landmark sequencing, and blocked route tasks suggest that H.C.'s representation continues to lack flexibility and remains impoverished in detail and coherence. To reconcile the discrepancy between results from the Google Street View paradigm and the re-testing of mental navigation tasks, other factors that could affect H.C.'s performance on the mental navigation tasks were considered.

H.C.'s impoverished representation of space is consistent with studies of adult-onset amnesic cases (Herdman et al., 2015) and could suggest that she lacks a detailed, perceptually rich representation of the environment in which she has lived her entire life. Alternatively, the lack of detail found in H.C.'s sketch maps and her difficulty sequencing landmarks that are close in space to one another could reflect a retrieval deficit. Further examination of the integrity of H.C.'s detailed representation of space is required.

H.C.'s poor performance on the sketch mapping, blocked route, landmark localization, and landmark sequencing tasks could indicate that H.C. has only a coarse, inflexible representation of her home environment in which spatial elements are not fully integrated. Her performance on the tasks hinted towards the possibility of additional deficits with working memory and relational memory, which also could have contributed to her impaired performance on these mental navigation tasks. It may be that an immersive virtual reality paradigm, such as that used in our Google Street View Study, provides additional cues or structure that aid in flexible navigation, or that it reduces the working memory demands as the environment is provided rather than conjured up by the participant. As proposed in the discussion in Chapter 2, it may be that mental navigation tasks are more sensitive to deficits in spatial memory than dynamic virtual reality tools. Results from this raise the possibility that the spatial deficits seen using mental navigation tasks could be better explained by broader deficits in working memory or relational memory, or perhaps H.C.'s difficulties on these tasks are due to a combination of these factors. Further examination of H.C.'s ability to bind objects and locations on a smaller scale than the environment is warranted, as is a more thorough investigation into her working memory.

# CHAPTER 4

## Study 3: Route description in developmental amnesia

When thinking of dissociations within spatial memory, researchers often focus on allocentric versus egocentric distinctions. Research in amnesic individuals with damage to the hippocampus points to another dichotomy: coarse or gist-like versus detailed representations of environments. Suggestion that the hippocampus may play an important role in maintaining or retrieving detailed representations of space is gleaned from several studies, beginning with an investigation of remote spatial memory in amnesic case K.C., a man with bilateral medial temporal lobe lesions incurred as an adult due to a motor vehicle accident (Rosenbaum et al., 2000). Adult-onset amnesic case K.C. was able to accurately estimate distance and direction on mental navigation tasks (such as those described in Chapters 1 and 3) designed for his home environment, which indicated that he had access to a representation of space that was sufficient for navigation. He included fewer landmarks and streets in his sketch maps and performed worse than control participants on a landmark recognition task, except for landmarks that were pertinent for navigation (Rosenbaum et al., 2000). These results led Rosenbaum and colleagues (2000, 2005) to surmise that the hippocampus was required for representing detailed features of remotely learned environments, but that individuals with hippocampal damage retained a schematic, gist-like representation of the same environment outside of the hippocampal system. Similar findings of impoverished sketch maps and difficulty on landmark recognition tasks were found in other adult-onset amnesic patients including D.G., a man who suffered anoxia secondary to cardiac arrest in 2010 and shows a characteristic amnesic pattern of preserved semantic memory in the context of impaired episodic memory, and D.A., a man who contracted herpes encephalitis in 1993 and shows severe damage to medial temporal lobe structures, including his hippocampi (Herdman et al., 2015). Further more, amnesic case T.T. reportedly could navigate along main artery roads to reach a destination, but had a hard time navigating along minor, non-artery roads (Maguire et al., 2006). Again, this is suggestive of impoverished representations of well-known environments that lack detail.

A study by Rosenbaum and colleagues (2015) provided evidence that H.C. had impoverished sketch maps and difficulty sequencing landmarks in close proximity to one another, which hinted that H.C. has an impoverished representation of her home environment that is lacking in detail and richness. As described in the previous chapter, H.C. was re-tested on mental navigation tasks to examine whether the seemingly coarse, inflexible representation of her home environment would change with an additional 8 years of frequent exposure. Results revealed few changes in H.C.'s performance: her sketch maps continued to be fragmented and lacked detailed elements such as landmarks and street segments. H.C. also had difficulty accurately placing well-known landmarks on a map consisting of only boundary streets, though her performance improved with added support in the form of pre-marked landmarks and streets. H.C. continued to have difficulty sequencing photographs of landmarks that were in close proximity to one another, and even greater difficulties when asked to correctly sequence landmarks on a map. In the latter case, she was provided with the name of the landmark rather than a perceptually rich visual cue (photograph).

H.C.'s pattern of performance on remote spatial memory tasks might indicate that she lacks access to a detailed representation of her home environment, resulting in the inclusion of fewer details on her sketch maps and impacting her ability to make fine-grained spatial-relational judgments. This interpretation could also help to explain H.C.'s intact ability to flexibly navigate familiar routes that had been mirror reversed in a virtual simulation using Google Street View as a platform (described in Chapter 2), where additional visual cues were provided. In effect, such cues could provide H.C. with a detailed representation of her home environment, which she has difficulty conjuring up in her own mind's eye, aiding in flexible navigation.

While her performance on mental navigation tasks hints that she may have an impoverished representation of space, a more thorough investigation of the integrity of H.C.'s detailed representation of her home environment is warranted. In this chapter, I reveal results from a route description study in which H.C. and healthy control participants were asked to provide detailed descriptions of very familiar routes. Transcriptions of these route descriptions were then segmented into meaningful bits of information that allowed for the evaluation of the proportion of spatial and detailed information within the description.

Further evidence implicating the hippocampus in vivid re-experiencing comes from Hirshhorn, Newman, & Moscovitch's (2011) route description study with healthy older adults, who experience normal age-related hippocampi volume reduction (Levine, Svoboda, Hay, Winocur, & Moscovitch, 2002). The collection of data was similar to that of this study - participants were asked to provide basic directions and, directly after, descriptive directions for a familiar route. Hirshhorn and colleagues (2011) found that the number of details on the route description task correlated with well-known tests of hippocampal integrity.

To rule out the possibility that healthy older adults' poor performance on the route description task was due to other brain structures that also undergo age-related changes, Herdman and colleagues (2015) tested three adult-onset amnesic cases (K.C., D.G., and D.A., previously described) on the route description task. While amnesic cases could provide intact descriptions of spatial properties along a route, their descriptions showed a paucity of perceptual features along the same routes (Herdman et al., 2015).

The impoverished representations of well-known environments are analogous to the impoverished descriptions of episodic events found in individuals with hippocampal compromise. Levine and colleagues (2002) found that older adults provide significantly less episodic details when recounting autobiographical memories compared to younger adults, and tend to favour semantic details that are context-independent. Kwan, Carson, Addis, & Rosenbaum (2010) found that developmental amnesic H.C. had significantly fewer episodic details in her constructions of past events. Indeed, several studies have found impaired episodic details in the context of relatively spared semantic facts in individuals with medial temporal lobe damage caused by a wide range of aetiologies (for reviews see Piolino, Desgranges, & Eustache, 2009 and Winocur & Moscovitch, 2011). Furthermore, functional neuroimaging studies show that hippocampal activation is positively correlated with the number of details or vividness of a recalled autobiographical memory (Sheldon & Levine, 2013) and indicate that it is the detailed representation of an event, not the temporal aspect, that is reliant on the hippocampus (Addis, Moscovitch, Crawley, & McAndrews, 2004; St-Laurent, Moscovitch, Levine, & McAndrews, 2009).

Findings of impoverished detailed representations of well-known environments or autobiographical events in the context of spared schematic or semantic representations in individuals with hippocampal damage or degeneration form the basis of the Trace Transformation Theory, which posits that the hippocampus is required for richly re-experiencing an environment or episodic event, as well as for richly experiencing non-mnemonic tasks, such as imagining a future or fictitious event (Rosenbaum, Winocur, & Moscovitch, 2001; Winocur &

Moscovitch, 2011). The Trace Transformation Theory builds off of the Multiple Trace Theory (Moscovitch, Nadel, Winocur, Gilboa, & Rosenbaum, 2006; Nadel & Moscovitch, 1997), which proposed that over time semantic information from a memory can be represented cortically, while episodic information continues to require the hippocampus, irrespective of the age of the memory. The Trace Transformation Theory accommodates the apparent dissociation of impoverished detailed representations, but spared schematic, gist-like representations of well-known environments, likening detailed representations to episodic memory and schematic representations to semantic memory. Winocur & Moscovitch (2011) argue that the initial, detailed memory and transformed, schematic memory can co-exist and interact. While it has been proposed that the hippocampus is always required for representing detailed, contextual features, it is unclear whether the hippocampus actually stores the detailed representation, or whether its involvement is related only to retrieving or binding objects with their spatial and temporal contexts to evoke the feeling of experiencing.

Another theory of hippocampal function, the Scene Construction Theory (Hassabis, Kumaran, Vann, & Maguire, 2007; Hassabis & Maguire, 2007; Maguire, Intraub, & Mullally, 2016), can also accommodate findings of impoverished descriptions of environments in amnesia. It suggests that the hippocampus enables the integration of spatial features into a coherent whole, which is critical for a sense of rich re-experiencing during spatial navigation, recollecting autobiographical memories, or imagining future events (Maguire et al., 2016). This theory proposes that spatially coherent scenes are at the center of hippocampal functioning, and form the context in which episodic memories can take place. Hassabis and colleagues (2007) found that adult-onset amnesic cases were unable to imagine future experiences within a spatially coherent, holistic representation of the environmental setting. Similarly, a functional neuroimaging study with healthy adults revealed extensive activation in the hippocampi when imagining fictitious and future scenes (Hassabis & Maguire, 2007).

The Scene Construction Theory, however, does not readily account for findings of intact schematic representations of well-known environments in adult-onset amnesic patients when tested on mental navigation tasks (Herdman et al., 2015; Rosenbaum et al., 2000). These studies suggest that coherent scenes or representations can exist in individuals with hippocampal damage, and is more in line with the Trace Transformation Theory. It is notable that Hassabis and colleagues' (2007; see also Hassabis & Maguire, 2007) studies were designed to evoke more of a sense of experiencing than would be expected with several of the mental navigation tasks. As several of the mental navigation tasks used in Herdman and colleagues' (2015) and Rosenbaum and colleagues' (2000) studies on which adult-onset amnesic cases were intact could be solved without envisioning a rich representation of the environment, the impaired scene construction seen in Hassabis et al. (2007) may be more reflective of a difficulty in richly imagining in the scenario, rather than a deficit in coherence.

The Hassabis and colleagues' (2007) study also involved the construction of a future, fictitious experience, rather than reconstruction of a past environment (as seen in Herdman et al., 2015, Rosenbaum et al., 2000). As such, we may see adult-onset amnesic cases' impairment on scene construction tasks (Hassabis et al., 2007) despite intact schematic representations of space (Herdman et al., 2015; Rosenbaum et al., 2000) because constructing future experiences is more challenging than past. Scene Construction theorists highlight that autobiographical memory and future thinking rely on a common neural network, and suggest that the scene construction deficit seen for imagining future events would likely extend to past events and environments. While Addis, Wong, & Schacter (2007) found considerable overlap in neural activity for past and future events when elaboration was required, they found that construction of a personal future event engaged the right hippocampus more so than remembering a past event, and likely requires greater cognitive demands. To our knowledge a scene construction task has not formally been applied to evaluate past experiences or environments.

The Scene Construction Theory seems to make sense of developmental amnesic case H.C.'s sketch maps that lacked cohesion and her difficulty describing a detour between two familiar landmarks on the blocked route task (see Chapter 3 and Rosenbaum et al., 2015). Therefore, it comes as a surprise that Hurley and colleagues (2011) found that H.C. was able to construct detail-rich future scenarios (but see Kwan et al., 2010). Maguire, Vargha-Khadem, & Hassabis (2010) suggest that discrepant findings of impaired imagination of future events in developmental amnesic H.C. by Kwan and colleagues (2010) can be explained by differences in methodology, whereby using single word cues for the construction of fictitious scenarios is more constraining than full sentences and makes the task more challenging. Preserved ability to construct spatially coherent fictitious scenes and future events has been found in other developmental amnesic cases, including Jon (Maguire et al., 2010) and school-age patients (Cooper, Vargha-Khadem, Gadian, & Maguire, 2011), suggesting that, unlike adult-onset amnesic cases, individuals with developmental amnesia can construct scenes, perhaps via use of functional residual hippocampal tissue or support of semantic memory. Although Maguire and colleagues (2010) reported that developmental amnesic Jon was able to construct coherent scenes, his ability to provide fine-grained sensory descriptions within those scenes was borderline impaired, which may suggest that his scene constructions are not very detailed, despite being coherent. H.C., on the other hand, was able to provide such details. Intact, sensory-rich scene construction for future imagined events in H.C. (Maguire et al., 2010) is at odds with the fragmented, inflexible, and impoverished representation of a well-known environment found by Rosenbaum et al. (2015).

In the current study, we aimed to examine whether the pattern of impoverished detailed representations of frequently travelled environments in adult-onset amnesic cases, which limits rich re-experiencing of the environment during recall (Herdman et al., 2015), is also present in developmental amnesic case H.C., despite the greater potential for functional reorganization. We adopted a modified version of Hassabis and colleagues' (2007) scoring procedure (as described in Herdman et al., 2015) to segment transcripts of familiar route descriptions into detailed and spatial information. In keeping with the Trace Transformation Theory, we predicted that H.C. would have an impoverished route description, based on findings of significantly fewer details contained within H.C.'s sketch maps of her home environment and difficulties on mental navigation tasks that require a fine-grained representation of the environment (Rosenbaum et al., 2015). It was also plausible that H.C. would perform similarly to controls on the route description task, as she had on tasks involving the construction of novel, fictitious scenes and future scenarios (Hurley et al., 2011), from which we derived our (slightly modified) scoring procedure. Here we report results assessing H.C.'s description of a familiar route within her frequently travelled home environment, rather than novel scenes and future, fictitious scenarios.

## Methods

### Participants

Developmental amnesic case H.C. (described above) was 28 years old when she took part in this study and her performance was compared with that of 31 healthy controls (19 female) matched in age ($\mu$ =28.935 years, *SD* = 4.358) and education ($\mu$ = 16.516 years; *SD* =

2.027). Controls were recruited through H.C.'s family, online advertisements, and by postings at York University. Twenty-three of the controls in this study also completed Study 1 (reported in Chapter 2), including H.C.'s sister and husband. Healthy control participants reported normal or corrected-to-normal vision and hearing, and no history of neurological or psychological illness. This study was approved by the ethics boards at York University and Baycrest Hospital. All participants gave informed written consent and were provided with monetary compensation for their time.

**Procedure**

Participants were asked to describe a very familiar walking route. Each route was unique to the participant, except for H.C. and her husband, who described the same route. To compare performance across participants, experimenters asked for routes that took approximately 10 minutes to walk. Participants were first asked to provide the basic directions necessary to get from their start point to their end location. They were then asked to provide descriptive directions. That is, describe the route again in as much detail as possible, providing information not only about what things looked like, but also where features of the environment were in relation to each other and to themselves as they progressed along the route. Participants were allowed to continue with their descriptions until they reached a natural end. The experimenter then probed participants for further detail about three landmarks that the participant had mentioned.

**Scoring Procedure**

Route descriptions were transcribed and then scored by a scorer blind to group allocation and double-checked by KH. Route descriptions were segmented into meaningful units of information, with statements classified into three categories (spatial reference, entity, or sensory description) based on a modified version of Hassabis and colleagues' (2007) scoring procedure (as described by Herdman et al., 2015). The entities category consisted of distinct items that were mentioned (e.g., landmarks, objects, or people). The spatial references category included statements about explicit measurements, the relative positions of entities in the environment as they pertain to each other and to the participant, and directions as described from the participant's vantage point. Descriptive statements about any entity were classified as sensory descriptions, regardless of modality, as were commentaries on weather. Any repeated or irrelevant statements that did not fit into the former categories were not included in the total output, as they did not make substantial contributions to our understanding of spatial-perceptual representations of very familiar routes. Unlike Hassabis et al. (2007), there was no limit on the score in each category, as we strived to represent the total content of the descriptions. Following the same method as Herdman et al. (2015), the number of statements in each category was divided by the participant's total output, allowing examination of the proportion of each individual's total output that was attributed to spatial references, entities, and sensory descriptions, while controlling for variations in total verbal output among participants. To examine whether additional support in the form of probing for extra details would boost H.C.'s proportion of fine-grained information (entities and sensory descriptions), we examined descriptions prior to probing, and again afterwards.

Each participant's route description, as a whole, was also subjectively attributed a quality judgment by the blind scorer. The descriptions were rated out of 10 and based solely on how vividly the scorer was able to envision the route after reading the participant's description. A score of 0 indicated that scorers were completely unable to imagine a detailed, vivid, perceptually rich route based off of the participant's description, while a score of 10 indicated that the description evoked a very rich picture in the mind's eye of the scorer.

## Results

H.C. was able to accurately describe the basic directions necessary for travelling a well-known route, which suggests that she retains a representation of her home environment that is sufficient for navigation. She described the basic directions for a very familiar walking route from the house in which she currently resides to her in-laws' house. As H.C.'s husband was also very familiar with this route, H.C.'s description of the route was compared directly to her husband's description. Sample transcripts of H.C.'s and her husband's descriptive directions of the route (before probing) are presented in Figures 4.1 and 4.2, respectively. Note that H.C. chose to describe only a portion of the route in detail, whereas her husband described the route in detail in totality. For comparison purposes, the part of the route where H.C. began her detailed description is marked on her husband's detailed description (Figure 4.2).

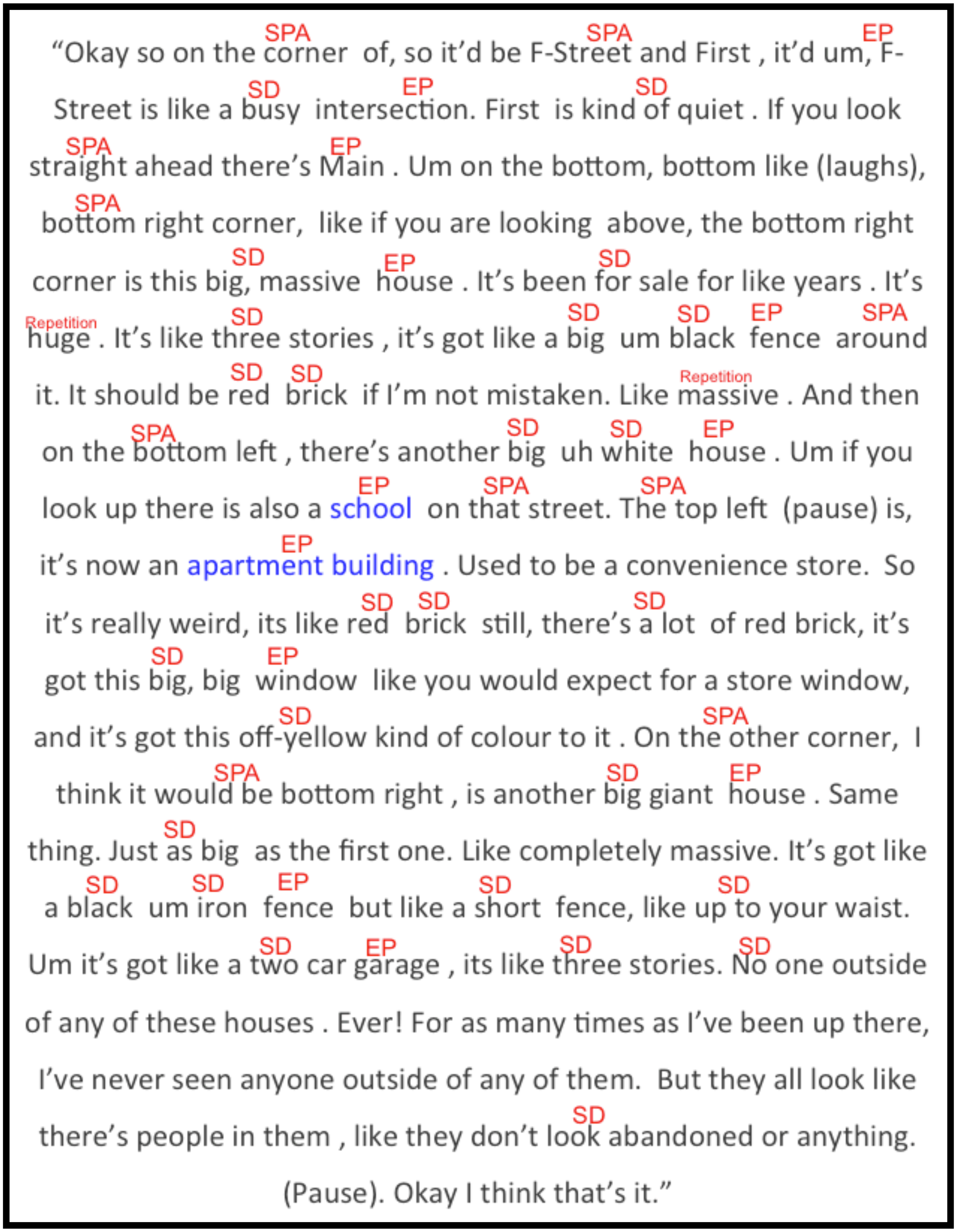


*Figure 4.1.* Developmental amnesic case H.C.'s descriptive directions from the route description task, before probing, with scoring using a modified version of Hassabis et al. (2007; as described in Herdman et al., 2015). Blue font represents landmarks that were incorrectly placed on the route.

"When we exit our house on the right side you'd see an open field with also a bike path. On the left side it would be all residential buildings . We walk down that to the left ... Um am I still using street names in addition to describe stuff if it makes things easier? (Sure). We turn down on, turn right on Third which is on the left side, it's just a couple subdivisions . On the right side it's, there's one business . It's uh I believe it's a dental office of some sort. We then take a left on Fisher Street , which is a mix of residential , mostly residential buildings. We would walk down that. Uh halfway down our path on Fisher on the left side there would be an automotive detailing business . On the right side it continues to just be residential buildings, residential areas. **[HC began detailed description here].** Continuing down that, it would just be houses until we hit First Avenue West , where we take a right . Standard houses , uh mostly um non-rental it seems , would be most of the way down until you hit roughly about Ferguson I believe where you'll run into a park on the right side . It's a monument in memory of our war veterans in which there is a statue of a soldier and on it it has the names of lots of soldiers that have passed. It's a pretty common park for people to sit at and large events usually gather at this location . Going more forward , right beside that would be a government building. Again this is on the right side. On the right side, it continues to just be residential . Then moving a little more forward , it's mostly a mix of commercial and residential on the right side, with the left side being completely residential . Right until you hit, right around Cassells , where the right side you would have Max Mart , and on the left side you'd have McGuinty Funeral Home . You'd cross the street continuing on down First Avenue West. On the right side you'd have the Casse Populaire and on the left side you would see a bunch of residential units , which would include my parents' house."

*Figure 4.2.* Developmental amnesic case H.C.'s husband's descriptive directions from the route description task, before probing.

H.C.'s performance on the route description task prior to probing and after probing was compared to that of controls using Crawford and Garthwaite's (2002) modified t-test procedure. All analyses were tested at a significance level of $p < .05$. H.C.'s total output generated without probing included a similar proportion of spatial references compared to controls (Figure 4.3). The proportion of spatial references in H.C.'s total output (0.300) did not differ significantly from that of controls (0.304 (*SD* = 0.095); $t = -0.041$ $p = .484$). This was unexpected, as we predicted that an impoverished description lacking in entities and sensory descriptions would cause the proportion of spatial references to be larger. While H.C.'s total output consisted of a significantly smaller proportion of entities (0.300) compared to controls (0.521 (*SD* = 0.089; $t = -2.444$, $p = .010$), she provided a significantly higher proportion of sensory descriptions (0.400) compared to controls (0.175 (*SD* = 0.105); $t = 2.109$, $p = .022$).

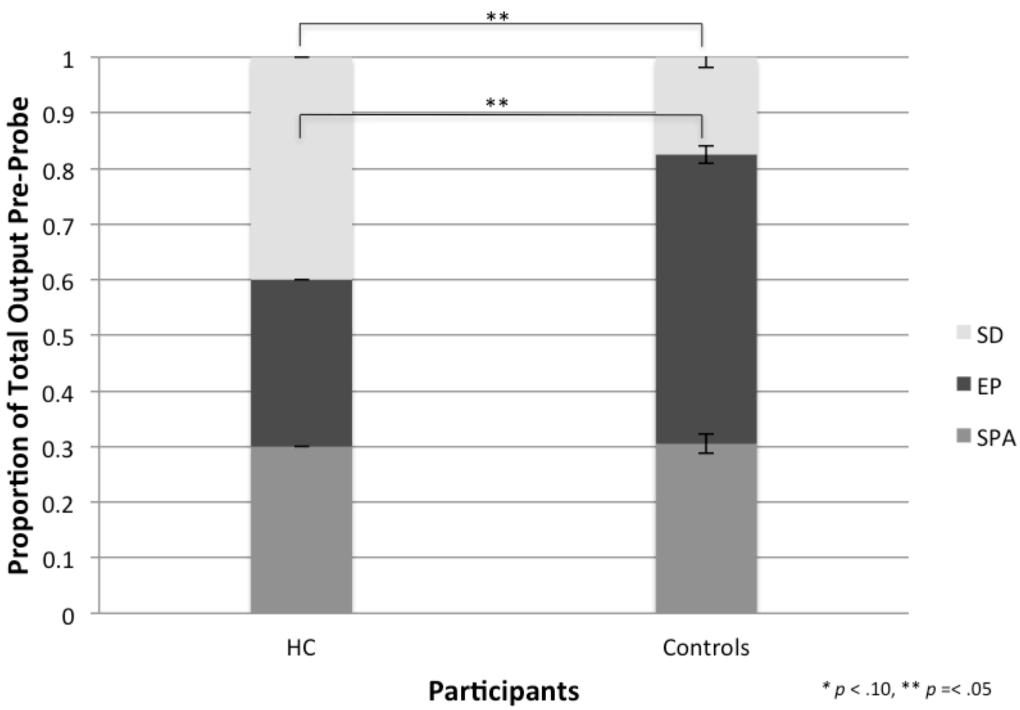


*Figure 4.3.* Developmental amnesic case H.C.'s and control participants' proportion of total pre-probe route description segmented into sensory descriptions (SD), entities (EP), and spatial references (SPA). Error bars represent standard error.

Post-probe analysis revealed that the proportion of H.C.'s total output attributed to spatial references, entities, and sensory descriptions remained roughly the same as seen pre-probe (Figure 4.4). The proportion of her post-probe output attributed to spatial references (0.278) remained similar to that seen in controls (0.251 (*SD* = 0.081; *t* = 0.328, *p* = .373). As seen in the pre-probe condition, her total post-probe output consisted of a significantly smaller proportion of entities (0.331) compared to that produced by controls (0.490 (*SD* = 0.092; *t* = -1.701, *p* = .050). The proportion of sensory details produced by H.C. in response to probing (0.391), however, continued to be higher than that of controls (0.259; *SD* = 0.093), and approached significance (*t* = 1.397, *p* = .086). Contrary to our predictions, these results suggest that H.C.'s ability to generate fine-grained sensory details of elements along her route is on par with controls, even without probing.

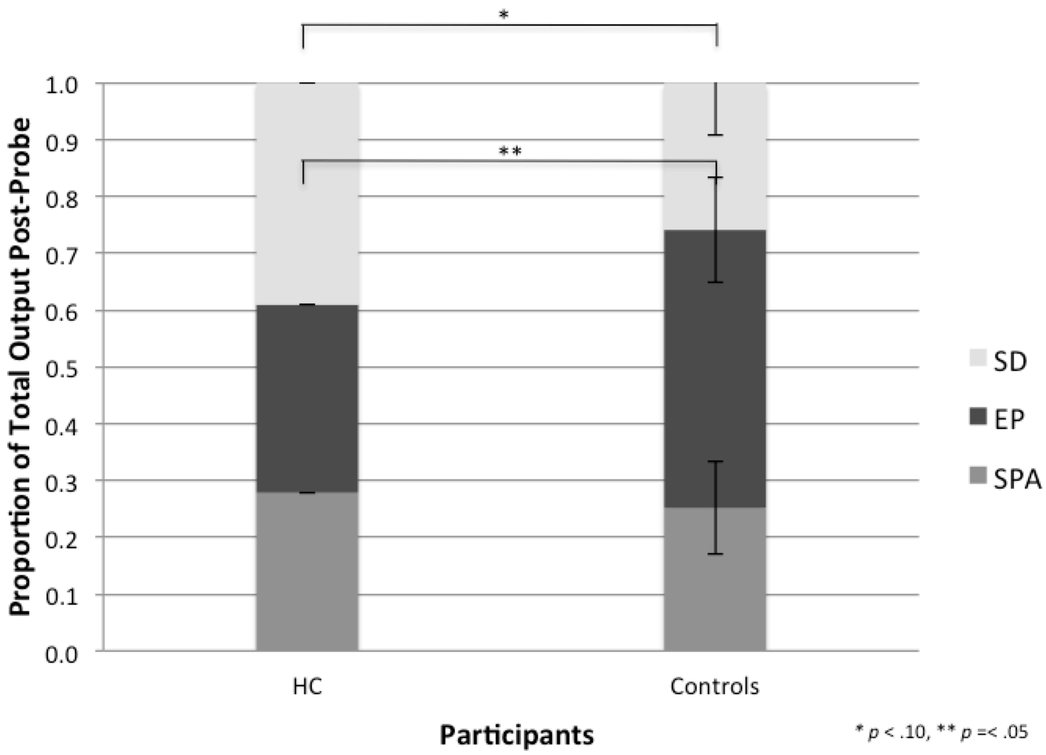


*Figure 4.4.* Developmental amnesic case H.C.'s and control participants' proportion of total post-probe route description segmented into sensory descriptions (SD), entities (EP), and spatial references (SPA). Error bars represent standard error.

A blind scorer's rating of the quality of H.C.'s route descriptions on a scale of 0 to 10 (7.5) did not differ significantly from ratings of healthy controls' descriptions ($\mu$ = 7.224 (*SD* = 0.830); $t = 0.327$, $p = .373$), meaning that the scorer was able to richly envision walking along the route that H.C. described just as well as she envisioned walking along controls' routes. This finding was unexpected, as previous research with mental navigation tasks showed H.C. had an impoverished representation of her home environment that we expected would not be sufficient to enable her to describe the route in a way that would evoke a sense of experiencing in the scorer.

A qualitative examination of H.C.'s route description revealed some curiosities. As seen in Figure 4.1, H.C. provided descriptive directions for only a portion of her route. Participants were asked to select two or three blocks of the route to describe in further detail and probing began only after the participant came to a natural end. It is noteworthy that she did not describe actually navigating along the route when providing descriptive directions, instead describing what one might see at a particular intersection, including information about where landmarks are located in relation to each other and in relation to herself as she envisioned the area, as well as detailed perceptual information about the appearance of visual features along the way. On the surface, her description seemed to be quite fluid and detailed, yet she included landmarks that are not actually located on her route or visible from her route. For example, she stated, "If you look up there is also a school on that street." While there is a school on the street, it is a block and a half from the intersection she was describing and would not be visible along the route. After mention of the school, she said, "The top left [pause] is, it's now an apartment building. Used to be a convenience store." In actuality, this apartment building exists one block west of the intersection, is hard to see from that vantage point, and would fall outside of H.C.'s route from her home to her in-laws' house.

Although H.C.'s directions were very fluid in terms of vocal quality, her actual descriptions of the locations of landmarks were quite fragmented. She described what can be found on various corners of the intersection, recalling a "massive house" on the "bottom right" corner (as she envisioned it) and a "white house" on the "bottom left" corner, which do stand opposite one another in reality. After mentioning the school, H.C. stated that the apartment building (described above) is on the “top left” of the intersection, which is incorrect. She then went on to re-describe the same “massive” house with the black iron fence as if she hadn’t mentioned it before.

The examiner did not have access to Google Street View to ascertain the veracity of H.C.’s description until after testing. As such, one of H.C.’s probes was the school. H.C.’s description of the school was very detailed and included information about what things looked like and where elements were located in relation to each other and to her. She also was asked to describe the “white house” in further detail and provided a rich description of what it looked like. Finally, she was asked to describe the convenience store that was converted into an apartment building in further detail. H.C., however, described another building that is, in reality, located along her route - a house that was converted into a store. The perceptual details that H.C. provided were consistent with what the examiner observed on Google Street View after testing.

## Discussion

The purpose of the current study was to examine the extent to which detailed representations of a familiar environment are preserved in a case of developmental amnesia. Developmental amnesic case H.C. was able to provide basic directions from her house to her in-laws’ home, which supports previous assertions that H.C. has an intact schematic representation of her home environment (or at least an intact representation of that particular route) that is sufficient for navigation. However, her route description was fairly simplistic in nature, requiring only three turns. Her route description without and with probing consisted of a similar proportion of spatial references as that of control participants. Although we anticipated that she would show a greater proportion of spatial references (owing to a smaller proportion of detailed entities and sensory descriptions), these results still suggest that H.C. retains a schematic, gist-like representation of her home environment, or at least of the particular route on which she was tested. Closer examination of H.C.'s route description revealed that H.C. included descriptions of landmarks that did not fall along her route and had difficulty accurately describing the spatial relations between landmarks at an intersection. It seemed as though H.C. could envision a scene along her route but was unable to envision the same scene from another viewpoint or bind that scene with the features around it.

Contrary to our predictions, the proportion of sensory descriptions in H.C.'s route description was similar to the proportion seen for control participants for the post-probe condition, and significantly higher for the pre-probe condition. This indicates that H.C. may have access to detailed, perceptual information about entities. Indeed, H.C. was able to describe several entities in detail, commenting on the colour and material of landmarks and other spatial features, although some of the landmarks she described were not actually located along her proposed route. Perhaps H.C.'s route description consisted of a higher proportion of sensory descriptions compared to controls because she may have chosen to describe those aspects of the environment with which she felt more confident. As she appeared to have difficulty binding the location of entities in relation to other entities, she may have described those aspects of the scene that were easier for her to envision, such as the internal features of landmarks, rather than the relation of those landmarks to surrounding spatial features.

H.C. had a significantly smaller proportion of entities than controls in her pre-probe and post-probe descriptions. It is notable, however, that when H.C.'s entities and sensory descriptions were combined (Pre: 0.700, Post: 0.722) they made up a similar proportion of the total output as seen in control participants (Pre: 0.696, Post: 0.749), which suggests that H.C.

had a similar proportion of her route description comprised of these detailed types of information about the environment. Interestingly, H.C.'s score on the blind quality judgment measuring the degree to which the route description evoked a sense of vividness and experiencing in the scorer also did not differ from controls' scores.

These results, particularly that H.C.'s total output consisted of a similar proportion of sensory descriptions describing the perceptual properties of entities, suggest that H.C. has access to a detailed, fine-grained representation of her home environment. This is discordant with the impoverished sketch maps found in Rosenbaum et al. (2015), however other factors, such as working memory or relational deficits, could have impacted the sketch map results. On the other hand, the current results are in keeping with Hurley and colleagues' (2011) study with H.C., where she was asked to construct a future scenario. When transcripts of future scenarios were segmented into categories, no significant differences were found between H.C. and controls on the number of spatial references, entities, or sensory descriptions (Hurley et al., 2011). Based on these findings, it seems that H.C. is able to access vivid representations of fine-grained aspects of well-known environments, but has difficulty locating landmarks in relation to other landmarks.

**How Might H.C. Generate Detail that is Sufficient for Imagining?**

It is unclear why H.C.'s route description differed from the impoverished descriptions of routes (Herdman et al., 2015) and impaired scene construction (Hassabis et al., 2007) found in adult-onset amnesic cases. Despite findings in adult cases, it may be that the hippocampus is not required for accessing detailed representations of well-known environments or constructing coherent scenes. Here we propose the following other possible reasons, which we believe represent more likely explanations for H.C.'s intact route descriptions:

**Residual hippocampal tissue.**

Although H.C.'s hippocampi are reduced in volume and atypically oriented (Olsen et al., 2013; Rosenbaum et al., 2014), she still has residual hippocampal tissue that could be sufficient for generating a detailed description of a well-known route. While Hassabis and colleagues (2007) found most adult-onset amnesic patients were unable to construct coherent future scenarios, implicating the hippocampus in scene construction, one patient with hippocampal damage, P01, was able to construct future scenarios. In a functional neuroimaging follow-up study with P01, Mullally, Hassabis, & Maguire (2012) identified that he activated residual tissue in his right hippocampus when constructing scenes. Adult-onset amnesic case P01 was able to utilize his right hippocampus, despite volume reduction of 46.2%. H.C. shows a volume reduction of 29.5% and 31.2% in the left and right hippocampi, respectively (Olsen et al., 2013). If residual hippocampal tissue in amnesic case P01 was sufficient to construct spatially coherent scenes, despite a 46.2% volume reduction, it stands to reason that H.C. may be able to do the same, given that her volume reduction is not as large. To investigate this possibility, a future study could use fMRI to examine the brain areas that are activated in H.C. when describing a familiar route.

**Functional reorganization.**

H.C.'s intact detailed representation of her home environment may also be explained by functional neural reorganization. Developmental amnesic cases possess a greater predisposition for functional reorganization compared to adult-onset amnesic cases, due to the fact that the brain of such an individual is presented with the opportunity to restructure itself during the early stages of life, when neural networks are being established. Evidence of functional reorganization has been found in developmental amnesic case, Jon. When asked to imagine future scenarios, Jon showed intact scene construction (Maguire et al., 2010). This led Mullally, Vargha-Khadem, & Maguire (2014) to examine the brain regions activated during scene construction in Jon using fMRI. They found that Jon activated several regions of the brain that have previously been implicated in imagining scenes, including the posterior parietal, retrosplenial, posterior cingulate, and ventromedial prefrontal cortices, but showed negligible activation in his hippocampi compared to controls (Mullally et al., 2014). They suggested that he relied on these other brain structures to successfully construct a coherent scene (Mullally et al., 2014). As such, successful recall of details from H.C.'s well-known environment could occur if that typically hippocampal-dependent task was taken over by (an)other brain structure(s). It is possible that an fMRI investigation while completing our route description task would show activation of similar brain regions in H.C as seen in developmental amnesic case, Jon.

If functional reorganization underlies H.C. and other developmental amnesic cases' intact performance on route description and scene construction tasks, the mechanism by which this could occur is unknown. Developmental amnesic cases typically show impaired episodic memory in the context of spared semantic memory (Vargha-Khadem et al., 1997). Gardiner and colleagues (2008) demonstrated that individuals with developmental amnesia could acquire semantic knowledge over an extended period of time. In a similar vein, H.C.'s previously reported intact performance on mental navigation tasks estimating distance and direction (Rosenbaum et al., 2015), and ability to navigate routes using Google Street View paradigm (Chapter 2) suggest that learning can also occur for a larger-scale environment with substantial exposure and time. It may be that developmental amnesic cases make use of their intact semantic memory to support their description of frequently travelled routes or construction of scenes.

***Possible mechanism: Semanticization of detailed information.***

Perhaps detailed information can be acquired in a similar way as semantic or schematic information in developmental amnesia, with extended time and exposure. It is possible that H.C.'s repeated exposure to her environment allowed her to "semanticize" the information, and overtime learn the intricacies, which could have not only helped her navigate, but also assisted in the creation of a relatively rich and coherent representation of the environment. With enough exposure, details of landmarks or features of the environment that are frequently encountered may undergo a type of "semanticization." If this were the case, H.C. would be able to recall detailed perceptual features of landmarks that she engages with on a regular basis more easily than those landmarks with which she has less experience. In a similar vein, Brandt, Gardiner, Vargha-Khadem, Baddeley, & Mishkin (2006) examined factors that could boost episodic-like recall in developmental amnesic case Jon. They found that his ability to recall words from a new word list was better after four trials compared to one, and speculate that the additional exposure was more effective for learning because it was less reliant on episodic memory as it "decontextualized the learning experience" (Brandt et al., 2006). Essentially it enabled episodic-like information to be encoded into semantic memory. Repetition may play a similar role for encoding detailed information about the environment into a schematic representation of space. They also found that Jon was better at remembering words that he had generated a semantic associate for, compared to a rhyming word, again suggesting that semantic memory can assuage the recall impairment typically seen in developmental amnesia (Brandt et al., 2006). Interestingly, Blumenthal and colleagues (2017) found that when H.C. was asked to write down as many features as possible for different concepts (e.g., pig, shoes), she generated a similar number of intrinsic features (e.g., colour and shape) as control participants, but significantly fewer extrinsic features (e.g., how something is used, where it is typically located). This distinction in semantic memory seems to parallel findings from the current study, where H.C. could generate perceptual features of landmarks (intrinsic), but had difficulty placing these landmarks in context relative to other landmarks (extrinsic).

It is possible that when H.C. was asked to describe a route in detail, she conjured up any aspects of the environment that she had extensive experience with, which might explain why some of the landmarks she described were not on the route. For example, the convenience store-turned-apartment building described in her descriptive directions is located on a main street that H.C. frequently travels along, which makes it possible that the details were learned with extended time and experience. In contrast, however, H.C. was able to provide a detailed description of a school that she never attended which was located off the route on a side street that she does not take as often.

#### ***Possible mechanism: Semantic and world knowledge increase detail in descriptions, but prevent a rich sense of experiencing.***

Results from Mullally and colleagues' (2014) fMRI study suggest that developmental amnesic case Jon is able to construct spatially coherent scenes for future scenarios without the hippocampus. They argue that preserved semantic memory and knowledge about the world, in conjunction with intact reasoning ability, may underlie this non-hippocampal dependent scene construction. If one knows how a particular type of event typically unfolds, this may aid in the construction of a future scenario. Klein (2013) also found that semantic memory enables future thinking. Conceivably semantic and world knowledge could also help generate details, or "fill in the blanks" in an individual's schematic representation of space. In the current study, H.C. could have been aware there was a school, but may have had difficulty conjuring up a picture of the school in her mind's eye. She could have successfully described features of and near the school using semantic knowledge, however, which could have enabled her to envision a school (albeit, not the actual one). For example, she mentions a basketball court and playground near the school, features which are found at most schools. H.C., however, was able to provide detailed information about the school that would go beyond what would be expected if she were solely relying on world knowledge. For example, she accurately described the relation of the basketball court and playground relative to the school, which is not consistent at every school, and she mentioned the location of a gravel pit, which would not be a stereotypical feature at a school.

Mullally and colleagues (2014) suggest that while developmental amnesic cases show intact performance on scene construction tasks, they may not be visualizing the scene in their mind's eye. Although Jon was reported to have intact scene construction, Jon showed borderline impairment on the number of sensory descriptions he conjured up in his future scenario (Maguire et al., 2010). This is consistent with the Trace Transformation Theory's idea that the hippocampus is always required for representing detail. Indeed, Jon has shared that he finds it difficult to visualize things in his mind's eye (Maguire et al., 2010). Conjuring up imaginary scenarios seems to be quite effortful for Jon, who told Maguire and colleagues (2010), "It doesn't come at the snap of a finger, like it does with other people, I have a starting point and then fill in the details" (p. 3191). This led Maguire and colleagues (2010) to suggest that the non-hippocampally-dependent scene constructions may not be based on true visualization, as would occur with a functioning hippocampus.

H.C., on the other hand, did not differ significantly from controls on the number of sensory descriptions provided when envisioning a future scenario (Hurley et al., 2011) and before probing, she had a higher proportion of sensory descriptions compared to controls for this study's route description task. She also did not report significantly different ratings for vividness of the scenario or sense of presence within the scenario (Hurley et al., 2011). Hurley and colleagues (2011) report that H.C. was unable to describe her strategy for constructing scenarios and suggest she may consider her representation to be vivid and coherent, but that the nature of her hippocampal damage might have made it impossible for her to truly visualize a scenario, so her perception of what constitutes vividness may differ from that of controls (Hurley et al., 2011). While this is a possibility, H.C.'s intact number of sensory descriptions compared to controls suggests that H.C. is able to vividly imagine a scenario. Unfortunately, ratings of vividness and a sense of re-experiencing were not collected for H.C.'s route description, which could have shed more light on H.C.'s ability to conjure up a rich representation of her home environment.

**Inaccurate details within descriptions.**

A third possibility that could explain how H.C. managed to have a comparable amount of detail in her route description as controls is that details she provided could have been inaccurate. Rose and colleagues (2012) found that H.C. recalled a larger number of intrusions than controls on a delayed-match-to-sample task for famous and non-famous faces. They speculated that H.C. might have a very liberal report criterion, such that she reports anything that comes to mind in an attempt to compensate for her memory deficit (Rose et al., 2012). A verbal task like the route description in this study may be more prone to such confabulation compared to a delayed-match-to-sample or paper-and-pencil task, as it might put more pressure on the participant to provide a description that sounds fluid. This could explain why we see detailed route descriptions but impoverished sketch maps in H.C. As described in the results, H.C. seemed to have difficulty forming a coherent representation of space, but the details provided to describe perceptual features of landmarks were found to be accurate. As such, we rule out the possibility that the proportion of sensory descriptions provided by H.C. were inflated by inaccurate details about entities.

It is important to note, however, that H.C.'s proportion of sensory descriptions, entities, and spatial references included those landmarks that she described that fell outside of her planned route. Since the examiner could not confirm the accuracy of entities along the route while H.C. was providing her detailed description, the examiner probed some of the landmarks off the route. As such, removal of those landmarks would have put H.C. at a disadvantage.

**Impact of Results on Theories**

On the surface, findings of rich route descriptions in developmental amnesic H.C. could be considered at odds with the Trace Transformation Theory (Winocur & Moscovitch, 2011), as it provides evidence that some detail may exist outside of the hippocampus and be readily accessed, even before cues or probes are provided. H.C.'s ability to recall details about entities, above what would have been expected if relying on a schema or semantic memory, further supports the notion that she has access to an intact detailed representation of her home environment. As previously noted, individuals with developmental amnesia have a propensity for functional reorganization. As such, findings of rich detailed representations of space in developmental amnesia would not debunk the proposal that the hippocampus is required for accessing detailed representations that enable re-experiencing in individuals with *typical* hippocampal development.

Moscovitch, Cabeza, Winocur, & Nadel (2016) suggest that the hippocampus is responsible for creating complex events, enabling a rich sense of experiencing by binding objects with their spatiotemporal contexts. They proposed that prior to reaching the hippocampus, sensory information is bound to objects and contexts in sensory and cortical medial temporal lobe regions (Moscovitch et al., 2016). From this perspective, the types of sensory details provided by H.C. in the current study would not rely on the hippocampus, whereas the integration of the entities into a spatial context would. Interestingly, a qualitative examination of H.C.'s route description revealed difficulty creating a cohesive representation that integrated various landmarks, even when those landmarks' perceptual features could be described in detail.

The suggestion of a lack of coherence in H.C's route descriptions is in contrast with H.C.'s reportedly intact scene construction for future scenarios (Hurley et al., 2011). One difficulty that arises when comparing studies is that a scene is not fully operationalized in Hurley and colleagues' study. Assuming that scene construction involves describing a scenario from only one point of view, then one could interpret H.C.'s ability to accurately describe an intersection from one point of view in the current study as intact based on the Scene Construction Theory. When required to alter her mental representation by shifting her point of view, however, H.C. had difficulty binding the original scene with the features around it. Mullally and colleagues (2014) believe that the non-hippocampal-dependent semantic strategy that may be used for scene construction in developmental amnesia would be inadequate for spatial navigation, where vivid visualization of the scene in one's mind's eye is required. As such, one might speculate that they would also predict impairment in shifting viewpoints. Perhaps H.C. was intact on the scene construction task because she had to bind a scene together, a less challenging task then binding several scenes together, as would be required for mental navigation of a route or rotation within an imagined intersection. It may also be the case that the ability to extend the boundaries of a representation and imagine what comes next may be impaired in developmental amnesia, despite intact scene construction. To our knowledge, boundary extension has not been formally tested in developmental amnesia.

**Revisiting the Possibility of a Relational Memory Deficit**

H.C.'s difficulty accurately describing the location of landmarks relative to other landmarks along a familiar route is consistent with a relational memory deficit. The Relational Memory Theory proposes that the hippocampus is required for creating memory representations of all types of relations, including spatial relations (Eichenbaum, 2017). The inability to bind spatial relations would lead to a fragmented representation of an environment, as was found in H.C.'s sketch maps (Chapter 3). H.C.'s difficulty binding entities to their locations and in relation to other entities limited her ability to mentally navigate a familiar route. While H.C. could accurately describe perceptual details of landmarks and a scene as imagined from a single viewpoint, she was unable to bind together the locations of landmarks to mentally navigate from one to the other. This is evident from her inclusion of landmarks that do not fall along the route and incorrect placement of landmarks on the corners of an intersection.
H.C. can retrieve landmarks from memory, but she does not seem able to retrieve the relations between them. It is also possible that H.C.'s hippocampal compromise affects her ability to encode the spatial relations in the first place, which is detrimental for subsequent recall or recognition. Olsen and colleagues (2015) reported that H.C. could not recognize faces studied from variable viewpoints but could recognize faces studied from a single viewpoint. This led the authors to propose that the hippocampus is needed to flexibly integrate item representations

across different viewpoints but that extrahippocampal regions are sufficient for encoding when the viewpoint does not vary across repetitions. Results from these studies highlight the important role of the hippocampus in binding elements into a flexible relational representation.

### Revisiting the Possibility of a Working Memory Deficit

Similar to her performance on the blocked route task (described in Chapter 3), when H.C. was asked to describe her familiar route in more detail, she seemed to have difficulty keeping track of what elements she had already described and where she “was” in her imagined scene. It seemed as though she had difficulty maintaining her viewpoint in her mind’s eye. This could be due to difficulty integrating various elements in an environment into a cohesive whole, or difficulty truly envisioning the scene. However, the fact that she seemed to jump from one scene to another and forget what she had described only moments before suggest that a deficit in working memory could also be at play. A possible deficit in working memory could underlie or contribute to the lack of coherence seen in the route description task.

### Limitations

This study aimed to assess the integrity of H.C.’s detailed representation of her home environment. H.C.’s ability to provide basic directions from her home to her in-laws’ house was intact, which was taken as support that she has a coherent representation of her home environment (or at least a coherent representation of a route within the environment) that is sufficient for navigation. Interestingly, she seemed to have difficulty forming a coherent representation of a portion of the same route when she was trying to imagine what she saw along the way. It is possible that H.C. was able to provide basic directions of the route because she could focus on a few pertinent features within the environment to aid navigation. With the added task of imagining a detailed representation of the route, she seemed to lose track of where she was, leading to an incoherent representation, even on a smaller-scale at just one intersection. This study would have benefited from the addition of vividness ratings, sense of experience ratings, and the Coherence Index (see Hurley et al., 2011). The Coherence Index asks participants to reflect on the level of fragmentation seen in the scene they just imagined. They provide a list of statements and ask participants to mark the ones that best describe their experience of recalling the scene. Statements include, " I could see individual details, but it didn't all fit together as a whole scene," "It wasn't so much a scene as a collection of images," and, "It wasn't a scene you could step into; it wasn't really joined-up." Comparing level of vividness and sense of experiencing ratings after the basic directions instruction and again following the instruction to provide detailed directions could have provided insight into whether the detail that H.C. was conjuring up was interfering with her ability to recall a coherent representation of her home environment. In addition, H.C.'s responses on the Coherence Index would have provided us with additional insight into whether the scenes H.C. described on the route description task felt incoherent to her.

**Summary**

Contrary to our hypotheses, H.C.'s proportion of detailed features was similar to, and at times better than, that of controls. This suggests that H.C. has a detailed representation of her home environment on which to call upon, despite having abnormal hippocampal development. Functioning residual hippocampal tissue may explain H.C.'s ability to describe perceptual features of entities. Alternatively, detailed information may be learned with extended time and exposure. Another possibility is that semantic knowledge may support the retrieval of detailed information. While semantic and world knowledge could allow H.C. to "fill in the details" of a schematic representation of space, her ability to describe non-stereotypical aspects of particular landmarks suggests that she does, in fact, have access to a detailed representation of her home environment. Strikingly, while H.C. was able to provide basic directions from her home to her in-laws' house, her description of an intersection along the route was incoherent when she was asked to describe what she saw along the route. It seems she is able to describe the very fine-grained detailed of objects and landmarks, but struggles to bind scenes together into a cohesive whole. H.C.'s inability to accurately describe certain entities' locations in relation to other entities may be best explained by a spatial-relational deficit, and be compounded by working memory difficulties.

# CHAPTER 5

## General Discussion

In this dissertation, I aimed to investigate the integrity of spatial representations of frequently travelled environments in an individual with developmental amnesia. I attempted to address three main research questions:

1) What is the status of spatial memory representations of large-scale environments learned over many years in a person with developmental amnesia?

2) Is the hippocampus needed for flexible navigation, to reconfigure or remap familiar routes in the service of navigation?

3) Are detailed representations of well-known, large-scale environments affected in developmental amnesia, as they are in individuals with adult-onset hippocampal amnesia?

Following the results of Study 1, a fourth question became integral to this dissertation, namely: How do representations of extensively travelled environments change over time in developmental amnesia?

Below I will elaborate on the main findings from each of the three studies, and discuss how they provide insight into the questions above. Next, I compare H.C.'s performance on spatial memory tasks to that of adult-onset amnesic cases to speculate about what differences between them may reveal about the necessity of the hippocampus for learning environments. I discuss findings of working memory difficulties in H.C. and in what way(s) working memory may contribute to the deficits described here. I then discuss how these results fit or fail to fit with several theories or hippocampal function. Finally, I discuss the clinical implications of these findings and future research to address outstanding issues.

## Summary of Studies

The studies in this dissertation demonstrate that developmental amnesic case H.C. is able to navigate in her home environment in which she has lived her entire life. Despite atypical hippocampal development and impaired episodic memory, H.C. has been able to form a representation of space that is sufficient for navigating familiar and less familiar routes. Given her intact ability to provide perceptual details about landmarks, H.C.'s impoverished sketch maps could be attributed to a strategic retrieval, relational memory, or working memory difficulty. She described landmarks on the route description task that fell outside the route and inaccurately described the placement of landmarks along the route, suggesting that she has difficulty mentally travelling along a route. This raised the possibility that, while she may have access to fine-grained perceptual details of landmarks, she has difficulty forming a coherent representation of space that allows for rich re-experiencing. At this time, it is unknown whether the incoherence in Studies 2 and 3 was observed because she only has access in memory to a coarse, inflexible representation of her home environment, or whether additional factors, such as a deficit in relational memory or working memory could also play a role. Notably, H.C. had difficulty when she had to generate or manipulate multiple landmarks or spatial features in mind, as seen on the landmark sequencing, landmark localization, sketch maps, and blocked route tasks from Study 2. This was also seen in Study 3, where she could give accurate basic directions but failed to integrate elements into a cohesive whole when asked to provide more descriptive directions. This may explain why H.C. performed comparably to controls on the Google Street View task (Study 1) – the dynamic virtual reality task bound together features in the environment and reduced retrieval, working memory, and relational memory demands.

The first study in this dissertation follows up on previous work showing that H.C. had formed a coarse, schematic representation of her frequently travelled home environment that was impoverished and lacked cohesion (Rosenbaum et al., 2015). Because the initial study was based on a battery of tests of mental navigation, I capitalized on technological advances with Google Street View that enables the virtual navigation of real-world environments to address the first two research questions: whether spatial learning of extensively travelled environments is possible in the context of an atypically developed hippocampal system, and whether the representations that are formed can be used flexibly. Here we used a more immersive set of tasks that enable virtual navigation along pre-experimentally familiar and less familiar routes to test whether the coarse, schematic representation suggested in previous work would be sufficient for actual navigation within the environment. Familiar routes that were mirrored-reversed were also used to examine the flexibility of H.C.'s representations of the environment. H.C.'s performance on outcome measures such as number of pauses, number of progression errors, latency between button presses, and directness of travel, was largely on par with that of controls, despite her atypical hippocampal development. Results arising from use of this dynamic, immersive virtual reality research tool indicate that normal development of the hippocampus is not critical for navigating routes within an extensively experienced environment. Furthermore, H.C.'s successful navigation of mirrored routes suggested that the hippocampus might not be required for flexible navigation.

While H.C.'s intact ability to navigate familiar and less familiar routes within her home environment was expected, her ability to navigate mirrored routes in Study 1 was unexpected and at odds with previous findings of inflexible representations of her home environment, reported in Rosenbaum et al. (2015). As there was a 6-year gap between navigation testing and Study 1, an improvement in H.C.'s mental representation of her home environment could have explained her intact ability to navigate her home environment flexibly. As such, this dissertation was amended to include an additional research goal: to examine how representations of frequently travelled environments might change over time in developmental amnesia. To this end, H.C. was re-tested on the mental navigation tasks on which she showed impairment when first tested in 2010 (as reported in Rosenbaum et al., 2015).  Contrary to expectations, H.C.'s representations of her home environment, as assessed using mental navigation tasks, did not improve over the 8-year period since she was first tested.  She continued to draw impoverished and incoherent sketch maps, and had difficulty placing multiple landmarks on a map, sequencing landmarks, and describing detours on blocked routes. The results suggest that although H.C. was able to represent some aspects of her home environment, it remained inflexible and seemed to be lacking in detail and cohesion. While H.C.'s representation of her home environment did not seem to change, it is notable that she was able to learn novel routes between her new home and work during this time. Unexpected findings that H.C. seemed to lose track of where she was when mentally navigating a blocked route raised the possibility that other non-spatial factors, such as an increased susceptibility to distraction and interference, poor working memory, or a deficit in relational memory, could have contributed to H.C.'s poor performance on these mental navigation tasks.

The third study in this dissertation provided a more thorough investigation of the integrity of H.C.'s detailed representation of her home environment, which was hypothesized to be impoverished based on the lack of detail included in her sketch maps (Rosenbaum et al., 2015 and Study 2) and the impoverished route descriptions that have been reported in separate studies of adult-onset hippocampal amnesic cases (Herdman et al., 2015). H.C.'s performance on the route description task revealed that she is, in fact, able to recall accurate perceptual details of landmarks within her environment. Consistent with her sketch maps (Study 2), however, she seemed to have difficulty binding these landmarks into a cohesive whole, as her description of landmarks along the route seemed disconnected. This could reflect an issue with relational processing of landmarks with their locations as well as in the context of other surrounding landmarks. Further evidence of a possible working memory deficit was also found in this study, as H.C. seemed to jump from location to location, forgetting what she had previously described when providing descriptive directions.

**What is the nature of spatial representations of large-scale, extensively experienced environments in developmental amnesia, and how do they affect real-world navigation?**

Results from this dissertation suggest that H.C. has developed a representation of her home environment, although it seems to be rather fragmented, which likely limits mental navigation. Evidence that H.C.'s poor performance on mental navigation tasks remains unchanged after 8 years (Study 2), in the context of an intact ability to learn new routes within her home environment (as demonstrated by successful navigation between H.C.'s new house and other landmarks in Study 1), may speak to the way in which H.C. learns spatial relations. She has been able to navigate particular routes between landmarks learned even within only the last few years (for example, from her current home to her work), but she still seems to have difficulty drawing a sketch map and placing landmarks accurately on a map, tasks believed to require an allocentric, map-like knowledge of the relations between landmarks themselves. It seems that H.C. is able to learn and follow routes, and perhaps with exposure to many overlapping routes, she has formed a coarse, topological representation of space that allows for some minor flexibility in navigation, but that is not a flexible, cognitive map of the environment that enables navigation of novel routes (Eichenbaum, 2017). The fragmented nature of H.C.'s sketch maps supports this interpretation.

On the Google Street View paradigm (Study 1), her ability to accurately navigate less familiar routes within her home environment was believed to provide evidence that she has a schematic, map-like representation of space, and that she was not merely "following well-worn routes." Upon further examination of her impaired performance on mental navigation tasks, however, it seems plausible that H.C. was engaging in topological navigation during the Google Street View task. Successful navigation of less familiar routes could have been achieved using habit memory and knowledge about overlapping routes to navigate along paths that have already been traversed. This may explain why she failed to take the most direct routes in several cases, as doing so might have required navigating down streets on which she has little experience travelling.

Following routes is consistent with H.C.'s self-report on the Navigation Strategies questionnaire, described in Chapter 2. She reported a preference for using a list of directions over a map to navigate. Consistent with her performance on the sketch map task, she indicated that she would have difficulty drawing a map of an area of the city that she knows well on the

Navigation Strategies questionnaire. This suggests that she navigates predominantly using an egocentric strategy, where she considers landmarks in relation to her own position, rather than the position of landmarks relative to one another. Interestingly, when planning a route in her mind, she reported that she pictures scenes of what she would see along the way. When navigating in the real world and perhaps in virtual reality, H.C. likely has recognition-triggered responses, where she recognizes and approaches sequential landmarks, allowing her to reach her goal without substantial planning (Eichenbaum, 2017).

While this recognition-triggered response strategy may be sufficient for H.C.'s navigation of routes in the real world and on virtual reality tasks, it does not seem to be adequate for navigating or envisioning a mental representation of the same environment. Being able to form a mental representation in one's minds eye that allows one to envision what comes next is important for planning navigation and providing directions to others. On the Navigation Strategies questionnaire, H.C. reported picturing travelling along a route via a street-level view. This is curious, as individuals with hippocampal amnesia typically do not have access to a vivid representation that enables a sense of experiencing. Indeed, while H.C. seems to be able to accurately conjure up perceptual details of landmarks, she seems to have trouble integrating landmarks into a scene and integrating multiple scenes, as would be needed for navigation. This might explain why she has difficulty on mental navigation tasks that benefit from an immersive perspective but is able to navigate successfully virtually and in the real world, which provide the immersive experience.

Virtual navigation of real-world environments provides visual cues that permit a rich sense of re-experiencing that H.C. seems unable to conjure up on her own. As such, a retrieval deficit may underlie H.C.'s difficulties on the mental navigation and route description tasks, which require mental imagery. Additional visual cues on maps (Study 2) benefited H.C.'s placement of landmarks on a map, but did not drastically benefit her ability to sequence landmarks on that map. While her performance might improve with additional cues, perhaps most useful to H.C. are cues that assist in the creation of a vivid, first person scene. An inability to conjure up a representation that enables a sense of re-experiencing might make it challenging for H.C. to adopt an egocentric perspective when there are no visual aids that encourage re-experiencing. Perhaps H.C.'s difficulty with forming a vivid spatial representation is not due to a lack of detail, as H.C. was able to describe accurate perceptual descriptions of landmarks, but a lack of coherence of fine-grained features within the environment. A fragmented sketch map, swap errors on the landmark sequencing task, and confusion about her location on the blocked route and route description task suggest that H.C. is unable to bind together these landmarks or scenes in her own mind's eye. This interpretation could be consistent with theories, including the Trace Transformation Theory, Scene Construction Theory, and Relational Memory Theory, which have in common the supposition that the hippocampus is required for binding information together.

**Comparing H.C.'s spatial representations to that of adult-onset amnesic cases**

Individuals with early-onset hippocampal damage have been found to differ in many ways from adults who acquired hippocampal damage later in life. Although both groups experience impaired episodic memory, individuals with early-onset hippocampal damage are able to form new semantic memories (Vargha-Khadem et al., 1997), whereas this process seems much more laborious for adult-onset cases (Elward & Vargha-Khadem, 2018). Adult-onset amnesic cases have difficulty acquiring new semantic information but continue to have access to factual information that was acquired prior to the onset of their amnesia (Elward & Vargha-

Khadem, 2018). Elward & Vargha-Khadem (2018) suggested that adult-onset amnesic cases might continue to rely more on their hippocampal system to encode and retrieve novel information, even though it is damaged. Given that the brain has increased plasticity early in development, they suggest that the absence of a functioning hippocampal system in early life in developmental amnesic cases likely results in functional reorganization that is sufficient for semantic learning (Elward & Vargha-Khadem, 2018). How might adult-onset and developmental amnesic cases differ when it comes to spatial memory?

Like H.C., adult-onset amnesic cases drew sketch maps of environments learned prior to the onset of their amnesia that were lacking in detail, but their maps were much more cohesive than those of H.C. (see Herdman et al., 2015 for examples). The reason that adult-onset amnesic cases are able to access a more cohesive representation of frequently travelled environments compared to HC is unclear. One possibility is that it has something to do with how the environments are learned. With a functioning hippocampus, allocentric representations might form prior to the onset of amnesia. Perhaps the hippocampus is needed to form a flexible representation, but over time is no longer required to store or retrieve it. Without a functioning hippocampus, it may be that H.C. could not form a flexible representation, instead relying on well-travelled routes and the overlap between them to navigate.

Unlike adult-onset amnesic cases, H.C. was able to describe just as many perceptual details (sensory descriptions) as controls on the route description task (Study 3). It may be that certain types of detailed information, such as perceptual details, can exist outside of the hippocampus in developmental amnesic cases, while other types of information, such as spatial relations between landmarks, cannot form in the presence of early-onset hippocampal damage and resulting episodic memory impairment. There is evidence that the perirhinal cortex, which is intact in H.C., is involved in binding perceptual features of landmarks together (Lee, Yeung, & Barense, 2012). This may explain why H.C. was able to provide a comparable proportion of perceptual details relative to control participants, whereas adult-onset amnesic cases, who have larger lesions, showed a paucity of perceptual details. Two of the three adult-onset amnesic cases that were tested on the route description task (Herdman et al., 2015), D.A. and K.C., were documented to have widespread lesions (D.A.: Rosenbaum et al., 2008; K.C.: Rosenbaum et al., 2005), which included the perirhinal cortex. Unfortunately, neuroanatomical scans for the third adult-onset amnesic case, D.G., could not be obtained due to contraindications for scanning. This highlights the necessity of considering lesion size and location when comparing early-onset and adult-onset amnesic case performance, especially since developmental amnesic cases tend to have more circumscribed lesions (Rosenbaum et al., 2011).

## Working Memory

Perhaps the most unexpected finding in this dissertation was H.C.'s possible working memory deficit. This was a challenge as it raised the possibility that deficits seen on spatial tasks may not solely reflect a spatial memory deficit, but could, at least in part, be due to non-spatial factors. H.C. had difficulty maintaining and manipulating information in mind and exhibited clear working memory deficits when providing detours for the blocked route task (Study 2) and giving descriptive directions in the route description task (Study 3). It may be that forming a vivid mental representation of her home environment places too great a demand on H.C.'s working memory. This finding was unanticipated, as working memory has traditionally been thought to rely largely on the dorsolateral prefrontal and superior parietal cortices (Baddeley, 2003) and be intact in developmental amnesia. Indeed, performance on standard working memory tests such as the Digit Span is typically intact, as seen with H.C. (Rosenbaum et al., 2015). Such tasks tend to require a low memory load, and often consist of simple numbers or figures.

Rose and colleagues (2012) tested H.C. on verbal and visual working memory tasks with familiar and novel verbal and visual stimuli and found that H.C. showed working memory deficits but only for novel material. This is incongruent with the difficulties H.C. displayed on the blocked route and route description tasks in this dissertation, which involved familiar environments. Yonelinas (2013) posited that working memory is hippocampal dependent when the stimuli require fine discrimination or are complex. It may be that with more complex stimuli, such as a scene, H.C. has a lower working memory capacity.

Interestingly, when H.C.'s impaired performance on several of the mental navigation tasks was considered in the context of the previously reported intact distance judgments, vector mapping, and proximity judgments, it was clear that H.C.'s performance was worse on those tasks that required the generation or manipulation of more than 3 landmarks. This parallels recent findings by Geva, Cooper, Gadian, Mishkin, & Vargha-Khadem (2016) who tested working memory capacity in developmental amnesic cases and found that working memory for abstract designs began to rely on the hippocampus beyond 4 items. They concluded that memory load is positively related to hippocampal function (Geva et al., 2016). The relationship between hippocampal lesions and deficient working memory has also been found in neonatal monkeys with bilateral hippocampal lesions, who showed impairment on a task well documented to be reliant on the dorsolateral prefrontal cortex (Heuer & Bachevalier, 2011). Indeed, many animal, lesion, and neuroimaging studies have implicated the hippocampus in working memory when the number of stimuli to be remembered increased (see Jeneson & Squire, 2011, for a review). Jeneson and Squire (2011) also note that working memory is compromised when attention is redirected, consistent with anecdotal evidence that H.C. gets lost in her home environment when she is distracted.

In light of the literature, H.C.'s apparent deficit in working memory could be directly due to her atypically oriented and small hippocampi. Alternatively, given that there are indirect connections between the hippocampus and dorsolateral prefrontal cortex, her atypical hippocampal development may have led to abnormal development of the dorsolateral prefrontal cortex (Geva et al., 2016).

## Contribution to Theories of Hippocampal Function

Many of the large strides made in understanding memory and the role of the hippocampus came from work with individual cases, such as H.M. (Scoville & Milner, 1957) and K.C. (Rosenbaum et al., 2005). Indeed, single cases have provided the foundation for some influential theories of hippocampal function. As functional reorganization is more common in developmental amnesia, it makes it difficult to draw strong conclusions about the necessity or lack thereof of the hippocampus in a typically functioning brain. It is, of course, unwise to try to dispute a particular theory based on of observations in one developmental amnesic case, as functional reorganization could have allowed other brain structures to compensate for performance on tasks that typically require the hippocampus.  As Rosenbaum and colleagues (2014) note, however, new theoretical and empirical ideas can be generated from seemingly small observations in a single case. I would argue that our work with H.C. has done just that. Discussion of how H.C.'s data fit into contemporary theories of hippocampal function helps inform the theories and highlight areas within the theories that could be better defined.

**Trace Transformation Theory**

According to the Trace Transformation Theory, the hippocampus is required for representing detail within a memory, regardless of when the memory was formed (Winocur & Moscovitch, 2011). Interpreting the integrity of H.C.'s detailed representation of her home environment requires considering "detail" at multiple levels. In previous work, my colleagues and I (2015) found that adult-onset amnesic peoples' ability to recognize landmarks and describe perceptual details along a route was impaired, suggesting that the hippocampus is required for recollecting perceptual details (see Sheldon & Levine, 2013 and St-Laurent, Moscovitch, Jadd, & McAndrews, 2014 for analogous findings in episodic memory). In this sense, H.C.'s ability to accurately describe perceptual details about landmarks, such as colour and texture, in Study 3 does not support the Trace Transformation Theory, as it suggests that a detailed representation of a frequently travelled environment may be able to exist independent of the hippocampus. Such detail might be considered integral for richly re-experiencing a memory or an environment.

On the other hand, detail has also been considered on a larger scale, as it relates to spatial relations. For example, the inclusion of fewer landmarks on a sketch map (Herdman et al., 2015; Rosenbaum et al., 2015; Rosenbaum et al., 2000), difficulties sequencing landmarks that are in close proximity to one another (Rosenbaum et al., 2015), and trouble navigating minor, non-artery roads (Maguire et al., 2006) have been taken as evidence to suggest an impoverished representation of an environment. Contrary to landmark recognition and route description tasks, these tasks do not require an immersive, first person view to solve.

Prior to this dissertation, studies did not seem to differentiate between perceptual and fine-grained spatial details when evaluating the integrity of detailed representations of space in adult-onset amnesic cases (Herdman et al., 2015; Rosenbaum et al., 2000). Work with developmental H.C. in this dissertation, however, demonstrates that although perceptual details and fine-grained spatial details could both be considered “details”, they are certainly not one and the same. In light of this disparity, we propose that the Trace Transformation Theory provide a more nuanced working definition of what constitutes “detailed” information in the context of the spatial memory.

The Trace Transformation Theory implicates the hippocampus in enabling a sense of re-experiencing of an event or location. Unfortunately, measures of vividness and sense of presence were not provided following the mental navigation tasks (Study 2) or the route description task (Study 3), so we cannot say with certainty whether H.C. believes that she is richly imagining the environment. Even if these measures had been provided, H.C. might not have a benchmark against which to measure her feelings of re-experiencing, immersion, and/or vividness. The lack of coherence seen in the blocked route task (Study 2) and route description task (Study 3), however, made it difficult for experimenters to follow along. Given the fragmentation, it seems unlikely that H.C. is able to richly envision scenes within her home environment. This suggests that access to perceptual details of landmarks may not be enough to enable a rich sense of re-experiencing, and fine-grained information about spatial relations may be integral to such re-experiencing.

The Trace Transformation Theory also posits that schematic, gist-like representations of frequently travelled environments can exist outside of the hippocampus. In this way, H.C.’s ability to draw parts of sketch maps (Study 2) and estimate distance and direction between landmarks (Rosenbaum et al., 2015) is consistent with the theory. She clearly has been able to form some kind of representation of her home environment, but it appears to be sufficient only for topological navigation along routes and overlapping routes when mental navigation is required. As seen in Study 1, H.C.'s representation is sufficient for virtually navigating within her home environment.

**Scene Construction Theory**

Scene Construction Theory posits that "scenes are the primary currency of the hippocampus" and that individuals with compromised hippocampal systems are unable to construct scenes (Maguire & Mullally, 2013). The fragmentation seen in H.C.'s sketch maps, as well as her difficulty on the route description task (Study 3) and blocked route task (Study 2) suggest that she has access to only a fragmented representation of her home environment. While this is consistent with what the Scene Construction Theory would expect for adult-onset amnesic cases, it is at odds with their findings of intact scene construction for fictitious and future scenarios in developmental amnesic cases Jon (Maguire et al., 2010) and H.C., herself (Hurley et al., 2011).

Results from this dissertation support the Scene Construction Theory in that H.C was able to describe landmarks and some visual features around them when picturing the landmark from a single viewpoint. It seems she was able to envision, at least to some degree, a scene from a real-world environment. H.C., however, had difficulty imagining walking a well-known route and even had trouble imagining one scene from multiple viewpoints. In her descriptions, it seemed that she could not bind the previous view with the features around it when her mental viewpoint shifted and would instead describe a landmark that was not located nearby. Similarly, when describing a detour on the blocked route task (Study 2), H.C. seemed to have difficulty binding distinct scenes or representations together fluidly. King and colleagues (2002) found that developmental amnesic case Jon was able to accurately identify spatial locations of objects when tested from the same viewpoint, but that he was impaired compared to controls when tested on the same scene from an altered viewpoint. Lee and colleagues (2012) suggest that one must be able to combine the complex spatial relationships between features that make up a scene in order to perceive the same scene from several viewpoints. A failure to accurately represent spatial relations would make it very difficult to vividly imagine movement along a route and would explain H.C.'s impaired landmark sequencing in Study 2.

Mullally and colleagues (2014) have suggested that developmental amnesic cases may rely on preserved world knowledge in semantic memory to facilitate mental simulation, and thus not vividly experience or truly visualize the scene in their imagination. Perhaps H.C. showed intact scene construction when constructing fictitious and future scenes (Hurley et al., 2011), but not when describing a portion of her route (Study 3), because it is more difficult to use world knowledge to construct a scene of an actual location. Her scene construction may have come across as fluid because she had greater leeway with the placements of landmarks and objects in a fictitious scene compared to a description of a real location, in which spatial relations are set. The intricate spatial relationships between features that make up the scene cannot be deemed incorrect in a fictitious scenario, but can be inaccurate when envisioning a route. This might explain why H.C.'s route description (Study 3) sounded fluid, but was incoherent in terms of the spatial relations between landmarks.

**Relational Memory Theory**

Cohen and Eichenbaum (1993) argued that the hippocampal system is a relational processing system. Unlike the Scene Construction Theory, the Relational Memory Theory posits that the hippocampus is involved in binding not only spatial relations, but also more generally, associative/co-occurring and sequential/temporal relations (Konkel & Cohen, 2009). The theory highlights that the distinct nature of the items is retained in addition to the relevant relationship between objects (Cohen & Eichenbaum, 1993). H.C. demonstrated having an incoherent representation of her spatial environment on multiple occasions in during the studies reported in this dissertation, including the sketch mapping and landmark sequencing tasks (Study 2). She also had difficulty mentally navigating routes while providing detours for a blocked route task (Study 2) and providing descriptive directions in the route description task (Study 3). As previously mentioned, it appears that H.C. is unable to bind features of the environment together to form a cohesive whole that enables mental navigation, and this is consistent with the Relational Memory Theory. Findings in this dissertation of swap errors during landmark sequencing (Study 2) provide particularly strong evidence for a deficit in relational memory. As the focus of this dissertation was on spatial memory and navigation, we cannot comment on whether difficulty binding information in developmental amnesia is found outside of the spatial realm. Other studies, however, have found non-spatial relational impairments in amnesia (see review in Konkel & Cohen, 2009) and developmental amnesia (D'Angelo, Rosenbaum, & Ryan, 2016).

Cohen and Eichenbaum (1993) argued that relational dimensions could include "sensory relationships, such as relative size, color, texture, shape, etc.; more integrative perceptual relationships such as relative positions of objects in space and time; and higher-order relationships based on the temporal contiguity of objects and events with other objects and events" (p. 62). It is not clear whether the theory would predict that different types of relations (such as binding texture and colour to shape versus integrating the relative positions of objects in space) rely on different components of the hippocampal system, or whether damage to any part of the system results in dysfunction of all relational memory. More recent research, however, suggests that binding visual features occurs in earlier sensory brain areas (Mishkin, Vargha-Khadem, & Gadian, 1998; Pickema, Rijpkema, Fernández, & Kessels, 2010). The results from this dissertation support the view that the hippocampus is required for relational memory, as predicted by the Relational Memory Theory, however, it may not be required for all types of relational memory, including semantic and fine-grained perceptual memories.

### Clinical Implications

The mental navigation tasks were found to be more sensitive to impairment in H.C. than the immersive virtual reality Google Street View tasks used in Study 1. Based on these findings, it might be erroneously concluded that static paper-and-pencil tasks are more advantageous than dynamic, immersive tools for accurately screening for spatial deficits. It seems to be the case that the mental navigation tasks are identifying a deficit that impinges on mental representations of space, but not spatial navigation itself. This dissertation provided a more nuanced understanding of spatial relational impairment in developmental amnesia and highlighted non-spatial deficits that could impact results on mental navigation tasks. I would suggest that the Google Street View tool could still be a valuable resource for investigating navigation, especially since dynamic, immersive tests are more ecologically valid. The mirror-reversed condition in the Google Street View study may not have adequately detected a deficit in flexible navigation in H.C. because such navigation may require a different type of flexibility than that assumed by the Cognitive Map Theory. Given H.C.'s impairment mentally navigating blocked routes, it would be interesting to investigate whether she can navigate around blocked routes in her environment using the immersive Google Street view platform. Studies that build on the findings from this dissertation and take into consideration other possible non-spatial deficits may be just as sensitive as mental navigation tasks in revealing deficits in developmental amnesia.

Given H.C.'s ability to form a representation of her frequently travelled home environment, I also speculate as to how spatial representations might form in the absence of episodic memory. This could serve as an important starting point for future research that inevitably could result in interventions that assist individuals with developmental amnesia in learning new environments. Although the focus of this dissertation was on developmental amnesia, such interventions may prove beneficial for other groups of individuals with hippocampal compromise, such as encephalitis or Alzheimer's disease.

Finally, our findings of possible working memory deficits also have important implications for how we understand amnesia, which is traditionally defined as an isolated deficit in episodic memory in the context of preserved general intelligence, semantic memory, attention, executive functioning, visuospatial abilities, and working memory (Vargha-Khadem et al., 1997).

## Future Directions

There were several unexpected findings across the three studies described in this dissertation that warrant follow-up research. It will be important to determine if the current results extend to other developmental amnesic cases and adult-onset amnesic cases. Also, functional magnetic resonance imaging (fMRI) while H.C. is navigating familiar, less familiar, and mirrored routes would allow us to understand whether H.C.'s preserved performance on any of the Google Street View task conditions are supported by residual hippocampal tissue or other brain structures.

A better understanding of the nature of H.C.'s impairment on the mental navigation tasks and route description task is also required. New paradigms using the Google Street View tool that alter perceptual features of landmarks or reconfigure the spatial layout may provide insight into what type of information is integral for navigation. It would also be interesting to see whether H.C. can identify landmarks from within her home environment from various points of view and, given her impairment mentally navigating blocked routes, whether she can navigate around blocked routes in her environment using the immersive Google Street View platform. Eye tracking software could be useful to gain a better understanding of the landmarks that she is relying on during navigation. The studies in this dissertation also examined navigation in a very insulated way, without regard to vestibular and kinesthetic feedback, factors that are well known to contribute to navigation (Brandt et al., 2005; Harris, Jenkin, & Zikovitz, 2000; for review see Cogné et al., 2017). As such, it would be important for future studies to integrate the Google Street View paradigm with other tools that allow for a more immersive and ecologically valid experience.

Mullally and colleagues (2014) have also suggested that while developmental amnesic cases can construct scenes, they do not seem to envision them as vividly as controls. However, on their future scenario task, H.C. was able to provide just as many sensory details as controls (Hurley et al., 2011). Similar results were found in our route description task (Study 3), where H.C. could describe perceptual features of landmarks. Future research should further investigate the ability to vividly imagine scenes or scenarios in developmental amnesia and be sure to incorporate self-report measures.

One of the most surprising findings in this dissertation was that H.C. seemed to have difficulty maintaining and manipulating information in mind. This working memory difficulty should be further explored to determine whether it extends to non-spatial information. Perhaps one could build on Rose and colleagues (2012) work with H.C., who found that she showed working memory deficits for novel words and faces, by examining H.C.'s ability to hold more complex visuospatial stimuli in mind, such as scenes. H.C.'s performance on the self-ordered pointing task described by Geva and colleagues (2016) would also allow assessment of spatial working memory with slightly less complex stimuli. It would also be prudent to test H.C. on a spatial working memory task, such as the Corsi Blocks, to rule out the possibility that the deficit observed is modality-specific, rather than related to the number and/or complexity of the stimuli.

**Conclusion**

The aim of this dissertation was to examine the status of spatial representations of extensively travelled environments in an individual with developmental amnesia. H.C.'s ability to navigate routes of varying familiarity on a virtual reality task using real-world pictures of H.C.'s home environment, provide coarse representations of her home environment in map-form on mental navigation tasks, and describe navigating between two well-known landmarks, provide evidence of spatial learning of large-scale environments. Speculation was offered that this could be accomplished in a method similar to how semantic information is acquired, with extensive experience and time.

This dissertation also aimed to examine whether the hippocampus was needed for reconfiguring or remapping familiar routes in the service of navigation. H.C.'s intact ability to navigate disorienting mirrored routes on the Google Street View paradigm (Study 1) suggested that the hippocampus might not be required for remapping. As it is plausible that this task could have been successfully solved using a habit-based, non-hippocampal strategy, further investigation is required. H.C.'s incoherent sketch maps and inability to successfully navigate the majority of the blocked routes in Study 2, on the other hand, suggest that the hippocampus is required for accessing a coherent large-scale representation of space that enables flexible navigation, but these tasks may be confounded by working memory demands.

In the second study, emanating from H.C.'s intact performance on the Google Street View paradigm, H.C.'s representations of her home environment did not seem to improve over the course of 8 years. The route description task in Study 3 provided evidence that, in contrast to adult-onset amnesic cases, H.C. does appear to have access to detailed representations of frequently travelled environments, in the sense that she can accurately describe perceptual features of landmarks from a single viewpoint. However, she seems to have difficulty altering that imagined viewpoint and lacks access to the fine-grained spatial relations between features within an environment. H.C. seemed to have the greatest difficulty binding together spatial information in her mind's eye. It is unlikely that her deficit is caused by a retrieval deficit alone because she can recall particular landmarks, but, at times, she seems unable to relate landmarks to one another to form a coherent representation.

When considering the findings from these three studies in the context of the extant literature, I would venture that the hippocampus is integral for binding together spatial features within environments, which allows for a rich sense of experiencing or immersion, and flexibility to change viewpoints. From this perspective, H.C. could have navigated her real-world home environment using the Google Street View paradigm because the immersive virtual reality display already presented spatial features in relation to one another. To navigate between landmarks in Study 1, H.C. would have needed to draw on some sort of representation of her home environment. Indeed, H.C.'s performance on the sketch mapping and landmark localization tasks (Study 2) show that she does have such a representation, although it seems to be coarse and fragmented. She likely navigates topologically, having created a mental representation of space that consists of overlapping routes, which enables navigation along known streets, but prevents the formation of a representation that integrates all routes for flexible use. As H.C. reported trying to solve several of the mental navigation tasks in Study 2 by envisioning walking along a route or envisioning what surrounds a particular landmark, it perhaps is unsurprising that she was impaired on those tasks. An inability to bind spatial features into a coherent whole to allow for a change in viewpoint would have been quite hindering when attempting to mentally navigate on the blocked route task (Study 2) and route description task (Study 3). While H.C. was able to accurately describe perceptual features of landmarks in Study 3, her inability to bind together fine-grained spatial relations within the environment prevented her from accurately describing an intersection. It may be that perceptual features of landmarks are bound together in other structures that are interconnected to the hippocampus, such as the perirhinal cortex (which is intact in H.C.), and that the hippocampus binds slightly larger-scale, more complex features, such as spatial relations (Lee et al., 2012). If a detailed representation of space refers to the fine-grained spatial features, then these findings could be considered as in line with the Trace Transformation Theory. While our findings of incoherence are at odds with H.C.'s intact scene construction for fictitious events described by Hurley and colleagues (2011), they are consistent with their report that H.C. likely was not richly imagining the scene and that this would impair her ability to mentally navigate it.

This dissertation also revealed non-spatial factors that have the potential to impact performance on spatial memory and mental navigation tasks, such as increased susceptibility to interference and distraction, impaired working memory, or a relational deficit. When designing future studies, it will be important to keep these factors in mind to limit confounds wherever possible or further explore them as factors of interest.

Overall, the results reported in this dissertation provide evidence that an individual with developmental amnesia is able to form representations of frequently travelled environments that incorporate perceptual details of landmarks, but that lack cohesive spatial relations that may be important for vivid re-experiencing and flexible navigation. H.C.'s spatial representation of her home environment does not appear to be sufficient for mental navigation, which has implications for her ability to provide directions and plan out routes. H.C.'s poor performance on mental navigation tasks and a route description task may be explained, at least in part, by a retrieval deficit. Her impairment seems to extend beyond this, however, as results indicated that she has difficulty accurately positioning retrieved landmarks relative to other landmarks in the environment. This difficulty binding landmarks to their locations and relative to each other is suggestive of a spatial-relational memory deficit. H.C.'s performance on mental navigation tasks and route description tasks may be further complicated by a working memory impairment. While evidence from the Google Street View study shows that H.C. has been able to learn new routes within her home environment, her overall mental representation of her home environment did not change substantially over time and remained inflexible. This suggests that H.C. may navigate by following routes and these routes likely underlie the formation of her spatial representations. When relational memory, working memory, and retrieval demands are reduced or eliminated, as is the case with virtual reality and real-world navigation, she appears to be able to use the visual cues to adopt a recognition-triggered or habit-based response that allows for successful navigation. Even though H.C. was able to navigate familiar, less familiar, and mirror-reversed routes on a virtual reality Google Street View paradigm, she may still be limited by her semi-flexible topological representation of the environment and may have difficulty navigating blocked routes or along unknown streets. This could be explored in future research using a virtual reality blocked route task. Nevertheless, the results reported in this dissertation add to our understanding of the role of the hippocampus in spatial memory and navigating extensively travelled environments.

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**Appendix A.**

*Table A.1.* H.C.'s ability to sequence landmarks on the landmark sequencing task, landmark localization task, and landmark localization re-test with increasing structure.

| | Landmark Sequencing Task | Landmark Localization Task | Landmark Localization Task Re-test with Increasing Structure | | |
|---|---|---|---|---|---|
| Type of Score | Proportion of photos of landmarks correctly sequenced | Proportion of landmarks placed on a map in the correct sequence | | | |
| Structure Provided | Photos | Boundaries | Boundaries | Boundaries + 3 marked landmarks | Boundaries + all streets within environment |
| H.C. 2018 | 0.643** | 0 | 0.5 | 0.2 | 0.6 |
| H.C. 2010 | 0.800* | N/A | N/A | N/A | N/A |
| Controls 2010 | 0.933 (*SD* = 0.073) | N/A | N/A | N/A | N/A |

* $p < .10$. ** $p =< .05$.