EXAMINING THE RELATIONSHIP BETWEEN AUTOBIOGRAPHICAL EPISODIC MEMORY AND THEORY OF MIND IN DEVELOPMENTAL AMNESIA AND WITH FMRI: THE ROLE OF PERSONAL FAMILIARITY

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A DISSERTATION SUBMITTED TO
THE FACULTY OF GRADUATE STUDIES
IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

GRADUATE PROGRAM IN PSYCHOLOGY
YORK UNIVERSITY
TORONTO, ONTARIO

May 2014

Abstract

The purpose of this dissertation was to examine if, and under what conditions, autobiographical memory (AM) supported by the hippocampus benefits theory of mind (ToM). To this end, I attempted to address two main research questions: (a) Are AM difficulties caused by early-onset hippocampal damage associated with impaired performance on standard measures of ToM (Experiment 1)? (b) Is AM and the brain regions that support it involved to a greater extent in imagining the experiences of personally known others compared to unknown others (Experiments 2, 3, and 4)? In Experiment 1, ToM abilities were examined in H.C., a young woman with impaired AM development due to early hippocampal damage. H.C. performed at the same level as controls on a wide range of ToM tests. These findings suggest that normal AM development is not critical for the development or expression of ToM, at least as measured by standard tests. In Experiment 2, healthy individuals were scanned with fMRI to test whether different neural and cognitive mechanisms support imagining the experiences of personally known others (pToM) versus unknown others (ToM). There was greater neural overlap between AM and pToM compared to pToM and ToM. Furthermore, a direct comparison between pToM and ToM revealed that midline regions associated with AM predominated during pToM, whereas more lateral regions associated with semantic memory predominated during ToM. These findings suggest that there are multiple routes to ToM and the extent to which AM is recruited depends, at least in part, on whether the target person is personally known. Experiment 3 corroborated the neuroimaging results reported in Experiment 2 by showing that H.C. was impaired at producing detailed descriptions of events relating to her own past as well as events relating to personally known others. In contrast, she was intact at describing events relating to unknown others. Experiment 4 explored the neural basis of H.C.'s performance on AM, pToM,

and ToM. Functional MRI analyses revealed that measures of percent signal change and functional connectivity were equivalent between H.C. and controls across all conditions. These finding suggest that BOLD fMRI cannot necessarily distinguish between preserved and impaired behavioural performance in developmental amnesia. Overall, these results contribute substantially to our current understanding of the functional and neural relationship between AM and ToM, and add to the literature suggesting that the hippocampus plays a broader role in cognition beyond that of recalling past events.

Acknowledgments

Firstly, I would like to thank and express a deep appreciation to my supervisor, Dr. Shayna Rosenbaum. Your guidance and mentorship over the past seven years has helped me to become a better critical thinker, researcher, and writer. I look forward to future collaborations with you and a continued friendship. I would also like to thank my dissertation committee, Drs. Jill Rich and Raymond Mar, for their helpful feedback and support. Finally, I am grateful to Drs. Asaf Gilboa, Rosanna Olsen, and Donald Stuss for their valuable comments, discussions, and advice.

I am thankful for the support I received from the Cognitive Neuroscience Lab. Everyone in the lab has been an invaluable part of my educational experience. I especially want to thank Donna and Nicole for the many good times we shared over the past few years.

Thank you to my family and friends for their enormous support, especially my mom, dad, Rachel, Michelle, and Daniel. Finally, I wish to express sincere thanks to Jesse for being the most supportive, generous, and patient husband. I am lucky to have you.

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CHAPTER 1

General Introduction

Autobiographical episodic memory (AM) refers to the ability to recall past personally experienced events. It is well established that structures within the medial temporal lobe (MTL), particularly the hippocampus, are critical for recollecting AMs (Addis et al., 2004; Cabeza & St. Jacques, 2007; Conway & Fthenaki, 2000; Moscovitch et al., 2005; Moscovitch, Nadel, Winocur, Gilboa, & Rosenbaum, 2006). As such, damage to the hippocampus typically results in an amnestic syndrome, the hallmark of which is the inability to recall past autobiographical experiences (Maguire, Vargha-Khadem, & Mishkin, 2001; Rosenbaum et al., 2005, 2008). However, there is growing evidence that other, non-mnemonic processes may be compromised in amnesia as well. The majority of this work has focused on the idea that AM is necessary for imagining future events (Addis, Wong, & Schacter, 2007; Andelman, Hoofien, Goldberg, Aizenstein, & Neufeld, 2010; Klein, Loftus, & Kihlstrom, 2002; Kwan, Carson, Addis, & Rosenbaum, 2010; Tulving, 1985), whereas much less consideration has been given to the role AM plays in social behaviour. Therefore, the purpose of the present dissertation was to address this gap in the literature and to examine if and under what conditions AM contributes to ToM, including the ability to imagine other people's experiences. Specifically, I address two main research questions in this dissertation:

1. Are AM difficulties caused by early-onset hippocampal damage associated with impaired performance on standard measures of ToM (Experiment 1)?
2. Is AM and the brain regions that support it involved to a greater extent in imagining the experiences of personally known others compared to unknown others (Experiments 2, 3, and 4)?

Before describing these experiments in more detail, I review the literature on AM and ToM. I begin by discussing the flexible nature of AM and how this flexibility may benefit non-mnemonic processes, such as ToM. This is followed by a brief review of the ToM literature. Next, I review several theories that have been proposed regarding how individuals infer other people's mental states during ToM. Here I introduce the main hypothesis tested in the current study – that individuals might rely on their own past experiences in order to understand and predict the thoughts and feelings of other people. Finally, I discuss several lines of research showing that a close relationship exists between AM and ToM. To do so, I bring together developmental, neuroimaging, and clinical findings.

The Flexible Nature of AM

Much research has shown that AM is not a literal reproduction of the past, but rather a reconstructive process in which bits of information from various sources are bound together via the hippocampus (Bartlett, 1932; Schacter, Addis, & Buckner, 2007; Schacter et al., 2012). Because memories are not tightly bound units, elements constituting a memory can be manipulated and recombined in novel ways, making AM flexible and adaptive (Moscovitch, 2008; Schacter & Addis, 2007; Schacter, Addis, & Buckner, 2008). Several researchers have suggested that this flexible property of the AM system may provide the building blocks to support other, non-mnemonic cognitive processes (Addis et al., 2007; Buckner & Carroll, 2007; Moscovitch, 2008; Schacter & Addis, 2007).

Several investigators have argued that AM may be critical for simulating and imagining oneself in possible future episodes (Addis et al., 2007; Schacter & Addis, 2007). Evidence supporting this idea comes from neuroimaging studies showing that imagining the future engages a similar set of brain regions as those that support AM, including the hippocampus (Addis et al.,

2007; Buckner & Carroll, 2007; Okuda et al., 2003; Szpunar, Watson, & McDermott, 2007). Consistent with this finding, amnesic individuals with hippocampal damage who are unable to recollect past events also have difficulty imagining themselves in future events (Andelman et al., 2010; Klein et al., 2002; Kwan et al., 2010; Race, Keane, & Verfaellie, 2011; Tulving, 1985). Other work has shown that imagination impairments in adult-onset amnesic individuals are not restricted to the future, but also extend to imagining novel scenes that do not require "mental time travel" per se (e.g., "Imagine you're lying on a white sandy beach in a beautiful tropical bay;" Hassabis, Kumaran, & Maguire, 2007; Hassabis, Kumaran, Vann, & Maguire, 2007; Maguire & Hassabis, 2011). These findings suggest that AM is not only critical for imagining the past and future but may play a broader role in imagining detailed scenarios. Extending from this idea, AM and its underlying properties (e.g., retrieval of details, relational processes, metacognitive reflection) may benefit other nontemporal, cognitive processes, such as imagining other people's mental states and experiences during ToM.

Theory of Mind

The term *theory of mind* (ToM) refers to the ability to infer other people's thoughts, feelings, beliefs, desires, and intentions. Having a ToM is essential for successful social interaction; it facilitates the capacity to communicate, cooperate, and empathize with others (Amodio & Frith, 2006; Baron-Cohen, 1999). It has also been suggested to be at the heart of understanding fiction and relating to characters in a story (Mar & Oatley, 2008). ToM is used spontaneously and effortlessly in everyday life. For example, when giving a presentation, the speaker might start to wonder whether the audience members are intently interested or just barely staying awake and hoping the presentation ends soon. Similarly, in competitive games, one

presumably attempts to infer the mental state of a competitor in order to predict his/her next move, such as in a game of chess or poker.

Over the last several decades researchers have developed numerous measures to assess ToM abilities in the laboratory. These ToM tests vary in the degree of cognitive versus affective content, in the use of narratives versus cartoons, and the type of cue used (e.g., multimodal, static vs. dynamic). One of the most commonly used ToM tests is the *False Belief test*. This test was originally created for use with children who develop ToM around the age 4 or 5 (Wellman, Cross, & Watson, 2001). This test requires participants to understand that other people can hold a false belief that is different from their own correct knowledge (Dennett, 1978; see also Stone, Baron-Cohen, & Knight, 1998). An example of a False Belief test item from Wimmer and Perner (1983) is as follows:

> Max eats half his chocolate bar and puts the rest away in the kitchen cupboard. He then goes out to play in the sun. Meanwhile, Max's mother comes into the kitchen, opens the cupboard and sees the chocolate bar. She puts it in the fridge. When Max comes back into the kitchen, where does he look for his chocolate bar: in the cupboard, or in the fridge?

To correctly answer this question one must infer that Max thinks that the chocolate is still in the cupboard (and ignore the true state of affairs, that is, that the chocolate is actually in the fridge). A more advanced test of ToM is the *Faux Pas* test, which requires participants to recognize that someone said something that should not have been said as a result of not knowing certain information. To know that a faux pas has occurred, one must integrate a false belief representation with a feeling of empathy (Stone et al., 1998). Another commonly used test is the *Animations* test, which assesses participants' ability to represent complex intentions based on the

interaction of moving pairs of triangles (Castelli, Frith, Happé, & Frith, 2002; Castelli, Happé, Frith, & Frith, 2000; Heider & Simmel, 1944). A final example of a commonly used ToM task is the *Mind-in-the-Eyes* test. In this task, participants view a series of photographs depicting the eye region of faces and select the mental state or emotion that best captures the expression in the eyes (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001). One criticism of most ToM tests is that they employ highly-controlled and artificial stimuli and therefore may not capture ToM as it occurs in everyday life (Spreng & Mar, 2012; Zaki & Ochsner, 2009, 2012). Unlike the laboratory tests described above, real life typically provides access to multimodal cues (e.g., visual, semantic, and prosodic information) and people infer the mental states of others they know quite well, such as family members, friends, and co-workers. Furthermore, standard ToM tasks typically involve momentary scenarios, yet in real life mental state inferences do not occur in isolation but rather are dynamic and involve the integration of information over time. In light of these concerns, an important goal for research in this area is to develop more ecologically valid measures of ToM.

Neural Basis of ToM

With the availability of neuroimaging techniques and lesion-based approaches, a growing body of research has focused on identifying the brain regions that support ToM. Neuroimaging studies show that a distributed set of brain regions supports ToM, including the medial prefrontal cortex (PFC), ventrolateral PFC, temporal poles, superior temporal sulcus, medial parietal cortex, temporal-parietal junction (TPJ), amygdala, and MTL regions (Amodio & Frith, 2006; Mar, 2011; Olson, Plotzker, & Ezzyat, 2007; Rabin, Gilboa, Stuss, Mar, & Rosenbaum, 2010; Saxe & Kanwisher, 2003; Spreng & Grady, 2010; Spreng, Mar, & Kim, 2009; Van Overwalle, 2009).

Importantly, these findings do not suggest that all of these areas are necessary for ToM, only that they are consistently activated across studies examining ToM.

Work with brain-damaged patients has also helped to identify the brain regions that support ToM. The majority of this research has focused on only a few regions, namely the medial PFC, temporal poles, and TPJ. With respect to the medial PFC, studies examining patients with damage to this area consistently show impairments across a number of different ToM and perspective-taking tasks (Lee et al., 2010; Rowe, Bullock, Polkey, & Morris, 2001; Shamay-Tsoory, Tomer, Berger, & Aharon-Peretz, 2003; Stuss, Gallup, & Alexander, 2001; cf. Bird et al., 2004). For example, patients with damage to the frontal lobes exhibit deficits on the Faux Pas task (Lee et al., 2010) as well as on tasks that require deception and visual perspective taking (Stuss et al., 2001), among others. In contrast, patients with lesions to either the TPJ or temporal poles have produced mixed findings, with some studies showing impaired ToM abilities (Apperly, Samson, Chiavarino, & Humphreys, 2004; Duval et al., 2012; Irish, Hodges, & Piguet, 2014; Samson, Apperly, & Humphreys, 2007) and others showing intact ToM performance (Channon et al., 2007; Michel et al., 2013; Shamay-Tsoory, Tibi-Elhanany, & Aharon-Peretz, 2006). Additional patient research is needed to help clarify whether the regions activated in neuroimaging studies are critical for the expression of ToM. Extant work has focused on better characterizing the role of the medial PFC, TPJ, and temporal poles; in contrast, little research has been dedicated to understanding the role of the hippocampus in ToM abilities (Rosenbaum, Stuss, Levine, & Tulving, 2007). Therefore, it remains unknown whether the hippocampus is necessary for ToM.

How is ToM Achieved?

Although humans regularly engage in ToM, the mechanism supporting this ability continues to be debated. In this section I discuss several theories that have been proposed regarding how individuals infer other people's invisible mental states. I begin by discussing the idea that individuals might rely on AM in order to understand and predict what other people are thinking and feeling. I then introduce the idea that ToM may also depend on semantic memory (memory for facts and general knowledge about the world) or an interaction of AM and semantic memory.

Reliance on AM

The idea that individuals rely on past personal experiences to infer and understand other people's mental states has been argued by philosophers, psychologists, and cognitive neuroscientists alike (e.g., Buckner & Carroll, 2007; Eklund, Andersson-Stråberg, & Hansen, 2009; Hume, 1957; Kohut, 1984). Individuals may understand how others feel because they recall having experienced similar episodes in their own lives and how they felt at that time. For example, one study showed that participants reported more empathy for women who experienced a similar upsetting life event compared to women who had not experienced a similar event (Batson et al., 1996). In another study, participants were asked to read two stories: one story involved a character who experienced love-related failures and the other involved a character who experienced work-related failures. In a subsequent faux pas recognition task, participants reported more empathy for the character unlucky in love in love-related faux pas scenarios, and more empathy for the character unlucky at work in work-related faux pas scenarios. These results suggest that recollecting previous episodes involving the protagonist enabled the participant to better understand how the character felt in various situations (Ciaramelli, Bernardi,

& Moscovitch, 2013; for similar results see Eklund et al., 2009). In a similar vein, a recent fMRI study reported increased hippocampal activity when participants made judgments of similar others' emotional states (e.g., How would Joe feel about losing his wallet?), but only when participants had a personal memory of the event that the similar other experienced (Perry et al., 2011). These studies suggest that relying on past episodes may be an important antecedent for understanding another person's experience. It may be the case that individuals replay specific past experiences or recombine details from stored memories to help them imagine and infer what another person might be thinking and/or feeling (Buckner & Carroll, 2007; Schacter et al., 2008; Schacter & Addis, 2007).

Some of these ideas are captured in *Simulation Theory*, which was proposed nearly three decades ago (Gordon, 1986; Goldman, 1992). This theory posits that individuals use their own mental processes as a model to understand and predict the thoughts and feelings of other people. This type of perspective-taking is akin to "putting oneself in another person's shoes." A recent series of papers suggested that individuals may preferentially rely on this strategy when making mental state inferences of others deemed similar to the self compared to others deemed dissimilar to the self (Mitchell, 2009; Mitchell, Banaji, & Macrae, 2005; Mitchell, Macrae, & Banaji, 2006; cf. Krienen, Tu, & Buckner, 2010). This theory was based on results that showed a double dissociation between thinking about similar versus dissimilar others, such that the former engaged a region of ventral medial PFC, a region linked to self-referential thought and AM, whereas the latter engaged a more dorsal subregion of the medial PFC. These results suggest that different ToM strategies may be employed depending on who the target person is. Taken together, the studies reviewed here demonstrate that access to past experiences may help to understand other people's mental states and experiences.

Reliance on Semantic Memory

Another possibility is that ToM may be achieved by relying on semantic memory, which refers to one's general knowledge and information about the world (Binder & Desai, 2011). Social semantic information, such as scripts and schemas, may help to interpret and predict other people's behaviour in particular situations (Gallagher & Frith, 2003). For example, to correctly identify whether something hurtful was said in the Faux Pas test, participants likely rely on their knowledge of social etiquette rather than on specific instances of such occurrences in their own lives. This interpretation is supported by recent fMRI findings that show greater activity within lateral frontal and temporal regions, regions associated with semantic memory, during ToM when it is directly compared to AM (Rabin et al., 2010; Spreng & Grady, 2010; St. Jacques, Conway, Lowder, & Cabeza 2011). Further evidence supporting the importance of semantic memory to ToM comes from studies of patients with semantic dementia, which results in a profound loss of semantic knowledge in the context of relatively preserved AM. Duval and colleagues (2012) found that this patient group performed significantly worse than control participants on a wide range of ToM tests (cf. Michel et al., 2013), thereby leading the authors to conclude that semantic memory contributes importantly to ToM.

Interaction Between AM and Semantic Memory

It is also possible that individuals do not simply rely on one strategy to infer another person's mental state, but rather ToM is achieved through various routes. For example, there may be some interplay between AM and semantic memory, such that in some instances AM is the preferred strategy, whereas in other situations semantic memory is the preferred strategy. These strategies are not viewed as mutually exclusive, and individuals likely draw on both types of memories to varying degrees to infer and imagine other people's mental states and

experiences. The extent to which each memory system is recruited during ToM likely depends on a number of factors including accessibility to AM and semantic memory, one's current goals, the information/cues available, and who the target person is. This idea is an extension of the transformation hypothesis, which suggests that there is a dynamic relationship between AM supported by the hippocampus and semanticized versions of the original memory supported by the neocortex (Winocur & Moscovitch, 2011; Winocur, Moscovitch, & Bontempi, 2010; see also Moscovitch et al., 2005, 2006; Rosenbaum, Winocur, & Moscovitch, 2001; Spreng & Mar, 2012). These semantic memories are thought to result from AMs undergoing a transformation process, which leads to the emergence of schematic memories that can be accessed independently of the hippocampus. Building on these ideas, Spreng and Mar (2012) proposed that personal and interpersonal information may be integrated for the strategic use of social conceptual knowledge, which in turn informs one's behaviour. This may include the generation of personality models that can be used to imagine and predict other people's thoughts and feelings (Hassabis et al., 2013).

The idea that AM and semantic memory interact is consistent with recent empirical studies of the default mode network (DMN) – an intrinsically organized set of brain regions that is active during rest (Raichle et al., 2001) and is known to overlap with the brain regions that support AM and ToM (Spreng et al., 2009). Recent reports suggest that the DMN can be fractionated into at least two distinct yet interacting subsystems: a medial temporal subsystem and a dorsal medial subsystem, both of which converge on midline regions (Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010). The medial temporal subsystem consists of the hippocampus, parahippocampal cortex, retrosplenial cortex, posterior inferior parietal lobe, and the ventromedial PFC, whereas the dorsal medial subsystem comprises the dorsal medial PFC,

TPJ, lateral temporal cortex, and temporal poles (Andrews-Hanna et al., 2010; Andrews-Hanna, Smallwood, & Spreng, 2014). Notably, the MTL subsystem closely resembles the regions that support AM, whereas the dorsal medial network closely resembles the regions that support semantic memory. Thus, these interacting subsystems may be responsible for retrieving and combining information stored in autobiographical and semantic memory in order to infer other people's thoughts and feelings.

Although there may be several additional routes to ToM (e.g., mirror neurons), the current dissertation focuses primarily on the idea that AM may be beneficial, or even necessary, for the expression of ToM abilities, at least under some circumstances. In the next section, I highlight several lines of research supporting the idea that AM and ToM are closely related.

Relationship Between AM and ToM

A close relationship between AM and ToM has been suggested by several observations: (a) AM and ToM emerge close in time in normal child development (Perner & Ruffman, 1995), (b) both abilities rely on a similar set of brain regions (Buckner & Carroll, 2007; Hassabis & Maguire, 2007; Rabin et al., 2010; Spreng & Grady, 2010; Spreng et al., 2009), and (c) several patient populations with ToM impairment also show deficits in AM (Adler, Nadler, Eviatar, & Shamay-Tsoory, 2010; Corcoran & Frith, 2003; Dimaggio, Salvatore, Popolo, & Lysaker, 2012).

Developmental Trajectory of AM and ToM

AM and ToM emerge close in time in ontogenetic development. Developmental studies of healthy children show that ToM improves with the development of AM (Naito, 2003; Perner, Kloo, & Gornik, 2007; Perner & Ruffman, 1995). For example, Perner and colleagues (2007) examined children between the ages of 3 and 5, and found a correlation between improvement on free recall and performance on several ToM tests. Their results were largely consistent with

those reported by Naito (2003) who studied a sample of Japanese children using different measures of memory recall and ToM. However, these studies included laboratory-based tasks to assess memory abilities (i.e., list-learning and recall) rather than tasks that require participants to recall past personal episodes. This is important to note given that these two types of memory tasks have been shown to rely on different brain regions (Gilboa, 2004; McDermott, Szpunar, & Christ, 2009).

Additional evidence supporting a developmental connection between AM and ToM comes from a study with adults diagnosed with developmental disorders such as high functioning Autism and Asperger's syndrome (Adler et al., 2010). This study found that ToM abilities could be predicted by performance on a test of AM in both patient groups, suggesting that difficulties in AM are closely related to impairments in ToM. It should be noted, however, that language and executive demands were not taken into account in that study.

Studies showing that AM and ToM develop in tandem have informed theories of child development. These theories propose that the ability to recall past personal experiences may be critical for the development of ToM (Fivush & Nelson, 2006; Nelson, 2009; Robinson & Swanson, 1990). Several researchers argue that insight into one's own mental experiences gained through the development of AM might enable the child to appreciate others' mental states (Robinson & Swanson, 1990) or to realize that others can have a unique perspective on a shared experience (Fivush & Nelson, 2006).

Overlap in the Functional Neuroanatomy of Autobiographical Memory, Theory of Mind, and the Default Mode Network

Several qualitative reviews have noted that the brain regions underlying AM are strikingly similar to those that underpin a host of other abilities including ToM, future thinking, and some forms of spatial navigation (Buckner & Carroll, 2007; Hassabis & Maguire, 2007).

This network of brain regions includes the medial PFC, medial and lateral parietal cortex, and regions within the MTL. There is also evidence of neural overlap between these domains and that of the DMN (Buckner & Carroll, 2007). Of note, a quantitative meta-analysis of neuroimaging studies of AM, ToM, future thinking, navigation, and the default mode showed that AM and ToM displayed the greatest degree of neural overlap of all the abilities examined (Spreng et al., 2009).

To further explore the functional and neural relationship between AM and ToM, Rabin and colleagues compared these two abilities within the same individuals using closely matched conditions (Rabin et al., 2010). This was an important step given that previous evidence of a shared brain network underlying AM and ToM was based on comparisons of independent neuroimaging studies investigating one ability or the other. In that study, a *family photos* task was employed (Gilboa, Winocur, Grady, Hevenor, & Moscovitch, 2004), in which participants recollected past events in response to personal photos (AM condition) and imagined other people's experiences in response to photos of unfamiliar people (ToM condition). AM and ToM were compared to a low-level baseline (i.e., scrambled photos) and directly to each other to systematically examine areas common to both abilities as well as areas of unique activity, respectively. A conjunction analysis confirmed that AM and ToM are supported by a common set of brain regions that includes medial PFC, MTL regions, lateral temporal cortex, and medial parietal cortex. Similar findings were reported in another study that directly compared AM and ToM using the International Affective Picture System (Lang, Bradley, & Cuthbert, 2005) as cues (Spreng & Grady, 2010).

Dissociations Between AM and ToM in Neuroimaging Studies

As mentioned above, a number of studies have shown that AM and ToM are supported by a common core network. However, there is also neuroimaging evidence showing dissociations between the two abilities. For example, Rabin and colleagues (2010) directly compared AM and ToM within the same individuals and found greater activity within midline regions, such as medial prefrontal and posterior cingulate cortex/precuneus, during AM and greater activity within more lateral frontal and temporal regions during ToM. When AM and ToM were separated into construction (i.e., initial search of event details) and elaboration (expanding on event details) phases, activity within the right hippocampus was associated with AM construction, whereas activity within the right TPJ was associated with ToM elaboration. In a similar vein, Spreng and Grady (2010) showed that autobiographical remembering (and prospection) engaged midline structures to a greater degree, whereas ToM engaged more lateral areas. Further evidence for a neural dissociation between AM and ToM comes from another fMRI study that also employed naturalistic stimuli as cues. In that study, AM recruited ventral medial PFC, whereas thinking about another person's perspective recruited a more dorsal region of the medial PFC (St. Jacques et al., 2011). Furthermore, these two regions were connected to separate neural networks. Specifically, the ventral medial PFC showed greater functional connectivity with the hippocampus and precuneus – a pattern consistent with the network of regions known to support AM, whereas the dorsal medial PFC exhibited greater connectivity with frontal and parietal regions, a set of regions that has been linked to controlled processes (Andrews-Hanna, Saxe, & Yarkoni, 2014; St. Jacques et al., 2011).

Comorbid Impairment of AM and ToM in Clinical Populations

Evidence from the developmental literature and neuroimaging studies suggest an intimate relationship between remembering the past and ToM. There are also data suggesting that the two abilities are linked in certain psychopathologies. For example, several researchers have found that both AM and ToM are impoverished in people with schizophrenia (Corcoran & Frith, 2003; Dimaggio et al., 2012), in individuals with personality disorders (Dimaggio et al., 2012), and in people with high functioning Autism and Asperger's syndrome, as mentioned above (Adler et al., 2010). ToM deficits have also been observed in individuals with mesial temporal lobe epilepsy, a chronic neurological disorder that typically results in compromised AM abilities (Giovagnoli, Reati, & Parente, 2011; Li et al., 2013; Schacher et al., 2006). In contrast to these findings, there is some patient work showing dissociations between AM and ToM (see below; Rosenbaum et al., 2007).

Dissociations Between AM and ToM in Clinical Populations

There are some clinical populations who demonstrate impaired AM with intact ToM. For example, two amnesic individuals with severely impaired AM due to hippocampal damage (K.C. and M.L.) performed at the same level as controls on a large number of objective ToM tests (Rosenbaum et al., 2007). The ToM tests employed in that study were the same tests shown to activate the common set of regions revealed in the reviews of the neuroimaging literature (Buckner & Carroll, 2007; Spreng et al., 2009). These tests included predicting a character's false belief about the location of an object (False Belief test; Stone et al., 1998), deciphering others' thoughts and emotions based only on the eye region of their faces (The Mind-in-the-Eyes test; Baron-Cohen et al., 2001), and identifying whether a character unintentionally said something hurtful to a second character as a result of not knowing certain information (Faux Pas test; Stone

et al., 1998). Findings of intact ToM in amnesic people with impaired AM suggest that access to past experiences may not be necessary to perform well on standard tests of ToM. It may be that when AM is compromised, ToM can be achieved via access to social semantic knowledge, as described above. It is important to note that the standard ToM tasks used by Rosenbaum and colleagues included strangers and fictional characters as the target of the mental state inference. Semantic memory (and not AM) may be sufficient to perform these types of inferences; however, it remains unknown whether AM abilities are more essential to ToM when personally known others are the subject of the mental state inference.

In the current dissertation, I explored the idea that AM makes an important, and at times necessary, contribution to ToM when the mental state inference involves personally known others (e.g., family members, close friends) versus unknown others. Indeed, knowing someone for a long period of time and observing that person's behaviour in many different situations provides a rich source of information from which one can draw when imagining that person's mental state in specific situations. For example, remembering how your best friend behaved during last year's Super Bowl party would likely help you predict how he or she might behave during this year's party. There is some evidence supporting this idea. For example, one study found that participants reported that they relied on a specific memory or anecdote significantly more often when making judgments relating to close friends compared to strangers (Krienen et al., 2010).

Overview of Experiments

The above review suggests that AM and ToM are closely related. In addition to a shared neural substrate that appears to include the hippocampus, the two abilities emerge close in time in ontogenetic development, and both abilities tend to be impaired in various psychopathologies.

However, at odds with these findings are observations that (a) individuals with adult-onset hippocampal amnesia show preserved performance on standard tests of ToM, and (b) neuroimaging studies demonstrate that the brain regions that support AM and ToM are not identical (Rabin et al., 2010; Spreng & Grady, 2010; St. Jacques et al., 2011). In the current dissertation, I closely examined the functional and neural relationship between AM and ToM in order to reconcile these discrepant findings. Experiment 1 sought to determine whether AM is necessary for the development of ToM. It is possible that once ToM is fully developed, it no longer depends on AM or the hippocampus. If this is the case, it would explain why the adult-onset amnesic patients, K.C. and M.L., show intact ToM performance in the study by Rosenbaum and colleagues (2007). To investigate this hypothesis, a wide range of standard ToM tests was administered to H.C., a young woman with impaired AM development as a result of early-onset hippocampal damage (Hurley, Maguire, & Vargha-Khadem, 2011; Kwan et al., 2010; Rosenbaum et al., 2011; Vargha-Khadem et al., 2003).

Another possible explanation for K.C.'s and M.L.'s intact ToM performance is that semantic memory may be sufficient to perform well on standard ToM tasks that employ strangers or fictional characters as targets (Rosenbaum et al., 2007). However, it remains unknown whether AM benefits, or is possibly necessary, for ToM involving personally known others. To investigate this possibility, Experiments 2, 3, and 4 examined whether AM is more beneficial for imagining the experiences of personally known others (pToM) than for unknown others (ToM). More specifically, using an adapted version of the family photos task (Rabin et al., 2010), Experiment 2 examined whether different cognitive and neural mechanisms support pToM and ToM in healthy control participants. To foreshadow the results, I found greater neural overlap between AM and pToM compared to pToM and ToM. Notably, the greatest amount of

neural overlap between AM and pToM was observed within midline regions, including the hippocampus. To further explore these findings, Experiment 3 and 4 tested whether AM supported by the hippocampus is necessary for pToM. To do so, I tested H.C. on the same family photos paradigm employed in Experiment 2. H.C.'s behavioural results are reported in Experiment 3, and her neuroimaging findings are reported in Experiment 4. The latter experiment provided the opportunity to examine the neural basis of impaired and spared aspects of ToM in a person with impaired AM and early hippocampal damage. In summary, the series of experiments presented in this dissertation investigated if, and under what conditions, AM, supported by the hippocampus, is important for imagining other people's mental states and experiences, aspects that comprise ToM.

CHAPTER 2

Experiment 1: Theory of Mind Development Can Withstand Compromised Autobiographical Episodic Memory Development

As discussed above, neuroimaging findings demonstrate that a common set of brain regions support AM and ToM, including the hippocampus and related MTL regions (Rabin et al., 2010; Spreng & Grady, 2010; Spreng et al., 2009). These findings are in line with developmental theories that propose that the ability to recall past personal experiences may be critical for the development of ToM (Fivush & Nelson, 2006; Nelson, 2009; Robinson & Swanson, 1990). For example, several researchers argue that insight into one's own mental experiences gained through the development of AM might enable the child to appreciate others' mental states (Robinson & Swanson, 1990) or to realize that others can have a unique perspective on a shared experience (Fivush & Nelson, 2006).

Contrary to suggestions from the neuroimaging and developmental literature, individuals with adult-onset hippocampal damage and severely impaired AM can perform well on a battery of standard ToM tests (Rosenbaum et al., 2007). However, these adult-onset cases experienced normal AM development, which may be critical for ToM to develop (Fivush & Nelson, 2006; Nelson, 2009; Robinson & Swanson, 1990). It is possible that once developed, ToM no longer depends on AM and can be achieved via alternate strategies and neural substrates, such as social semantic memory, which remains relatively intact in amnesia. However, the causal nature of this relationship has not been tested empirically. This is surprising given the implications for understanding how ToM develops and why ToM is vulnerable in a host of developmental, psychiatric, and neurological disorders.

In Experiment 1, I examined whether normal AM development is necessary for the normal development of ToM. To investigate this, I tested H.C on a wide range of objective ToM tests. As mentioned earlier, H.C. is a young woman with normal intellectual function despite never having developed normal autobiographical episodic memory as a result of damage to the extended hippocampal system believed to have occurred during fetal development (Olsen et al., 2013; Rosenbaum et al., 2011, in preparation; Vargha-Khadem et al., 2003). In the current study, a sample of widely used tests of ToM were selected that (a) varied in the degree of cognitive versus affective content, use of narratives, and type of cue used; (b) are known to activate the set of brain regions that support AM (Spreng et al., 2009); and (c) are sensitive to ToM impairment in a variety of patient groups (Gregory et al., 2002; Stone et al., 1998; Stone, Baron-Cohen, Calder, Keane, & Young, 2003; Stuss, Gallup, & Alexander, 2001). Findings of intact ToM in H.C. would provide compelling evidence that the development of AM is not necessary for ToM to emerge, and that non-mnemonic strategies are sufficient for successful performance on standard ToM tasks. This study will also help to inform theories of cognitive development and the resilience of brain function to early disruption.

Method

Participants

H.C. is a right-handed woman who was 20 years old at the time of testing. She was born prematurely and has reduced bilateral hippocampal volume by approximately 30% relative to healthy controls (see Figure 2.1, Hurley, Maguire, & Vargha-Khadem, 2011; Olsen et al., 2013). H.C.'s compromised bilateral hippocampal development appears to have precluded normal development of her autobiographical episodic memory. H.C.'s autobiographical episodic memory impairment has been well-documented by several groups (Hurley et al., 2011; Rosenbaum et al., 2011; Vargha-Khadem et al., 2003). She has impaired memory for personal

and public life events, but relatively intact personal and general semantic memory (Rosenbaum et al., 2011), which is consistent with other developmental amnesic individuals (Gadian et al., 2000). H.C. consistently shows specific impairment on standardized tests of anterograde and retrograde autobiographical episodic memory (see Table 2.1 and Appendix B for scores on neuropsychological tests). Experimental testing has corroborated a significant autobiographical episodic memory deficit based on a variety of tests with different methods of cueing and scoring (Hurley et al., 2011; Kwan et al., 2010; Rosenbaum et al., 2011). These deficits also extend to her ability to imagine future personal experiences (Kwan et al., 2010; cf. Hurley et al., 2011).

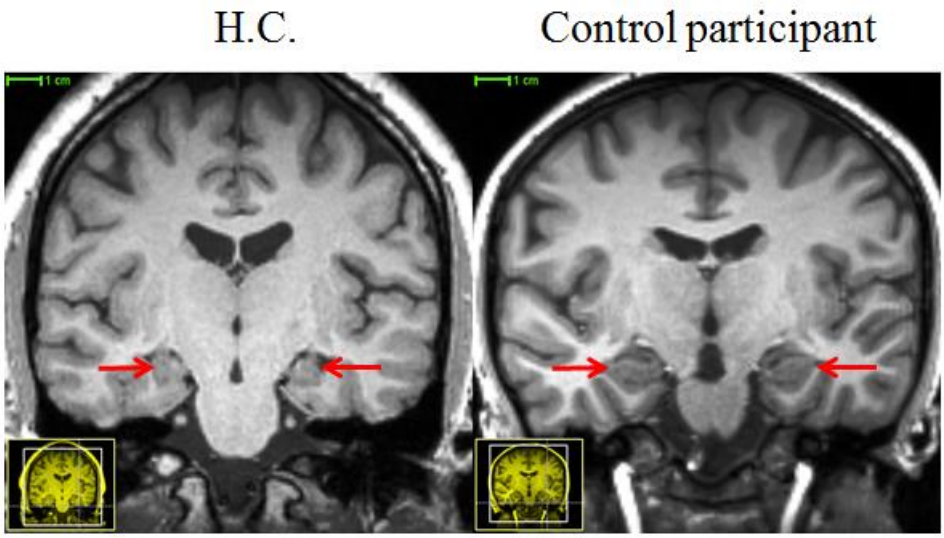


Figure 2.1. Selected Coronal Slices of an MRI Scan in H.C. (left) and an Age- and Sex-Matched Healthy Control Participant (right).

Table 2.1

H.C.'s Performance on Standardized Tests of Autobiographical Episodic Memory

Standardized Test	H.C.'s Test Score
RBMT (raw score)[1]	7 (impaired)
RBMT-Extended (raw score)[2]	10 (impaired)
California Verbal Learning Test-II[3]	
Acquisition (T-score)	38
Short delay free recall (Z-score)	-4
Long delay free recall (Z-score)	-3
Recognition (Z-score)	-2
Rey Osterrieth Complex Figure (T-score)[3]	
Immediate recall	<20
Delayed recall	<20
Delayed recognition	22
Wechsler Memory Scale-III (standard score)[2]	
General memory	49
Verbal – Immediate Recall	71
Verbal – Delayed Recall	46
Visual – Immediate Recall	71
Visual – Delayed Recall	59
Delayed Recognition	75
Wechsler Memory Scale –III (scaled score)[3]	
Logical Memory I – Immediate recall	4
Logical Memory II – Delayed recall	1

RBMT, Rivermead-Behavioural Memory Test;
[1]Score reported in Vargha-Khadem et al., 2003; [2] Scores reported in Hurley et al., 2011; [3]Scores reported in Rosenbaum et al., 2011.

Despite H.C.'s impaired autobiographical episodic memory, she is an otherwise healthy individual. She successfully graduated from a mainstream high school, completed one year of technical college, and was enrolled in a postsecondary culinary program at the time of testing,

although withdrew from this program a year later. She was engaged to be married at the time of testing.

In the current study, H.C.'s performance was compared to that of 17 right-handed, healthy women with no reported history of neurological or psychiatric illness (mean age = 19.3 years, *SD* = 1.2; mean education = 13.3 years, *SD* = 1.1). All participants gave informed written consent in accordance with the ethics review boards at York University and Baycrest.

Materials and Procedure

Participants were tested on several standard ToM tasks that are commonly used in patient and neuroimaging studies. The tasks varied in terms of cognitive versus affective content, use of hypothetical verbal narratives, and the type of cues available for inferring a mental state (Rosenbaum et al., 2007). Data were analyzed using a two-tailed modified *t*-test procedure, which compares test scores of a single patient to that of a small control sample (Crawford & Howell, 1998).

False Belief Test (Stone et al., 1998): Participants were assessed on their ability to represent another person's mistaken belief about the location of an object that differed from their own belief (first-order) as well as a second person's mistaken belief about the first person's belief about the location of an object (second-order). There were five first-order and five second-order passages. For each passage a maximum of 2 points were assigned (1 point each for identifying the actual location of the object and for identifying the character's belief about the object's location).

Faux Pas Test (Stone et al., 1998): On this more affective measure of ToM, participants were asked to determine if a character unintentionally hurt a second character's feelings as a result of not knowing certain information. Ten passages were presented to participants, with a

maximum score of 3 points per passage (1 point each for correctly identifying the faux pas, explaining why it should not have been made, and inferring how it might have affected the recipient).

Mind-in-the-Eyes Test (Baron-Cohen et al., 2001): Participants were tested on their ability to infer thoughts and emotions from 36 black and white photographs of the eye region of faces. Participants were asked to choose among four adjectives that best described what the person in each photograph was thinking or feeling.

Sarcasm and Empathy Test (Dennis, Purvis, Barnes, Wilkinson, & Winner, 2001): This task assessed participants' appreciation of literal and nonliteral utterances from visual and intonation cues. Twelve real-world scenarios were presented to participants, with an equal number of scenarios assessing participants' understanding of literal truths, deceptive praise (i.e., the opposite of what is said is meant, with an empathic intent), and ironic criticism (i.e., the opposite of what is said is meant, with a sarcastic intent). One point was assigned to each response that demonstrated the participant's ability to make a first-and second-order inference with respect to the characters' beliefs about their own actions as well as the intentions of the other character (i.e., a maximum of 4 points per scenario).

Visual Perspective-Taking and Deception Tests (Stuss et al., 2001): In the "Transfer of Inference" condition, participants were asked to make an inference about the location of a ball that was hidden under one of five cups based on the pointing of one of two confederates with the same vantage point as the experimenter across six trials. Scoring was based on the number of correct trials. The "Deception" condition involved only two possible locations, and participants were asked to infer the deceptive intent of a confederate who pointed to the wrong location. The

measure of interest for the "Deception" condition was the trial number corresponding to the first of five consecutive trials correct (i.e., fewer trials indicate better performance).

Animations Test (Castelli, Happé, Frith, & Frith, 2000): Participants were tested on their ability to represent complex intentions based on the movement of pairs of triangles. Action sequences (3 practice, 12 test) were presented, with an equal number of sequences depicting random movements (e.g., drifting), goal-directed movements (e.g., dancing), and more complex interactions requiring ToM (e.g., mocking). After viewing each sequence, participants judged whether an interaction took place and the nature of the interaction. Responses were scored for appropriateness of the descriptions (0–3), that is, how well the underlying script was captured as well as the level of intentionality between the triangles (0–5), that is, the degree of appreciation of mental states. Responses were scored by two independent raters who achieved a similar level of agreement based on the criteria described in Castelli and colleagues (2000). Discrepancies, which were few, were resolved by a third rater.

Results

H.C. and the control participants' performance on the various ToM tests is shown in Table 2.2. H.C.'s performance was equivalent to controls on all six ToM tests. More specifically, she achieved perfect or near perfect scores on the False Belief test, the Faux Pas test, and Sarcasm and Empathy tests. On the Animations test, H.C.'s performance did not differ from that of controls in terms of the appropriateness and intentionality ratings given to descriptions of random and goal-directed animations. For the ToM animations, there was a trend towards H.C. scoring lower on the appropriateness measure, but there was no significant difference in performance based on the intentionality measure.

Table 2.2

H.C. and Controls' Performance on Theory of Mind Tests

ToM test	H.C.	Control mean (*SD*)	*t*-test results
False Belief Test			
First-order (/10)	10	9.9 (0.2)	t_{16} = 0.49, p = .63
Second-order (/10)	9	9.4 (0.8)	t_{16} = -0.49, p = .63
Faux Pas Test (/30)	30	25.3 (5.6)	t_{16} = 0.82, p = .43
The Mind-in the-Eyes Test (/36)	29	26.5 (3.9)	t_{16} = 0.62, p = .54
Sarcasm and Empathy Test			
Literal truth (/16)	16	15.8 (0.75)	t_{16} = 0.26, p = .80
Ironic criticism (/16)	16	15.8 (0.97)	t_{16} = 0.20, p = .84
Deceptive praise (/16)	16	15.5 (1.12)	t_{16} = 0.43, p = .67
Visual-Perspective Taking and Deception Tasks			
Transfer of inference (/6)	6	5.7 (0.85)	t_{16} = 0.34, p = .74
Deception condition (lower score indicates better performance)	2	5.4 (4.6)	t_{16} = -0.72, p = .48
Animations Test			
Random			
Appropriateness (/3)	2	2.6 (0.47)	t_{16} = -1.2, p = .23
Intentionality (/5), target score = 1.0	1.5	0.5 (0.67)	t_{16} = 1.5, p = .16
Goal-directed			
Appropriateness (/3)	2.8	2.6 (0.39)	t_{16} = 0.50, p = .63
Intentionality (/5), target score = 3.0	2	2.3 (0.39)	t_{16} = -0.75, p = .47
Theory of mind			
Appropriateness (/3)	2	2.5 (0.27)	t_{16} = -1.8, p = .09
Intentionality (/5), target score = 5.0	3.5	4.0 (0.54)	t_{16} = -0.90, p = .38

The number in parentheses in the left-hand column indicates the maximum score for each section

Discussion

The current study tested the claim that the development of AM is critical for the development of ToM. To do so, ToM abilities were examined in H.C., a young woman with impaired AM development due to hippocampal damage during fetal development. Specifically, H.C. was tested on a comprehensive battery of objective measures known to be sensitive to ToM impairment. Despite impaired AM development, H.C. performed normally on all tests of ToM. Previous research has shown that performance on these same ToM tests correlates with normal AM development and with activation in the set of brain regions associated with AM. Nevertheless, H.C. had no difficulty inferring other people's mental states as revealed by tests assessing her ability to detect a false belief, faux pas, or intent that is sarcastic, empathic, or deceptive, nor did she have difficulty inferring others' mental states by relying on the eye region of faces or visual cues. Together with similar findings in the adult-onset amnesic cases K.C. and M.L. (Rosenbaum et al., 2007), it is apparent that AM is not necessary for intact performance on laboratory tests of ToM. This appears to hold true whether AM fails to develop normally or is impaired later in life, after it has fully developed. Anecdotal observations in both H.C. and patient Jon, the most studied case of developmental amnesia, also support the notion that individuals with impaired AM development are nonetheless capable of basic ToM. For example, both patients are capable of understanding and performing 'remember-know' memory tasks in which participants are asked to introspect and judge whether their memory of items involves a recollective experience or is based on familiarity (Brandt, Gardiner, Vargha-Khadem, Baddeley, & Mishkin, 2006; Düzel, Vargha-Khadem, Heinze, & Mishkin, 2001; Horner et al., 2012). H.C. and Jon's respective capacities to understand such instructions suggest that they can appreciate

fine distinctions of how others experience memory and can apply these distinctions to their own internal representations.

The current data suggest that rather than referring to specific episodes from one's past, ToM may be achieved via social semantic memory, which appears to be relatively intact in hippocampal amnesia. This may include reliance on scripts and social norms in order to understand how the average person is likely to think and feel in a given situation (Lieberman, 2012). This interpretation is supported by the finding that patients with semantic dementia, who suffer from a profound loss of semantic knowledge in the context of relatively preserved AM, perform poorly on a wide range of ToM tests (Duval et al., 2012; cf. Michel et al., 2013 for a case study on the same topic). Furthermore, recent fMRI studies directly comparing AM with ToM in healthy people show greater activity during ToM in lateral frontal and temporal regions, which are known to be involved in semantic memory. In contrast, midline regions, such as medial prefrontal cortex, hippocampus, and posterior cingulate cortex are activated to a greater extent during AM (Rabin et al., 2010; Spreng & Grady, 2010). Indeed, there is strong evidence to suggest that individuals with developmental amnesia are capable of learning new semantic information, albeit in a more laborious way (Gardiner, Brandt, Baddeley, Vargha-Khadem, & Mishkin, 2008; Vargha-Khadem et al., 1997), presumably via temporal neocortex (McClelland, McNaughton, & O'Reilly, 1995; Sharon, Moscovitch, & Gilboa, 2011). Therefore, it is possible that semantic memory, rather than AM, is crucial for the development and expression of ToM; however, further work is needed to help understand its precise contribution.

The present findings do not rule out the possibility that under certain conditions non-amnesic individuals might rely on AM to infer other people's mental states or, alternatively, that a common process underlies AM, ToM, and other abilities associated with the default mode

network. Healthy people recruit regions known to be involved in AM when performing laboratory tests of ToM, such as the ones included in the current study (Buckner & Carroll, 2007; Hassabis & Maguire, 2007; Spreng et al., 2009). However, when the two abilities are directly compared in neuroimaging studies of healthy adults, differences in regional activity emerge (Rabin et al., 2010; Spreng & Grady, 2010). Furthermore, in contrast to findings in the developmental literature, the evidence of a behavioural relationship in healthy adults is sparse. Two behavioural studies that report an association between AM and ToM involved pathological populations (Adler et al., 2010; Corcoran & Frith, 2003) and report only a partial association in healthy controls (Adler et al., 2010) or were unable to explore the relationship due to a limited range of scores on both AM and ToM tests (Corcoran & Frith, 2003).

It is possible that ceiling effects account for the absence of a detectable difference in ToM on the False Belief, Faux Pas, and Sarcasm and Empathy tests on which H.C. and controls achieved perfect or near-perfect scores. However, several clinical populations show impaired performance on these same tasks (Dennis et al., 2001; Duval et al., 2012; Gregory et al., 2002; Stone et al., 1998). Notably, H.C.'s performance did not differ from that of controls on tests that did not produce ceiling effects, including (a) The Mind-in-the-Eyes test; (b) a deception test, which has proven sensitive to ToM impairment in patients with focal lesions in medial PFC (Stuss et al., 2001); and (c) the intentionality measure of the Animations test. There was, however, a trend towards worse performance in H.C. than controls on the ToM appropriateness measure of the Animations test. H.C's score on this measure may suggest that she has a general understanding of the underlying scenario but has subtle difficulties in deciphering the specific interactions between two agents. In these circumstances access to relevant past episodes may facilitate a precise understanding of current situations (White, Coniston, Rogers, & Frith, 2011;

Zwickel, White, Coniston, Senju, & Frith, 2011), and therefore may explain her poor performance. For instance, H.C.'s reduced ability to access specific situations in which she experienced a complex interaction, such as being coaxed, may hinder a complete appreciation of this type of interaction in other people. To reduce the possibility of ceiling effects, future research should focus on developing and implementing more sensitive real-world tests of ToM, such as those used in several recent studies (St. Jacques et al., 2011; Rabin et al., 2010; Spreng & Grady, 2010). Taken together, the current findings demonstrate that successful performance on a wide range of laboratory tests of ToM can be achieved without the normal development of AM.

The finding that ToM does not depend on the normal development of AM highlights the danger in interpreting correlations in behaviour as causal, whether in neuroimaging, in child development, or in clinical populations. These findings instead suggest that the relationship between AM and ToM is mediated by other factors. One possibility is that both abilities improve independently over the same time period as a result of higher order domain-general neurocognitive maturation (Fivush, 2011; Perner & Ruffman, 1995; Perner et al., 2007; Wellman, Cross, & Watson, 2001). It may also be the case that, in the face of AM impairment, ToM can be achieved via implicit, automatic processes, which were not assessed in the current study (Frith & Frith, 2012; Low & Perner, 2012). However, it is unlikely that this explanation provides a complete account of H.C.'s successful performance on the tasks administered here given that only overt responses were scored. Another possibility is that both AM and ToM depend on semantic memory or general language abilities, which are not always taken into account (Perner & Ruffman, 1995; Perner et al., 2007; Welch-Ross, 1997). The latter is particularly important to control for in studies employing tasks that rely heavily on verbal output.

For example, a relationship between AM and ToM identified in children (Welch-Ross, 1997) was dismissed once language skills were properly controlled (Reese & Cleveland, 2006).

In conclusion, H.C. performed normally on tests of ToM that correlate with AM development and that activate the set of brain regions known to support AM. These findings provide convincing evidence that the normal development of AM is not essential for the development of ToM, thereby urging caution in interpreting correlations in neuroimaging or behavioural data as causal. Theories of child development that view AM as a prerequisite for the development of ToM should be revisited in light of the current findings.

CHAPTER 3

Experiment 2: Familiarity Modulates the Functional Relationship Between Theory of Mind and Autobiographical Memory

In the previous experiment I showed that the normal development of AM is not necessary for the normal development of ToM, as measured by a battery of standard ToM tests. One criticism of standard ToM tests is that they employ highly-controlled and artificial stimuli and use strangers or fictional characters as targets (Baron-Cohen et al., 2001; Stone et al., 1998; Stuss et al., 2001). In real life, however, ToM typically involves repeated interactions with personally known others, such as family members, close friends, and co-workers. Indeed, knowing someone for a long period of time and observing that person's behaviour in different situations provides a rich source of information on which one can draw when imagining that person's mental experiences. Therefore, AM might preferentially benefit ToM when the target person is personally known.

Several recent fMRI studies suggest that a personal relationship or the ability to identify with the target person in a ToM or perspective-taking task can modulate neural activity. In one study, imagining painful scenarios from one's own perspective and the perspective of a loved one showed overlapping activity within the anterior cingulate cortex and anterior insula, whereas imagining the scenarios from a stranger's perspective elicited greater activity in the superior frontal gyrus and right TPJ (Cheng, Chen, Lin, Chou, & Decety, 2010). Separate work by Mitchell and colleagues (2005, 2006) has shown that perceivers selectively engage in self-referential strategies supported by the ventral medial PFC when inferring the mental states of similar others but not when inferring the mental states of dissimilar others. Another study

examined the contribution of AM, as measured by hippocampal activity, to emotion judgments of others. In that study, participants were scanned while making judgments relating to the self as well as protagonists deemed similar to the self and those deemed dissimilar from the self. The authors found increased hippocampal activity when participants made judgments about similar versus dissimilar others, but only when participants had a personal memory of the event involving the similar other (Perry et al., 2011). Taken together, these studies suggest that the strategy adopted to infer another person's mental state depends on whether that person is personally known or is perceived as similar to oneself.

In this experiment, I tested the idea that AM and semantic memory interact in different ways during ToM depending on whether the target person is personally known or unknown. This idea extends from the transformation hypothesis, which suggests that there is a dynamic relationship between AM supported by the hippocampus and semanticized versions of the original memory supported by the neocortex (Moscovitch et al., 2005, 2006; Rosenbaum, et al., 2001; Winocur & Moscovitch, 2011; Winocur et al., 2010; for similar ideas see Spreng & Mar, 2012). To this end, I modified the paradigm used in a previous fMRI study (Rabin et al., 2010) and included a ToM condition that involved imagining events from the perspective of personally familiar others (i.e., relatives and close friends). Therefore, in the current study, participants were scanned with fMRI as they recollected past events in response to personal photos (AM condition) and imagined the experiences of other people in response to photos of personally familiar others (pToM condition) and unfamiliar others (ToM condition). In the latter two conditions, participants selected one person from the photo and imagined an experience from that person's perspective. I predicted that familiarity with the target person would modulate the functional relationship between AM and ToM such that AM would show greater neural overlap with pToM

than with ToM. Furthermore, it was expected that relative to ToM, pToM would elicit greater activity within midline regions, including the hippocampus, suggesting some reliance on past autobiographical experiences. Conversely, ToM was expected to show greater activity than pToM within lateral frontal and lateral temporal regions – a pattern that has been associated with accessing semantic knowledge (Martin & Chao, 2001). Nevertheless, AM and semantic memory are not viewed as mutually exclusive; instead, they are believed to interact to support ToM (at least in healthy people), although one type of memory may dominate depending on whether one has a personal relationship with the target person.

In the current study, fMRI data were analyzed with Spatiotemporal partial least squares (ST-PLS), a multivariate technique that identifies time-varying distributed patterns of activity that differentiate experimental conditions (McIntosh & Lobaugh, 2004). Unlike univariate event-related analyses, ST-PLS does not make assumptions about the shape and time course of the hemodynamic response function. Moreover, ST-PLS can provide a more sensitive statistical assessment than univariate analyses, as all voxels are analyzed in one single analytic step, thus eliminating the issue of multiple comparisons. In the present study, I focused on early and late phases of event generation in order to capture differences that may exist during the construction and elaboration of events, respectively (Addis et al., 2007; Rabin et al., 2010).

Method

Participants

Eighteen right-handed, healthy women with normal or corrected-to-normal vision and no reported history of neurological or psychiatric illness participated in the study (mean age =19.3 years, S*D* =1.2; mean education = 13.3 years, *SD* =1.1). Note that this is the same sample used in Experiment 1 with one additional participant. Participants gave informed written consent in

accordance with the ethics committees at York University and Baycrest. Participants received monetary compensation for their time.

Stimuli

A real-world family photos test of mental state attributions was modified to include a ToM condition that involved personally known others (Rabin et al., 2010). Three conditions were developed for presentation to participants during scanning: personally experienced events (AM), events experienced by personally known others (pToM), and unknown events involving unfamiliar others (ToM). The AM condition consisted of 15 personal family photos of events that took place within the past 1 to 5 years. Thirteen of the 18 participants appeared in each AM photo. Analyses confirmed that the presence or absence of participants in the AM photos did not affect the behavioural or fMRI results (see Results section). A relative or close friend of each participant collected the photos to reduce the likelihood that the events in the photos were rehearsed prior to scanning. The pToM condition consisted of 15 photos depicting specific events that had been experienced by family members and close friends but not by the participant him/herself. This was to ensure that the pToM events were not confounded with AM. These photos were also collected by a relative or close friend of the participant to ensure that the photos were not seen prior to scanning and that photo selection was not biased in any way. The ToM condition consisted of 15 photos depicting unfamiliar people engaged in specific events that were matched to each AM photo by the experimenter according to theme (e.g., birthday party, picnic), scenery (e.g., indoor vs. outdoor), and time period from which the photo was taken. All photos were resized and converted to gray scale (see Figure 3.1 for an example of the stimuli employed).

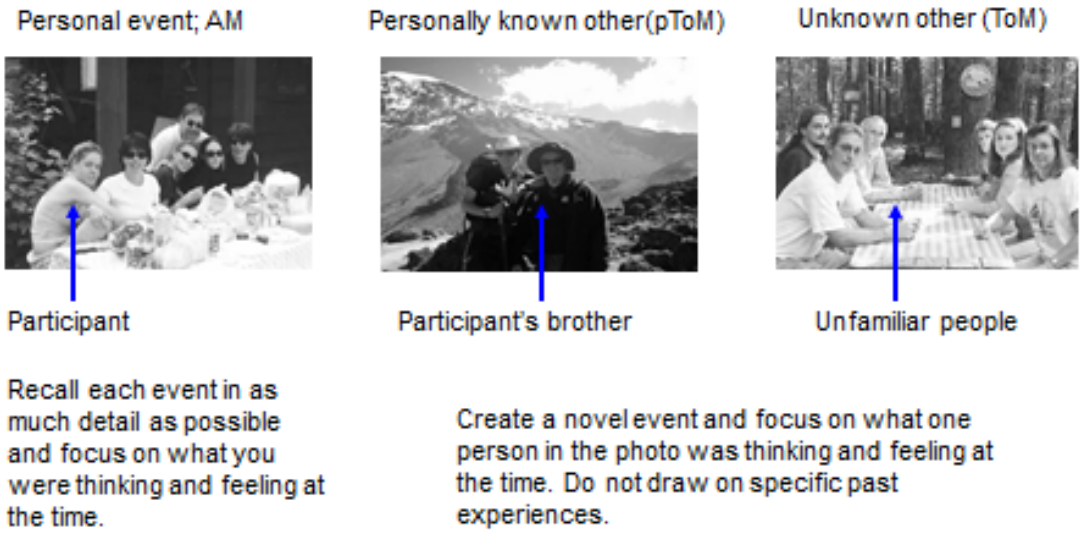


Figure 3.1. An Example of the Stimuli Used in the Family Photos Task.

Two control conditions were included in this study. One control condition consisted of luminance judgments made in response to scrambled photos. Matlab was used to scramble the pixels of each AM, pToM, and ToM photo to produce a corresponding image matched in visual complexity and luminance. The second control condition consisted of an odd–even number judgment task. This second control condition was included because it has been shown that activity, particularly within the MTL, can vary depending on the type of control condition used (Stark & Squire, 2001).

E-Prime software (Psychology Software Tools, Pittsburgh, PA) was used for the presentation of stimuli as well as for the collection of reaction times and response data. Responses were made on an MR-compatible four-button response box.

Task

At the beginning of each run, participants viewed a set of instructions that corresponded to one of the three conditions (i.e., AM, pToM, or ToM). Each run contained five photos from

one of the conditions. Each photo was presented for 20 seconds and was followed by three rating scales (see below). Trials were separated by a 2-second rest period during which a fixation cross was presented. There were three runs for each condition (for a total of nine runs), which were presented in pseudorandom order. Each run lasted for 5 minutes and 4 seconds. As indicated in Figure 3.1, in the AM condition, participants were presented with their own photos and asked to recollect the event depicted in each photo in as much detail as possible. They were told to focus on what they were thinking and feeling at the time. For the pToM and ToM conditions, participants were presented with photos of other people and asked to generate a novel event for each photo while focusing on what one person in the photo might have been thinking and feeling at the time. Participants were specifically instructed to not draw on past experiences when generating these events. Participants were told to press a specified button on the response box once an event had come into mind, whether remembered or imagined. Response times were recorded and demarcated the end of an initial construction phase (i.e., searching/initial generation of the event) and the beginning of an elaboration phase. For the elaboration phase, participants were told to continue to retrieve or generate as many details as possible for the event. The elaboration phase continued until the photo was no longer present on the screen. All photos remained on the screen for 20 seconds, regardless of when responses were made, to maximize the recollection/generation of details associated with each event.

Following the presentation of each photo, participants rated the event they recollected/imagined on a number of dimensions known to influence neural activity. Three ratings scales were presented after each photo. The first rating scale differed for AM and pToM/ToM events. AM events were rated on the extent to which events were recollected or familiar (1 = don't know event; 2 = familiar with event; 3 = remember event; (Gardiner,

Ramponi, & Richardson-Klavehn, 1998; Tulving, 1985). Participants were instructed to select "remember" if the event was specific to a time and place and they could re-experience it, to select "familiar with event" if the event was familiar to them, but they could not recall any specific contextual or other experiential details associated with the event, and to select "don't know event" if they were unable to recall any aspect of the event. The imagined pToM and ToM events were rated on a 4-point scale for likeness to an actual memory in which 1 = exactly like a memory and 4 = nothing like a memory. The next two ratings scales were employed for all conditions. One scale assessed the amount of detail retrieved or imagined for each event (ranging from 1 = not vivid to 4 = very vivid), and the other scale assessed the spatial coherence of each event (contiguousness of the spatial context: 1 = fragmented scenes to 4 = continuous scene; Hassabis, Kumaran, & Maguire, 2007; Hassabis, Kumaran, Vann, & Maguire, 2007). The responses from the spatial coherence scale are not reported here, as participants had difficulty making these ratings. Following the rating scales, the corresponding scrambled photo was presented, and participants were asked to indicate with a button press whether the photo was dark or light in brightness. The second baseline task followed and consisted of an odd–even number judgment task, in which participants were presented with a number from 1 to 9 and were asked to indicate with a button press whether the number was odd or even. Immediately prior to the scan, a short training session was provided to ensure that participants fully understood the task instructions. The photos used in the training session were not used during the scan.

Postscan Interview

Immediately following the scan, participants took part in an interview in which they viewed the same photos that had been presented in the scanner. To help prevent re-encoding or repeated retrieval of events in the scanner, participants were not told of the postscan interview

until after the scanning session. Participants were asked to think back to the events they had generated in the scanner and to rate each event on the same three scales that were presented in the scanner. Postscan ratings were collected in case a within-scanner rating was not provided. The photos with the highest vividness ratings (approximately two-thirds of all photos) were selected for a semistructured interview in which participants described the events as they had been recollected or imagined in the scanner. The events were recorded and then transcribed for scoring. Narratives were scored using an adapted Autobiographical Interview scoring procedure described by Levine, Svoboda, Hay, Winocur, and Moscovitch (2002). The Autobiographical Interview was developed to quantify episodic and semantic contributions to AM, but has been successfully employed in a number of studies examining non-mnemonic abilities, such as future thinking (Addis, Wong, & Schacter, 2008; Kwan et al., 2010) and describing pictures of scenes (Race et al., 2011). Narratives were segmented into distinct details, which were classified as internal (including event-specific, temporal, perceptual, spatial, and thought/emotion details) or external (including semantic facts, repetitions, or metacognitive statements; see Appendix A for an example of a scored narrative). Analyses of the postscan narratives were conducted by a trained rater who achieved high interrater reliability on the Autobiographical Interview (intraclass correlation coefficient, two-way random effects model; Shrout & Fleiss, 1979) using a standard set of previously scored memories (Levine et al., 2002).

Data Acquisition

Brain imaging data were acquired with a Siemens Trio 3T magnet with a 12-channel head coil. Anatomical scans were acquired using a T1- weighted volumetric MRI (TR=2000 ms, TE=2.63 ms, 160 oblique axial slices, 1.0mm thick, FOV=256 mm). Functional scans were acquired with a whole-head T2*-weighted EPI pulse sequence (TR=2000 ms, TE=30 ms, flip

angle=70°, FOV=200 mm, 64×64 acquisition matrix), consisting of 30 contiguous, 5-mm-thick axial slices. Physiological data (heart and respiration rate) were acquired during the scanning session. Stimuli were presented visually through a mirror mounted on a coil that reflected images from a projector located at the bottom of the scanner. Images were reconstructed and preprocessed with AFNI (Cox, 1996). The initial 10 time points of each run, in which transient signal changes occur as brain magnetization reaches a steady state, were excluded. The data were first corrected for respiration and heart rate. Next, slice-timing was corrected to the first slice, followed by motion correction using a 3-D Fourier transform interpolation using a functional volume that minimized the amount of motion to less than 2 mm. The images were spatially normalized to the Montreal Neurological Institute (MNI) template and smoothed using an 8-mm FWHM Gaussian kernel. The final voxel size was 4 mm × 4 mm × 4 mm.

Data Analysis

Data analysis was restricted to AM events that were successfully recollected (i.e., events rated as "remembered"), pToM and ToM events rated as novel (i.e., "nothing like a memory," corresponding to a rating of 3 or 4), and AM, pToM, and ToM events rated as vividly recollected/imagined (i.e., vividness rating of 3 or 4), as vividness is known to influence activity in regions associated with the generation of AM and ToM events (Gilboa et al., 2004; Rabin et al., 2010). Within-scanner ratings (vs. postscan ratings) were used, as these were believed to be more reliable. However, in four instances in which a within-scanner rating was missing, the corresponding rating provided during the postscan interview was used (three vividness ratings for AM events and one rating indicating 'likeness to an actual memory' for a pToM event).

The fMRI data were analyzed with ST-PLS (McIntosh et al., 2004), a multivariate technique similar to principal components analysis that identifies time-varying distributed

patterns of activity that differentiate experimental conditions. Unlike univariate event-related analyses, ST-PLS is not dependent upon assumptions about the shape and time course of the hemodynamic response function. Moreover, it is more sensitive than univariate analysis, as all voxels are analyzed in a single analytic step and therefore eliminates the need for post hoc correction due to multiple comparisons. For the current study, a 20-second temporal window was specified for each event (i.e., 10 TRs), and the onset of trials was specified at 2 seconds after stimulus onset.

Using singular value decomposition applied to the covariance matrix of task and functional activation, ST-PLS extracts ranked latent variables (LV), or orthogonal patterns of brain activity, that express how well brain activity covaries with each condition. When applying ST-PLS to event-related data, patterns of brain activity reliably related to task conditions are calculated for each poststimulus TR for each LV (McIntosh & Lobaugh, 2004). This provides information on the time course of activity associated with the experimental conditions. Each voxel is given a weight within each LV, known as a salience, which indicates how that voxel is related to the LV. A salience can be positive or negative, depending on whether the voxel shows a positive or negative correlation with the pattern identified by the LV. These salience values are then multiplied by the blood-oxygen-level dependent (BOLD) signal value in that voxel and summed across all voxels to derive an estimate of how robustly each participant displays that spatial pattern (known as a 'brain score'). That is, the brain score indicates how strongly individual subjects express the patterns of the LV.

PLS uses two different methods to test statistical significance. Permutation tests assess whether the effect represented in a given LV captured by the singular value is sufficiently strong to be different from random noise. For the current experiment, 500 permutations were used. If

the probability was less than .05, the LV was considered significant. To provide reliability measures of the contribution of each voxel to the LV, a bootstrap that resampled the data 100 times to estimate the standard error of each voxel's salience was used. The ratio of each salience to its standard error (bootstrap ratio; BSR) was calculated and is roughly equivalent to a z-score. Peak voxels with a BSR of ±3, $p < .001$, and containing a minimum size of 5 voxels were considered reliable. The bootstrap also estimated the 95% confidence intervals for the mean brain scores in each condition. The confidence intervals provide estimates of whether activity in each condition is reliably different from other conditions as well as different from the overall mean. I examined activity during an early phase (TRs 1 and 2, corresponding to activity 0–4 s after stimulus onset) and a late phase (TRs 4 and 5, corresponding to activity 6–10 s after stimulus onset) of event generation. The coordinates for the maximum peak of each cluster are reported in MNI space.

First, I computed a PLS analysis that included AM, pToM, and ToM along with the two baseline conditions to ensure consistency with previous findings. In subsequent analyses I wanted to focus on the relationship among the three experimental conditions and therefore computed a PLS analysis that included only AM, pToM, and ToM. Because I had an a priori prediction regarding differences between pToM versus ToM and such an LV did not emerge (see Results section), I computed an additional ST-PLS analysis that included only pToM and ToM.

Results

Participants' Presence in the AM Photos

To make a case for collapsing across the two AM subgroups (i.e., participants who appeared in their AM photos and participants who did not appear in their AM photos), it was

important to determine that there were no differences between the two subgroups. In order to do so, I examined participants' behavioural data from the postscan interview and the fMRI data.

With respect to the behavioural data, a between-group *t*-test was used to compare the number of internal details generated in response to AM photos in which participants appeared versus AM photos in which participants did not appear. The analysis revealed no differences between the groups, suggesting that the type of AM photo used did not affect the number of internal details participants generated, $t(17) = -.47$, $p = .64$, 95% CI [-2.78, 1.76], $d = -0.32$.

To examine the fMRI data, a between-group ST-PLS analysis was computed that compared the AM photos in which participants appeared versus the AM photos in which participants did not appear. The results of this ST-PLS analysis were not significant, suggesting that the participants' presence in the photos did not influence the pattern of neural activity. To provide additional support for collapsing across the two subgroups, I also ran two rotated ST-PLS analyses that contained all three experimental tasks, with the AM condition differing between analyses. The two analyses included the AM photos in which participants were or were not present in their photos, respectively. These two ST-PLS analyses revealed the same results, once again helping to confirm that participants' presence in their own photos did not influence the neural pattern of activity. Specifically, both analyses revealed one significant LV, which contrasted AM and pToM with ToM. LV2 was not significant in either of these analyses.

Phenomenology of the AM, pToM, and ToM Events

As mentioned above, only the following events were included in the analyses: AM events that were successfully recollected, pToM and ToM events rated as novel (i.e., different from a memory), and AM, pToM, and ToM events rated as vividly recollected/imagined. Events that did not have button response data distinguishing construction versus elaboration phases were

also excluded. Therefore, each participant contributed an average of 12.39 AM events (*SD* = 2.0, range 7 – 15), 10.61 pToM events (*SD* = 3.0, range 5 – 14), and 10.22 ToM events (*SD* = 3.0, range 5 – 14) to the analysis (out of 15 possible events for each condition). A repeated measures ANOVA indicated that the length of the construction phase significantly differed across AM (*M* = 1799 ms, *SD* = 719 ms), pToM (*M* = 2066 ms, *SD* = 843 ms), and ToM events (*M* = 2341 ms, *SD* = 850 ms; $F(2, 34) = 8.86$, $p = .001$). Post-hoc tests were computed using a Bonferroni adjustment that maintained a family-wise error rate of < .05. Results indicated that AM construction took significantly less time than pToM, $t(17) = -2.69$, $p = .015$, 95% CI [-479, -58], $d = -0.35$, and ToM construction, $t(17) = -3.54$, $p = .003$, 95% CI [-865, -219], $d = -0.71$. There was no difference between the construction of pToM and ToM events, $t(17) = -2.1$, $p = .047$, 95% CI [-445, -4], $d = -0.33$.

Postscan Interview

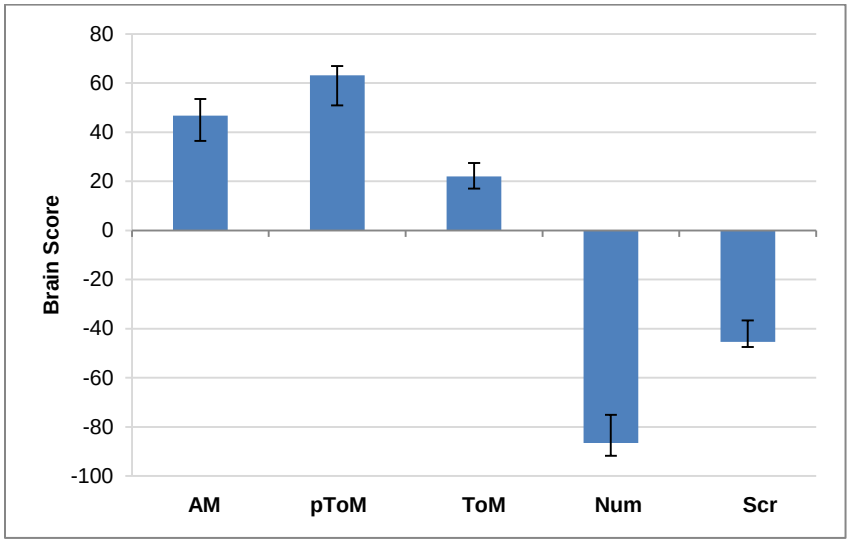
A repeated measures ANOVA indicated that the number of internal details generated in response to AM (*M* = 8.53, *SD* = 1.99), pToM (*M* = 6.13, *SD* = 1.58), and ToM events (*M* = 6.16, *SD* = 1.85) differed significantly, $F(2, 34) = 29.1$, $p < .0001$. Post-hoc tests were computed using a Bonferroni adjustment that maintained a family-wise error rate of $p < .05$. Results indicated that participants produced significantly more internal details in response to AM photos than pToM photos, $t(17) = -5.76$, $p < .0001$, 95% CI [1.52, 3.29], $d = 1.37$, and ToM photos, $t(17) = -6.82$, $p < .0001$, 95% CI [1.64, 3.10], $d = 1.27$. The number of internal details did not differ in response to pToM and ToM photos, $t(17) = -.11$, $p = .91$, 95% CI [1.64, 3.10], $d = -0.02$.

fMRI Results

Common regions involved in AM, pToM, and ToM.

I computed a PLS analysis that included the three experimental conditions (AM, pToM, and ToM) and the two baseline conditions (scrambled task and odd-even task) to ensure consistency with previous findings (Rabin et al., 2010). In this analysis, I examined brain activity only during the early phase of event generation because both baseline conditions were only 4 seconds (and therefore comparisons could not be made beyond this 4-second period). This PLS analysis yielded two significant patterns of brain activity (i.e., LVs). As predicted, the first LV differentiated a pattern of brain activity contrasting AM, pToM and ToM with the two baseline conditions ($p < .0001$, explained variance = 70.5%; Figure 3.2A). The positive saliences listed in Table 3.1 and presented in warm colours in Figure 3.2B correspond to greater activity during AM, pToM, and ToM relative to the two baseline conditions. Common regions activated included the medial PFC, medial and lateral temporal regions, as well as medial and lateral parietal regions. In contrast, the negative saliences, presented in cool colours, correspond to greater activity during the baseline conditions. The second significant LV differentiated a pattern of brain activity contrasting AM and the odd-even baseline with the scrambled baseline (pToM and ToM were not significantly different from the mean and therefore did not contribute to this LV; $p < .0001$, explained variance = 17.89%). Given that this LV did not yield a meaningful pattern of activity, the results were not interpreted.

A



B

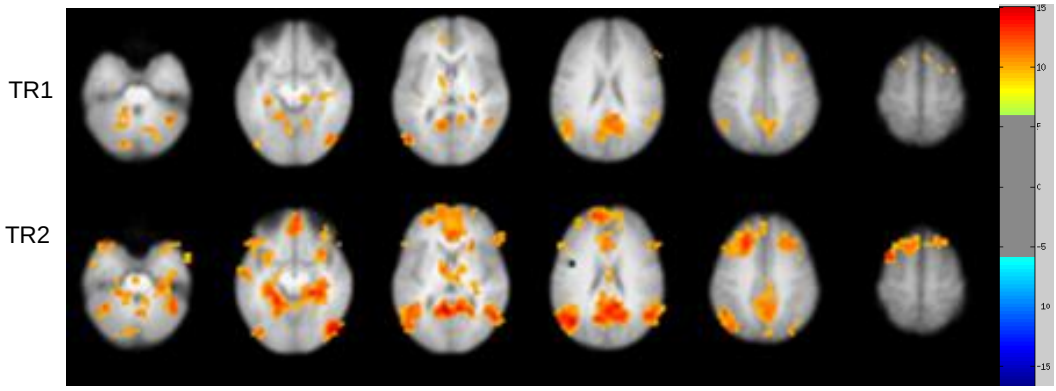


Figure 3.2. Common Pattern of Activity During AM, pToM, and ToM Versus Two Control Conditions (Latent Variable 1, $p < .0001$). (A) A plot of brain scores indicating the amount of correlation between each task and the associated pattern of brain activity. (B) Axial slices of the brain regions associated with AM, pToM, ToM (warm colours) vs. the two control conditions (cool colours). Activity is shown during an early phase (TRs 1 and 2) of event generation. The functional maps are overlaid on the average anatomical image from all participants. Left side of the brain is presented on the left. AM, autobiographical memory; pToM, personal theory of mind; ToM, theory of mind; NUM, odd-even number control condition; SCR = scrambled control condition.

Table 3.1

Coordinates of Regions Associated with AM, pToM, and ToM Versus Two Control Conditions

Hemis	Region	BA	*x*	*y*	*z*	*TR*	*BSR*	*vol.*
AM, pToM, and ToM > Control conditions during TR1 and TR2								
L	Paracingulate Cortex	32/10	-8	44	4	1	6.9	7
L	Medial PFC	9	-20	28	28	1	8.6	19
R	Middle Frontal Gyrus	9	36	24	40	1	8.4	34
L	Middle Frontal Gyrus	9	-40	8	44	1	7.7	9
L	Middle Frontal Gyrus	6	-32	8	48	2	12.1	1339
R	Superior Frontal Gyrus	9/8	16	28	48	1	7.8	6
R	Ventrolateral PFC	47	52	24	0	2	9.9	55
L	Ventrolateral PFC	47	-48	24	-4	2	9.5	156
R	Hippocampus	-	32	-28	-16	1	8.8	33
L	Hippocampus	-	-32	-28	-12	1	8.6	20
L	Amygdala	-	-32	-4	-20	2	6.9	5
B	PCC/RSC*	23/30	0	-52	12	1	10.7	516
R	Middle Temporal Gyrus	21	60	0	-20	2	9.3	41
L	Middle Temporal Gyrus	21	-60	-4	-20	2	10.6	61
R	pSTS	22	48	-52	8	1	9.0	68
R	Angular Gyrus	39	48	-64	24	1	7.3	17
L	Angular Gyrus	39	-44	-64	16	2	14.7	541
R	Fusiform Gyrus	37	40	-48	-24	1	10.9	72
R	Fusiform Gyrus	37	44	-56	-24	2	16.3	2154
L	Middle Occipital Gyrus	19	-48	-72	4	1	12.1	190
R	Cerebellum	-	8	-60	-28	1	7.8	16
R	Cerebellum	-	16	-76	-36	1	6.9	9
L	Cerebellum	-	-16	-76	-28	1	8.6	13
L	Cerebellum	-	-12	-80	-36	2	7.5	26
Control conditions > AM, pToM, and ToM during TR1 and TR2								
No regions								

MNI coordinates of the maximally activated voxel within each cluster are reported. AM = autobiographical memory condition; pToM = theory of mind condition involving personally known others; ToM = theory of mind condition involving unknown others; Hemis = hemisphere; BA = Brodmann area; Vol. = cluster volume in voxels; L = left; R = right; PFC = prefrontal cortex; PCC = posterior cingulate cortex; RSC = retrosplenial cortex; pSTS = posterior superior temporal sulcus.
*Activation in this region extended bilaterally

AM and pToM versus ToM.

The PLS analysis that included AM, pToM, and ToM identified two significant patterns of brain activity (i.e., LVs). The first LV showed a pattern contrasting AM and pToM with ToM ($p < .005$, explained variance = 61.3%; Fig. 3.3A). The positive saliences, presented in warm colours, correspond to greater activity during AM and pToM relative to ToM, whereas the negative saliences, presented in cool colours, correspond to greater activity during ToM relative to AM and pToM (See Table 3.2 for a list of regions and Fig. 3.3B for a depiction of the saliences). I examined activity during early and late phases of event generation. During the early phase, all regions activated correlated with AM and pToM (vs. ToM) and included medial frontal, medial and lateral temporal, and medial parietal regions. During the late phase of event generation, AM and pToM continued to be supported by a similar network, but MTL regions were no longer involved. The opposite contrast showed that during the late phase ToM was associated with increased activity in bilateral ventrolateral PFC (BA 44), left insula, left lingual gyrus, right inferior temporal gyrus extending into middle occipital cortex, and bilateral occipital cortices (BA 19).

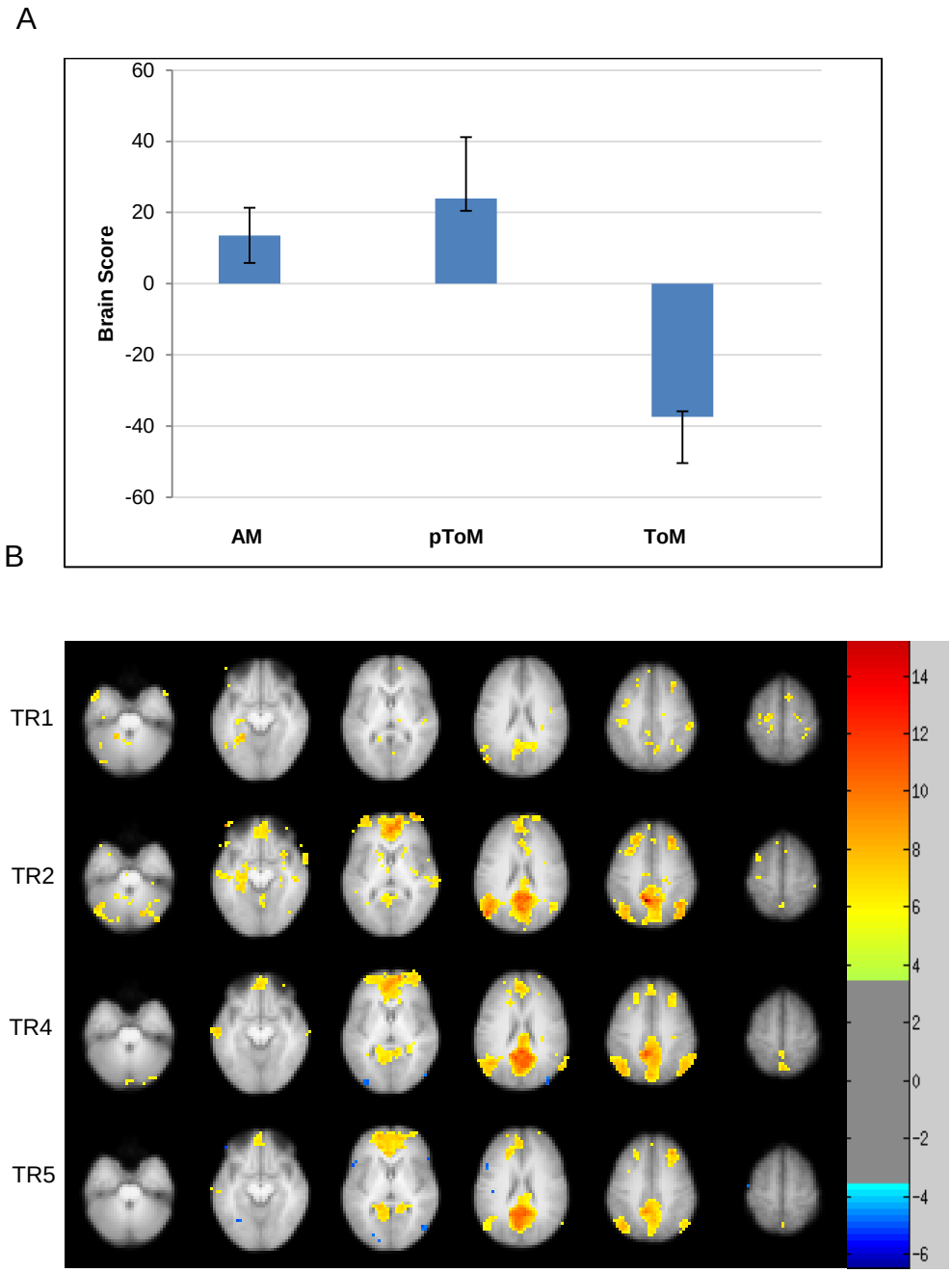


Figure 3.3. Differential Activity During AM and pToM Versus ToM (Latent Variable 1, $p < .005$). (A) A plot of brain scores, indicating the amount of correlation between each task and the associated pattern of brain activity. (B) Depicts axial slices of the brain regions associated with AM and pToM (warm colours) or ToM (cool colours). Activity is shown during an early phase (TRs 1 and 2) and a late phase (TRs 4 and 5) of event generation. The functional maps are overlaid on the average anatomical image of all participants. Left side of the brain is presented on the left. AM, autobiographical memory; pToM, personal theory of mind; ToM, theory of mind.

Table 3.2

Coordinates of Regions Associated with AM and pToM Versus ToM (LV 1)

Hemis	Region	BA	*x*	*y*	*z*	*TR*	*BSR*	*vol.*
AM and pToM > ToM during TR1 and TR2								
R	Frontal Pole/medial PFC*	10/32	8	56	0	2	9.1	346
R	Superior Frontal Gyrus	6	4	12	48	1	5.8	11
L	Middle Frontal Gyrus	6	-36	0	44	1	6.1	17
L	Middle Frontal Gyrus	8	-32	20	40	2	6.5	37
R	Middle Frontal Gyrus	8	24	32	40	2	9.4	39
R	Middle Frontal Gyrus	8	28	24	36	1	5.3	9
L	Cingulate Gyrus	24	-24	-16	48	1	5.4	5
R	Insula	13	40	-8	24	1	4.8	6
L	Hippocampus	-	-28	-20	-12	2	4.8	8
L	Parahippocampal Gyrus	19	-16	-44	-4	2	5.8	6
L	Parahippocampal Gyrus	36	-24	-44	-12	1	5.9	12
R	Parahippocampal Gyrus	30	20	-40	-4	2	5.5	21
R	Parahippocampal Gyrus	28	28	-24	-16	2	5.1	9
L	Parahippocampal Gyrus	36	-28	-36	-12	2	5.1	15
R	PCC/RSC/Precuneus*	23/30/31	8	-60	28	1	8.3	84
L	Precuneus*	31/7	-4	-52	36	1	5.1	5
L	Precuneus*	31/7	-8	-52	36	2	15.2	517
L	Angular Gyrus	39	-36	-64	32	2	8.9	200
R	Temporal Pole	38	44	20	-36	2	4.9	6
L	Superior Temporal Gyrus	22	-48	-20	-8	2	5.4	7
L	Superior Temporal Gyrus	22	-60	16	-4	2	5.4	13
R	Superior Temporal Gyrus	22	64	4	-8	2	5.4	6
L	Cuneus	18	-8	-80	36	2	4.7	10
R	Cerebellum	-	8	-48	-44	1	6.0	21
R	Cerebellum	-	40	-60	-52	2	5.3	10
R	Cerebellum	-	24	-68	-40	2	4.8	13
R	Cerebellum	-	8	-48	-48	2	5.3	6
ToM > AM and pToM during TR1 and TR2								
No regions								

Table 3.2 cont.

Coordinates of Regions Associated with AM and pToM Versus ToM (LV 1)

Hemis	Region	BA	*x*	*y*	*z*	*TR*	*BSR*	*vol.*
AM and pToM > ToM during TR4 and TR5								
R	Frontal Pole/medial PFC	10	12	56	8	4	7.5	674
L	Paracingulate Cortex*	32	-8	32	0	5	8.1	543
L	Middle Frontal Gyrus	6	-32	20	44	4	5.3	15
R	Middle Frontal Gyrus	8	28	32	40	5	7.2	72
L	PCC/RSC/Precuneus*	31/30/7	-12	-56	28	4	10.8	704
L	PCC/RSC/Precuneus*	23/30/31	-4	-44	28	5	9.8	749
L	Angular Gyrus	39	-40	-68	36	5	5.9	142
R	Supramarginal Gyrus	40	52	-64	28	4	7.0	157
L	Middle Temporal Gyrus	21	-60	-16	-12	4	5.2	25
L	Middle Temporal Gyrus	21	-60	-8	-16	5	4.0	8
R	Thalamus	-	32	-32	0	4	4.5	13
R	Cerebellum	-	8	-48	-52	4	5.6	35
ToM > AM and pToM during TR4 and TR5								
R	Ventrolateral PFC	44	52	20	8	5	-4.4	9
L	Ventrolateral PFC	44	-48	12	16	5	-4.9	27
L	Insula	13	-48	16	12	4	-4.9	8
L	Lingual Gyrus	-	-28	-76	8	5	-4.2	6
R	Inferior Temporal Gyrus	37	44	-68	0	5	-4.5	11
R	Middle Occipital Gyrus	19	36	-84	16	4	-4.7	11
R	Middle Occipital Gyrus	19	48	-72	8	4	-4.5	6
L	Middle Occipital Gyrus	19	-36	-84	8	4	-4.5	12

MNI coordinates of the maximally activated voxel within each cluster are reported. AM = autobiographical memory condition; pToM = theory of mind condition involving personally known others; ToM = theory of mind condition involving unknown others; Hemis = hemisphere; BA = Brodmann area; Vol. = cluster volume in voxels; R = right; L = left; PCC = posterior cingulate cortex; RSC = retrosplenial cortex; PFC = prefrontal cortex.
*Activation in this region extended bilaterally.

The second significant LV differentiated a set of brain regions supporting AM from a separate set of regions supporting pToM (p = .026, explained variance = 38.7%; Fig. 3.4A). ToM was not significantly different from the mean and therefore did not contribute to this LV. The positive saliences, presented in warm colours, correspond to greater activity during AM, whereas

the negative saliences, presented in cool colours, correspond to greater activity during pToM (See Table 3.3 for a list of regions and Fig. 3.4B). During the early phase of event generation, the set of regions supporting AM included left cingulate gyrus (BA 32), right middle frontal gyrus (BA 46), left caudate, and right cerebellum, whereas left insula and right ventrolateral PFC activity emerged during pToM. Later in event generation, AM was associated with activity in the right posterior cingulate cortex/precuneus (BA 23/31), whereas pToM was associated with a much more extensive set of regions that included the right frontal pole (BA 10), bilateral dorsomedial PFC (BA 9), bilateral ventrolateral PFC, left insula, bilateral lateral temporal cortex, left temporal pole (BA 38), bilateral thalamus, and bilateral occipital regions.

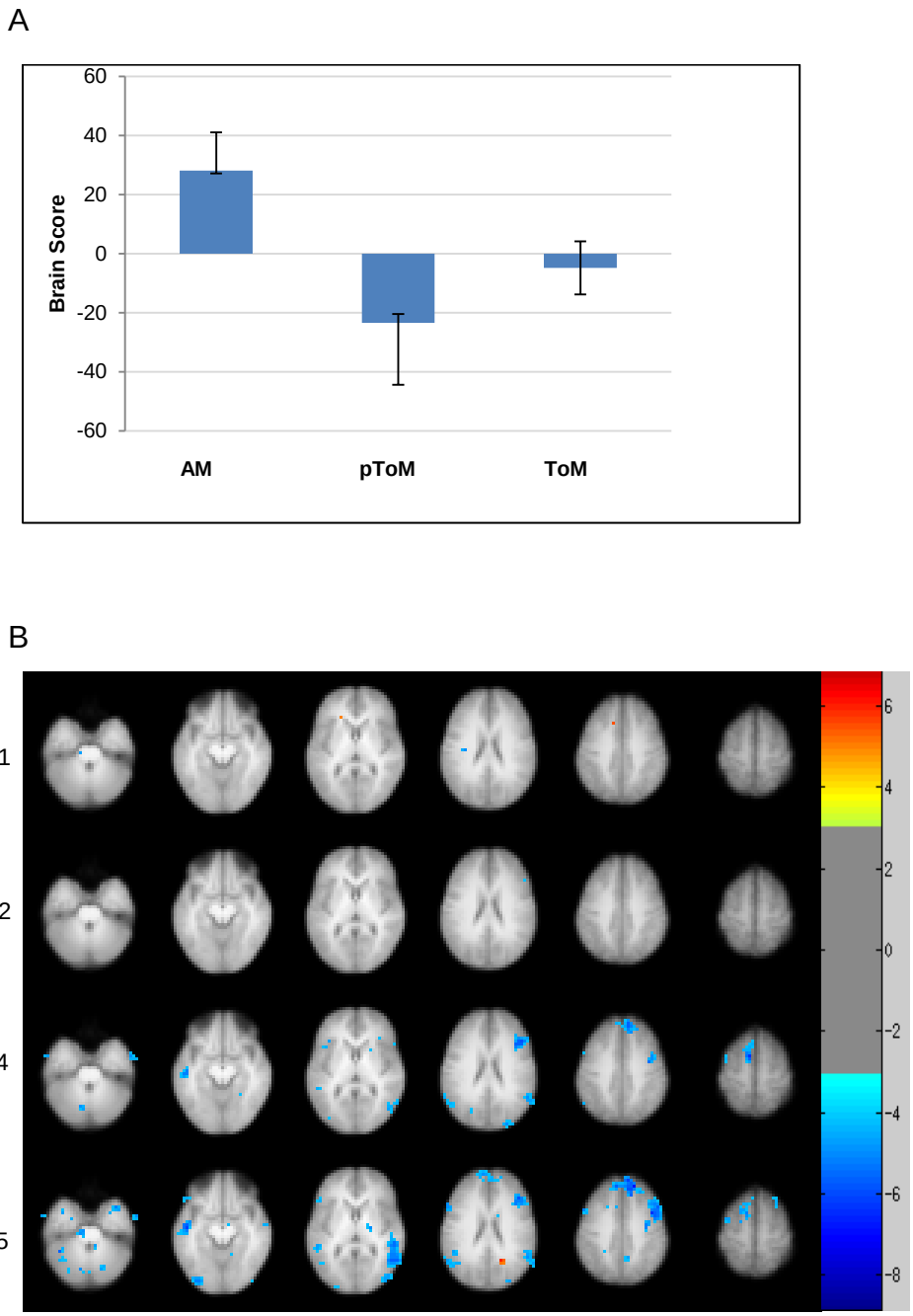


Figure 3.4. Differential Activity During AM Versus pToM (Latent Variable 2, $p < .05$). (A) A plot of brain scores, indicating the amount of correlation between each task and the associated pattern of brain activity. (B) Depicts axial slices of the brain regions associated with AM (warm colours) or pToM (cool colours). Activity is shown during an early phase (TRs 1 and 2) and a late phase (TRs 4 and 5) of event generation. The functional maps are overlaid on the average anatomical image from all participants. Left side of the brain is presented on the left). AM, autobiographical memory; pToM, personal theory of mind; ToM, theory of mind.

Table 3.3

Coordinates of Regions Associated with AM Versus pToM (LV 2)

Hemis	Region	BA	*x*	*y*	*z*	*TR*	*BSR*	*vol.*
AM > pToM during TR1 and TR2								
L	Cingulate Gyrus	32	-12	20	36	1	4.1	9
R	Middle Frontal Gyrus	46	52	44	8	2	4.1	6
L	Caudate	-	-20	28	8	1	3.4	5
R	Cerebellum	-	24	-68	-48	1	5.4	14
pToM > AM during TR1 and TR2								
L	Insula	13	-40	-4	-4	1	-4.2	5
L	Insula	13	-32	-16	20	1	-4.1	5
R	Ventrolateral PFC	45	48	24	20	2	3.3	10
AM > pToM during TR4 and TR5								
R	PCC/Precuneus	23/31	16	-56	20	5	4.7	8
pToM > AM during TR4 and TR5								
R	Frontal Pole	10	20	64	8	4	-4.3	14
R	Dorsomedial PFC*	9	8	44	32	5	-7.5	549
R	Dorsomedial PFC*	9	8	36	40	4	-5.6	123
L	Superior Frontal Gyrus	6	-40	0	52	4	-3.6	7
L	Superior Frontal Gyrus	6	-8	4	52	4	-5.9	81
R	Middle Frontal Gyrus	9	36	20	28	5	-5.6	65
L	Middle Frontal Gyrus	9	-52	12	36	5	-4.5	15
L	Middle Frontal Gyrus	9	-40	8	28	4	-3.7	19
L	Ventrolateral PFC	47	-56	16	16	5	-5.1	73
R	Ventrolateral PFC	46/9	44	20	16	4	-5.7	125
R	Ventrolateral PFC	44	36	16	-28	5	-4.4	19
R	Cingulate Gyrus	31	12	-52	32	5	-4.6	29
R	Precentral Gyrus	6	40	8	36	5	-6.0	83
L	Insula	13	-36	-12	12	4	-3.6	5
R	Middle Temporal Gyrus	21	56	0	-24	4	-4.9	32
R	Middle Temporal Gyrus	21	64	-32	-4	4	-3.8	11
L	Middle Temporal Gyrus	21	-56	4	-28	4	-4.0	5
L	Superior Temporal Gyrus	22	-40	-60	12	4	-4.3	60
R	Superior Temporal Gyrus	22	40	-60	12	4	-5.4	138
R	pSTS	39	56	-56	8	5	-6.2	378
L	Temporal Pole	38	-36	12	-24	5	-4.2	6
R	Thalamus	-	16	-12	-4	4	-3.7	12
L	Thalamus	-	-12	-28	-4	4	-3.8	5

Table 3.3 cont.

Hemis	Region	BA	*x*	*y*	*z*	*TR*	*BSR*	*vol.*
L	Lingual Gyrus	19	-24	-72	16	4	-3.7	6
R	Inferior Occipital Gyrus	19	36	-72	-4	5	-3.9	33
R	Middle Occipital Gyrus	18	24	-88	20	4	-4.2	25
L	Inferior Occipital Gyrus	18	-36	-88	0	4	-3.6	20

MNI coordinates of the maximally activated voxel within each cluster are reported. AM = autobiographical memory; pToM = theory of mind involving personally known others; Hemis = hemisphere; BA = Brodmann area; Vol. = cluster volume in voxels; L = left; R = right; PFC = prefrontal cortex; PCC = posterior cingulate cortex; pSTS = posterior superior temporal sulcus. *Activation in this region extended bilaterally.

pToM versus ToM.

The PLS analysis that included only pToM and ToM revealed one significant LV that differentiated pToM from ToM ($p < .0001$, explained variance = 100%; Fig. 3.5A). The positive saliences, presented in warm colours, correspond to greater activity during pToM, whereas the negative saliences, presented in cool colours, correspond to greater activity during ToM (See Table 3.4 for a list of regions and Fig. 3.5B). During the early phase of event generation, all activated regions correlated with pToM including bilateral frontal pole/paracingulate cortex (BA 10/32), bilateral medial parietal cortex, bilateral hippocampus, bilateral lateral temporal cortex, bilateral temporal poles, and bilateral cerebellum. During the later phase of event generation, pToM continued to be associated with a very similar set of regions, with the exception of hippocampal activity, which was no longer present. In contrast, during the latter part of event generation, relative to pToM, ToM was associated with activity within left ventrolateral PFC (BA 44/45), left middle frontal gyrus (BA 6), left inferior temporal gyrus (BA 37), and left lingual gyrus extending into the superior occipital gyrus.

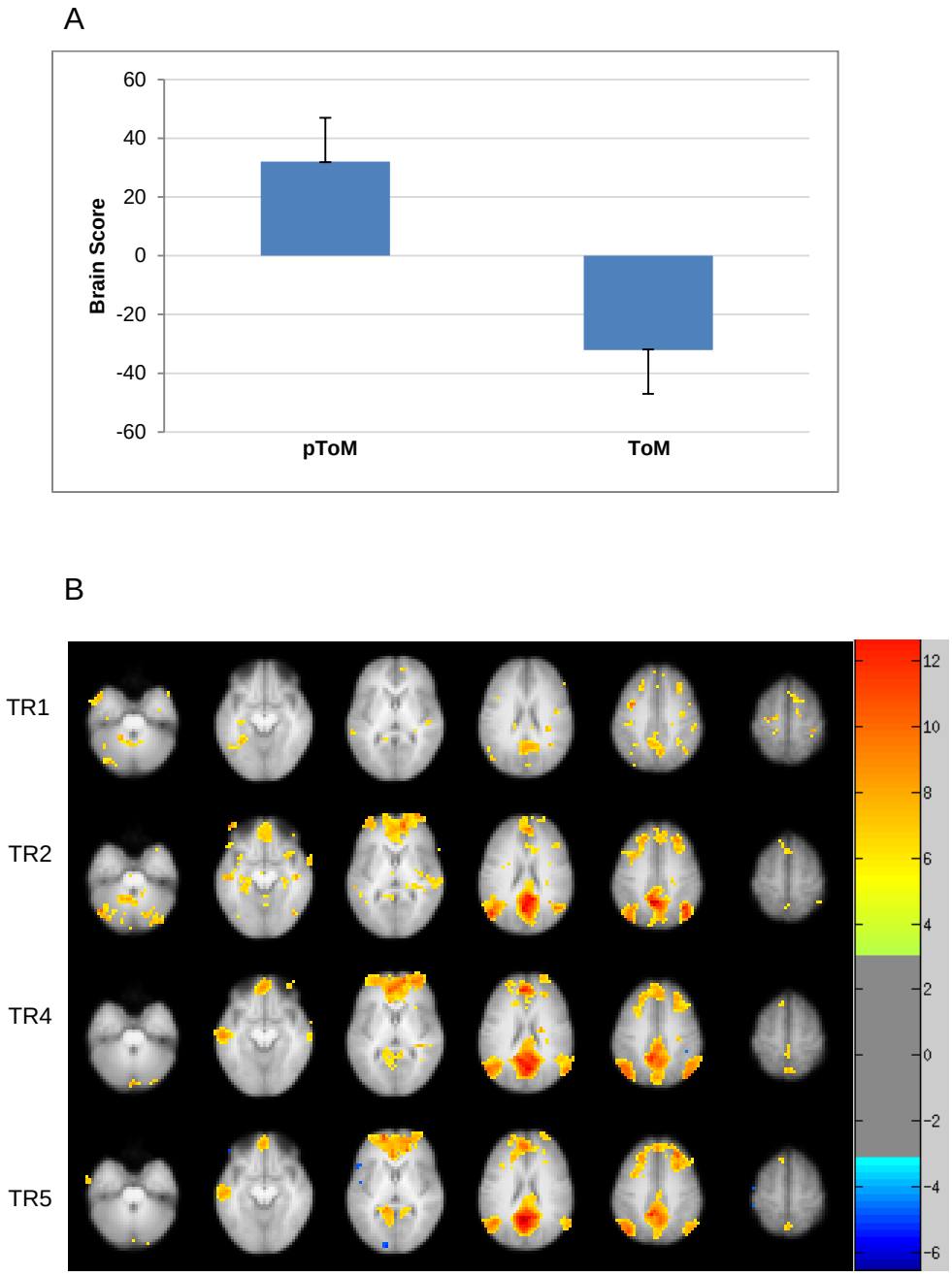


Figure 3.5. Differential Activity During pToM Versus ToM (Latent Variable *1* ($p < .0001$) depicts brain activity during pToM vs. ToM. (A) A plot of brain scores, indicating the amount of correlation between each task and the associated pattern of brain activity. (B) Depicts axial slices of the brain regions associated with pToM (warm colours) or ToM (cool colours). Activity is shown during an early phase (TRs 1 and 2) and a late phase (TRs 4 and 5) of event generation. The functional maps are overlaid on the average anatomical image from all participants. Left side of the brain is presented on the left). pToM, personal theory of mind; ToM, theory of mind.

Table 3.4

Coordinates of Regions Associated with pToM Versus ToM

Hemis	Region	BA	*x*	*y*	*z*	*TR*	*BSR*	*vol.*
pToM > ToM during TR1 and TR2								
R	Frontal Pole/medial PFC*	10/32	12	52	4	2	6.6	751
R	Middle Frontal Gyrus	8	28	20	40	1	5.5	19
R	Middle Frontal Gyrus	8/9	24	32	40	2	7.2	104
L	Middle Frontal Gyrus	8	-28	12	44	2	5.7	61
L	Superior Frontal Gyrus	8	0	20	48	1	4.6	44
L	Superior Frontal Gyrus	8/9	-12	32	48	2	3.8	9
L	Cingulate Gyrus	24	-4	-16	44	1	3.1	6
R	Inferior Frontal Gyrus	6/9	44	0	32	1	3.9	11
L	Inferior Frontal Gyrus	6/9	-36	4	36	1	6.4	61
R	Inferior Parietal Cortex	40	28	-40	56	2	3.8	7
R	Parahippocampal Gyrus	-	40	-16	-16	2	5.0	122
L	Parahippocampal Gyrus	-	-36	-16	-24	1	4.2	11
R	Hippocampus	-	28	-24	-16	2	4.9	99
L	Hippocampus	-	-24	-28	-12	2	3.9	35
R	PCC/RSC/Precuneus*	23/30/31	8	-60	28	1	6.8	230
L	Precuneus*	31/7	-8	-52	36	2	10.1	704
R	Middle Temporal Gyrus	22	56	-32	0	1	4.0	7
L	Middle Temporal Gyrus	22	-56	-32	4	2	4.1	5
L	Middle Temporal Gyrus	22	-48	-20	-8	2	5.1	71
L	Middle Temporal Gyrus	22	-48	-44	0	2	4.5	27
L	Inferior Temporal Gyrus	37	-48	-52	-12	1	3.8	7
R	Superior Temporal Gyrus	22	48	-20	4	1	3.8	8
R	Temporal Pole	38	48	16	-40	2	4.3	10
L	Temporal Pole	38	-48	12	-28	1	4.3	28
L	Temporal Pole	38	-32	12	-24	2	3.7	13
R	Angular Gyrus	39	36	-60	32	1	5.4	51
R	Angular Gyrus	39	44	-60	24	2	8.8	176
L	Angular Gyrus	39	-48	-72	20	1	4.1	11
L	Angular Gyrus	39	-48	-68	20	2	7.7	285
L	Fusiform Gyrus	37	-32	-44	-16	1	5.2	17
R	Insula	13	40	-8	24	1	4.4	22
R	Middle Occipital Gyrus	19	40	-68	-12	2	4.7	7
R	Thalamus	-	8	-20	8	1	3.6	5

Table 3.4 cont.

Hemis	Region	BA	*x*	*y*	*z*	*TR*	*BSR*	*vol.*
R	Cerebellum	-	8	-52	-56	2	5.3	189
R	Cerebellum	-	16	-64	-16	1	3.7	11
L	Cerebellum	-	-16	-40	-28	1	4.2	29
L	Cerebellum	-	-32	-76	-28	1	4.7	32
ToM > pToM during TR1 and TR2								
No regions								
pToM > ToM during TR4 and TR5								
L	Paracingulate Cortex*	10/32	-4	48	16	4	8.4	1035
L	Frontal Pole/medial PFC*	10/32	-12	56	8	5	8.4	1143
R	Paracingulate Cortex*	9/32	24	32	24	4	5.8	150
L	PCC/RSC/Precuneus*	31/30/ 7	-12	-56	28	4	10.4	1209
L	PCC/Precuneus*	23/31	-4	-56	20	5	9.9	873
R	Middle Temporal Gyrus	21	52	-8	-20	4	4.2	7
L	Middle Temporal Gyrus	21	-56	-20	-12	4	5.5	89
L	Middle Temporal Gyrus	21	-56	-12	-16	5	5.3	77
R	Supramarginal Gyrus	40	56	-64	24	4	7.6	224
R	Supramarginal Gyrus	40	56	-64	24	5	6.1	130
L	Angular Gyrus	39	-40	-72	36	5	6.7	204
R	TP/Ventrolateral PFC	38/47	32	12	-16	4	3.8	5
R	Cerebellum	-	36	-72	-36	4	5.0	55
R	Cerebellum	-	4	-48	-48	5	6.8	85
R	Cerebellum	-	12	-84	-36	5	4.5	21
L	Cerebellum	-	0	-84	-28	4	5.0	12
ToM > pToM during TR4 and TR5								
L	Ventrolateral PFC	44	-48	16	12	4	-3.7	10
L	Ventrolateral PFC	44/45	-52	16	8	5	-3.3	7
L	Middle Frontal Gyrus	6	-52	0	44	5	-3.9	5
L	Inferior Temporal Gyrus	37	-56	-68	-4	4	-5.5	6
R	Supramarginal Gyrus	40	40	-40	36	4	-3.1	12
L	Lingual Gyrus	17	-12	-92	0	4	-3.6	5
L	Superior Occipital Gyrus	17	-12	-92	4	5	-3.7	10

MNI co-ordinates of the maximally activated voxel within each cluster are reported. pToM = theory of mind condition involving personally known others; ToM = theory of mind condition involving unknown others; Hemis = hemisphere; BA = Brodmann area; Vol. = cluster volume in voxels; R = right; L = left; PCC = posterior cingulate cortex; RSC = retrosplenial cortex; TP = temporal pole; PFC = prefrontal cortex.
*Activation in this region extended bilaterally.

Discussion

In the present study, I tested whether different neural and cognitive mechanisms support mental state inferences of personally known versus unknown others and how these abilities relate to AM. Using ST-PLS, I replicated the finding that AM and ToM recruit a common pattern of activity that includes medial frontal, medial and lateral temporal, and medial parietal regions (Buckner & Carroll, 2007; Hassabis & Maguire, 2007; Rabin et al., 2010; Spreng & Grady, 2010; Spreng et al., 2009; Spreng & Mar, 2012). I also showed that when AM and ToM are directly compared, midline regions predominate during AM and more lateral regions predominate during ToM. Unique to the current study was the finding that the pattern of activity associated with pToM involving familiar others resembled the pattern of activity associated with AM to a greater extent than the pattern associated with ToM involving unfamiliar others, with the greatest degree of overlap within midline regions. This finding suggests that personal experience with the target person in a ToM task influences the functional and neural relationship between AM and ToM. A complementary finding was the observation of striking neural differences between pToM and ToM, suggesting that participants relied on different cognitive mechanisms to carry out these two tasks despite identical task instructions.

Neural Overlap Between AM and pToM Versus ToM

The results of the current study provide direct evidence that shared past experience with the target person in a ToM task modulates the functional relationship between AM and ToM. This was evident in the first latent variable (LV1) of the PLS analysis that included all three experimental conditions. This LV, which accounted for the greatest amount of variance in the analysis, revealed that the pattern of activity supporting pToM shares more in common with AM than with ToM. The greatest degree of neural overlap between AM and pToM was found within

bilateral medial PFC, medial parietal cortex, as well as hippocampus and related MTL structures – regions previously associated with autobiographical recollection (Svoboda, McKinnon, & Levine, 2006), self-referential processing (Amodio & Frith, 2006), and social relevance (Krienen et al., 2010).

The shared set of regions recruited during AM and pToM suggests a strategy of relying on past personal experiences when considering the mental states of personally known others. This idea is in line with Buckner and Carroll's (2007) self-projection hypothesis, which suggests that one draws on past experiences in order to project oneself into another person's mind (for similar ideas see Corcoran, 2000, 2001; Gallagher & Frith, 2003). It is also consistent with other simulation theories, which suggest that individuals rely on their own thoughts and feelings to predict the mental states of close and similar others. For example, using the medial PFC activity as an index, Mitchell and colleagues have shown that perceivers use the self as a proxy only when the target person is deemed similar to the self (Mitchell et al., 2005, 2006). Although participants in the present study did not rate how similar they perceived themselves to the people depicted in the pToM photos, other research indicates that individuals tend to share similar values with family members and close friends (Mashek, Aron, & Boncimino, 2003). However, more recent research has demonstrated that regions within the medial PFC respond more strongly when participants make judgments about friends compared to strangers, regardless of whether the other person is perceived as similar to the self (Krienen et al., 2010). This finding indicates that personal relevance (closeness), and not similarity is likely driving the neural overlap between AM and pToM. Lieberman (2012) suggests that individuals possess idiosyncratic theories about themselves as well as personally known others. Therefore, it is possible that these person-specific theories influenced how participants thought about themselves

in the past during the AM condition and how they thought about personally known others during the pToM condition.

Participants in the present study were instructed not to refer to personal memories when generating pToM (and ToM) events, and only events rated by participants as different from a memory were included in the analysis. Because participants rarely rated pToM (and ToM) events as similar to a memory, I was unable to determine if the neural overlap between AM and pToM was modulated by the extent to which participants relied on specific AMs. Although it is unlikely that the pToM events were replicas of specific past experiences, it remains possible that participants consciously recalled past experiences in response to the pToM photos, yet rated these events as 'dissimilar to a memory' in order to comply with the experimenter's instruction to generate novel events. Given that only the events rated as different from a memory were included in the analysis, a more likely explanation is that previous episodes unintentionally influenced participants' current social processing (Greenberg, Keane, Ryan, & Verfaellie, 2009; Sheldon & Moscovitch, 2010). It has been suggested that the mere perception of a familiar individual is associated with the spontaneous retrieval of personal knowledge about that individual (i.e., personal traits, attitudes, biographical facts and episodic memories; Gobbini & Haxby, 2007). This information may then be used to infer the familiar other's mental state.

A related possibility is that the overlap may result from constructive processes that are at play during both AM and pToM. In AM past episodes are reconstructed, whereas in the pToM condition event details contained within AMs may be flexibly recombined to generate the novel events. This idea is captured by the "constructive-episodic-simulation hypothesis" proposed by Schacter and Addis (2007) to account for the neural overlap between AM and thinking about oneself in the future. The process of recombination is thought to rely on relational processes

mediated by the hippocampus (Davachi, 2004; Eichenbaum, 2001; Ryan, Althoff, Whitlow, & Cohen, 2000), which may be important for generating and/or binding autobiographical details for both past memories and imagined events (Rosenbaum, Gilboa, Levine, Winocur, & Moscovitch, 2009).

It remains the case, however, that all three conditions are supported by a common set of regions, albeit to a lesser degree for ToM involving unfamiliar others. Thus, AM may be called upon to infer others' mental states in general, though it may be less critical and used together with other strategies, such as semantic memory, when unfamiliar others are concerned.

Differences Between pToM Versus ToM

The finding that AM and pToM bear close resemblance in the regions that they recruit, along with the observation of differences between pToM and ToM, suggest that participants relied on different cognitive mechanisms to carry out the two ToM tasks. This finding is all the more remarkable given that the two ToM conditions involved identical task instructions and differed only in terms of familiarity with the target person and, in some cases the setting depicted in the photos. As expected, relative to ToM, pToM engaged midline regions that closely resembled those involved in AM during both the early and late phase of event generation. In contrast, ToM versus pToM recruited a more lateral set of regions known to be involved in semantic memory during the late phase of event generation (Martin & Chao, 2001). The greater involvement of the left ventrolateral PFC during ToM along with lateral temporal activity may reflect participants' reliance on social scripts and general knowledge about the world in order to infer the mental states of unfamiliar others. This may include rules for understanding how the average person is likely to experience and respond to different situations and events (rather than relying on specific AMs or idiosyncratic representations). Greater occipital activity also emerged

during ToM versus pToM (and AM), which may reflect greater reliance on the visual information presented in the photos (e.g., facial expression, the spatial relations between the people in the photo) in order to construct the novel ToM events and to infer the mental states of unfamiliar others. Participants likely employ these types of strategies when carrying out standard laboratory tests of ToM. This idea is supported by the finding that patients with semantic dementia and impaired semantic memory perform poorly on a variety of laboratory tests of ToM (Duval et al., 2012).

Differences Between AM Versus pToM

Despite the clear correspondence between AM and pToM, the second LV (LV2) in the analysis that included all three experimental conditions differentiated a set of regions supporting AM from a separate set of regions supporting pToM. This LV revealed very few neural differences during the early phase of event generation, but as the events continued to unfold over time, more widespread differences emerged. The failure to find robust differences between AM and pToM during the early phase of event generation in LV2, along with the similarities revealed in LV1, suggest that the processes supporting AM and pToM are most similar during the initial construction of events. As mentioned above, it is possible that this shared activity early on represents reliance on past experiences during both AM and pToM. However, in the AM condition the recollection is conscious, whereas in the pToM condition this process is likely automatic given that participants were told to generate novel events without resorting to specific past memories.

During the latter part of event generation, relative to pToM, AM was associated with greater activity within the right posterior cingulate cortex/precuneus (BA 23/31); at a slightly relaxed threshold (BSR > 2.4, $p < .05$), activity within the medial PFC (BA 10) and

paracingulate cortex (BA 32) was also present. This pattern of activity likely reflects self-referential and visuospatial aspects of autobiographical remembering that have been identified in previous studies (Addis, Moscovitch, Crawley, & McAndrews, 2004; Fletcher et al., 1995; Gilboa et al., 2004; Rosenbaum, Ziegler, Winocur, Grady, & Moscovitch, 2004; Summerfield, Hassabis, & Maguire, 2009; Svoboda et al., 2006).

In contrast to AM, the regions engaged to a greater extent during pToM are consistent with those reported in the ToM literature and include the right frontal pole (BA 10), bilateral dorsomedial PFC (BA 9), bilateral ventrolateral PFC, left insula, bilateral lateral temporal regions, left temporal pole (BA 38), and bilateral middle occipital cortex (BA 18/19; Amodio & Frith, 2006; Gallagher & Frith, 2003; Spreng et al., 2009). The involvement of the left ventrolateral PFC and lateral temporal regions suggest greater reliance on general semantic processing during pToM relative to AM (Martin & Chao, 2001). It is likely that imagining a novel event that has never occurred requires increased generative processing relative to retrieving a past event from memory (Addis, Pan, Vu, Laiser, & Schacter, 2009). Furthermore, previous work has identified the anterior temporal cortex as a region important for representing social knowledge (for reviews, see Olson et al., 2007; Simmons & Martin, 2009). The left temporal pole, in particular, has been characterized as a storehouse for personal semantic memories and is thought to be responsible for linking high-level sensory representations, such as familiar faces, with semantic information (Olson et al., 2007).

Some of the differences observed between AM and pToM during the latter part of event generation may relate to differences between remembering actual events and constructing events from imagination. Therefore, the greater midline activity observed during AM versus pToM (at a BSR > 2.4) may reflect differences in the ‘realness’ of events. This interpretation converges with

recent work showing greater medial PFC and posterior cingulate cortex activity during the recollection of personally experienced events relative to events that were previously imagined but not experienced (Summerfield et al., 2009). Based on these findings, it was suggested that midline regions may help to distinguish actual experiences from imagined ones (Hassabis, Kumaran, & Maguire, 2007). A related explanation to account for the differences between AM and pToM is that the conditions vary with respect to personal significance, with AM events most relevant, followed by pToM events. Therefore, it may be the combination of 'realness' and personal significance that explains the greater activity within medial frontal, paracingulate, and medial parietal regions during AM versus pToM. Though conceivable, this was not reflected in hippocampal activity, which would have been expected to differ based on previous work showing that activity in this region is modulated by personal significance (Addis et al., 2004).

Alternatively, the increased midline activity, particularly the precuneus, during AM versus pToM may reflect the greater visual detail with which AM events were recollected. Although vividness was equated across all three conditions (using within-scanner ratings), participants did, in fact, generate significantly more internal details for the AM versus pToM and ToM events during the postscan interview. Therefore, it is possible that participants made their vividness ratings relative to events within a condition rather than across all conditions. If so, the increased number of details generated for the AM events may represent more vividly generated events.

Theoretical Implications

In the context of the current set of fMRI results, the common core network supporting AM and ToM involving personally familiar and unfamiliar people may reflect an interplay between AM and semantic memory. This idea is consistent with the transformation hypothesis,

whereby a dynamic interplay exists between AM for vivid contextual details of a personally experienced event, supported by the hippocampus, and semanticized versions of the original memory, supported by the neocortex (Winocur et al., 2010; see also Moscovitch et al., 2005, 2006; Rosenbaum et al., 2001). Similar to the transformation hypothesis, Spreng and Mar (2012) recently proposed that the shared network supporting AM and ToM reflects a distributed integration zone that provides a means for past personal experience to transform into social conceptual knowledge, knowledge that is then used to guide social processes and behaviour.

Building on these ideas, I suggest that AM and semantic memory work together to support ToM abilities (at least in healthy people). The extent to which each memory system is involved will depend on whose mind one is inferring in addition to the processing demands of the task at hand and the social–perceptual cues that are available. ToM involving unfamiliar others, whether in the laboratory or real world, is likely to rely more heavily on semantic or schematic memory, whereas ToM involving well-known others is more likely to rely on AM. The capacity to readily access semantic and autobiographical information about personally known others likely sets the stage for successful social interactions with people with whom we have close relationships. However, in the face of AM loss, the semantic memory system is likely sufficient for successful performance on standard laboratory measures of ToM (Rosenbaum et al., 2007) and possibly real-world ToM tests involving unfamiliar people, such as the one used here. It remains to be determined whether AM is critical for real-world ToM processes that involve personally familiar others. Taken together, the current results suggest that ToM is not solved by a single strategy but rather a flexible set of mechanisms that call upon autobiographical episodic memory and semantic memory representations to varying extents, depending, in part, on the level of familiarity with the subject of the mental state inference.

Conclusion

In sum, the current study suggests that there are multiple routes to ToM that involve some balance between autobiographical episodic memory and semantic memory among other processes. The particular strategy adopted likely depends on one's relationship with the target person and the type of social knowledge gained through past experiences with that person. This in turn, interacts with one's current goals and the cues or processing resources available to make the inference. These findings suggest that individuals engaging in ToM more readily draw on past personal experiences when reasoning about the mental states of personally familiar others and on semantic memory or script-like social knowledge when inferring the mental states of unfamiliar others, although both types of processes are likely at play in healthy people. ToM tasks that involve personally familiar others may better reflect ToM abilities as they occur in the real world and highlight the need for more ecologically valid ToM paradigms.

CHAPTER 4

Experiment 3: Imagining Other People's Experiences in a Person With Impaired Autobiographical Episodic Memory: The Role of Personal Familiarity

The results of Experiment 2 revealed that healthy individuals more readily draw on past personal experiences mediated by the hippocampus to infer the experiences of personally known others (i.e., family members and friends) compared to unknown others. This suggests that the hippocampus is preferentially involved in imagining personally known others' experiences, but leaves unanswered whether it is needed to do so. To address this question, I assessed whether H.C., a person with hippocampal amnesia of developmental origin and impaired AM, is able to imagine events experienced by personally known others.

In the current study, I employed the same family photos test used in Experiment 2, which required participants to describe the experiences of other people in response to photos of personally known others (i.e., relatives and close friends; pToM condition) and unknown others (ToM condition) as well as recollect past experiences in response to personal photos (AM condition). This naturalistic task was selected because it is less constrained than most standard tests of ToM and therefore better captures ToM as it occurs in everyday life. Findings of impaired pToM that parallel H.C.'s AM deficit would suggest that pToM relies on AM or that a common process mediates both abilities. Alternatively, it may be the case that intact aspects of H.C.'s semantic memory are sufficient to support mental state inferences involving pToM and ToM, and therefore H.C. would show intact performance on both tasks, similar to her performance on standard ToM tests (see Experiment 1).

Method

Participants

H.C.'s performance was compared with the same sample used in Experiment 2. That is, 18 right-handed, healthy women with normal or corrected-to- normal vision and no reported history of neurological or psychiatric illness participated in the study (mean age =19.3 years, S*D* = 1.2; mean education = 13.3 years, *SD* =1.1). All participants gave informed written consent in accordance with the ethics committees at York University and Baycrest. Participants received monetary compensation for their time.

Stimuli

I employed the same naturalistic test of ToM used in Experiment 2 (see Experiment 2 for a full description of the task). Following the scan, participants took part in an interview in which they viewed the same photos that had been presented in the scanner. Participants were asked to think back to the events that they had generated in the scanner and to rate each event on the same three scales that had been presented in the scanner. The photos with the highest vividness ratings (approximately two-thirds of all photos) were selected for a semistructured interview in which participants described the events as they had been imagined/recollected in the scanner. It should be noted that during Session 2 H.C. was interviewed on all of the photos presented during the scan as well as eight additional AM events, which had not been presented in the scanner, in order to increase power. There was no time limit for participants to describe the events, and participants continued with their descriptions until they came to a natural ending point. Participants were then provided with a single, standardized probe to elicit additional details (e.g., "Can you tell me anything else?"). The events were recorded and transcribed for later scoring. Control participants were tested on the family photos paradigm once, whereas H.C was tested on

the paradigm on two separate occasions for reliability purposes. The two testing sessions took place three years apart. The AM events that were included during H.C.'s first testing session were excluded because it was subsequently learned that she frequently views these photos.

Adapted Autobiographical Interview Scoring Procedure

Narratives were scored using an adapted Autobiographical Interview scoring procedure developed by Levine and colleagues (2002; see Appendix A for example scoring). The Autobiographical Interview was developed to quantify episodic and semantic contributions to AMs, but has been successfully employed in a number of studies examining non-mnemonic abilities, such as future thinking (Addis et al., 2008; Kwan et al., 2010) and describing pictures of scenes (Race et al., 2011). The pToM, ToM, and AM narratives were first segmented into distinct details, which were classified as internal (e.g., event-specific, temporal, perceptual, spatial, and thought/emotion details) or external (i.e., semantic facts that were irrelevant to the central event, repetitions, and metacognitive statements). Given the use of visually rich photos as cues, it was important to ensure that participants' performance was not inflated due to merely describing the details depicted in the photos (i.e., describing exactly what participants see in the photo). Therefore, internal details were further classified as either descriptive (i.e., details that describe the visual content of the photo) or elaborative (i.e., details that go beyond what is literally depicted in the photo). The criteria developed to classify details as either descriptive or elaborative are presented in Table 4.1.

Table 4.1

Classification of Descriptive Versus Elaborative Details for the Autobiographical Interview

Type of detail	Descriptive details	Elaborative details
Event	Any detail referring to an action that is depicted in the photo (e.g., sitting, walking, standing, posing for the photo)	Any detail describing an action that is not obvious from the photo
Character	Any detail explaining who the people are in the photo (only for the pToM and AM conditions)	Any detail referring to the relationships between people depicted in the photos (only for the ToM condition)
Temporal	Season (depending on the information presented in the photo)	Details referring to a specific time period (e.g., year, month, date, day of week)
Perceptual	Perceptual details that are depicted in the photo (e.g., big crowd of people, candles everywhere) Describing or naming an object, monument or statue that is depicted in the photo (e.g., statue of liberty)	Perceptual details that are not visible in the photo
Emotion/Thought	Any detail describing a facial expression (e.g., smiling, frowning)	Any detail describing an emotion or mental state (e.g., happy, sad, tired)
Spatial/Place	Any detail describing a location (e.g., country, city, street, location within a room) that can be inferred from information presented in the photo (e.g., sign)	Any detail describing a location (e.g., country, city, street, location within a room) that is not apparent from information depicted in the photo

Analyses of the narratives were conducted by a trained rater who achieved high interrater reliability on the Autobiographical Interview (intraclass correlation coefficient, two-way random effects model; Shrout & Fleiss, 1979) using a standard set of previously scored memories (Levine et al., 2002). Interrater reliability was also calculated for the elaborative and descriptive details based on criteria developed by JSR (see Table 4.1). Intraclass correlation analyses indicated high agreement among scorers for pToM (Cronbach's $\alpha = .994$), ToM (Cronbach's $\alpha = .992$), and AM events (Cronbach's $\alpha = .994$).

Data were analyzed using a modified *t*-test procedure, which compares test scores of a single patient to that of a small control sample (Crawford & Howell, 1998). Two-tailed *t*-tests were used to compare H.C.'s performance with that of controls on the pToM and ToM conditions, whereas a one-tailed *t*-test was used for the AM condition given a priori hypotheses regarding H.C.'s AM performance. Like other case studies reported in the literature, values associated with $p < .05$ were considered to be significant (Bowles et al., 2007; Hassabis, Kumaran, Vann, & Maguire, 2007; Hurley et al., 2011; Levine, Svoboda, Turner, Mandic, & Mackey, 2009; Maguire et al., 2010; Rosenbaum et al., 2008, 2009), and values associated with $p < .09$ were considered to be trends (Rosenbaum et al, 2009). Given the low statistical power associated with case studies, this level of correction provides a desirable balance between type I and type II error rates. Effect sizes (z_{cc}) and 95% confidence intervals on the effect sizes are reported (Crawford, Garthwaite, & Porter, 2010).

Results

As mentioned above, H.C. was tested on two separate occasions. For completeness, I reported the data separately for the two testing sessions. Each control participant contributed an average of 8.9 pToM events (*SD* = 0.72), 9.1 ToM events (*SD* = 0.9), and 9.3 AM events (*SD* =

0.49) to the analyses. In Session 1, H.C. contributed 7 pToM events and 9 ToM events to the analyses. In Session 2, H.C. contributed 15 pToM events, 12 ToM events, and 18 AM events to the analyses.

Phenomenology of the pToM, ToM, and AM Events

Participants' postscan ratings were entered into the analyses (as opposed to the within-scanner ratings) as these were believed to better correspond with the events described by participants during the postscan interview. Table 4.2 presents participants' ratings of the pToM, ToM, and AM events. In terms of vividness, H.C. rated the pToM events in Session 1 as less vivid than that of controls, $t(17) = -2.50$, $p = .023$, $z_{CC} = -2.57$ [-3.54, -1.59]; there was no difference for the pToM events in Session 2, $t(17) = -0.81$, $p = .43$, $z_{CC} = -0.83$[-1.36, -0.29]. With respect to the ToM events, vividness ratings did not differ between H.C. and controls for Session 1, $t(17) = -1.10$, $p = .29$, $z_{CC} = -1.13$ [-1.71, -0.52] or for Session 2, $t(17) = -1.52$, $p = .15$, $z_{CC} = -1.56$ [-2.25, -0.86]. For the AM events, H.C.'s ratings were significantly less vivid than that of controls, $t(17) = -3.09$, $p = .003$, $z_{CC} = -3.17$ [-4.32, -2.01]. In terms of the ratings assessing likeness to an actual memory, no significant differences emerged between H.C. and controls for the pToM and ToM events in Sessions 1 or 2 [pToM Session 1 and Session 2, $t(17) = -1.35$, $p = .19$, $z_{CC} = -1.39$ [-2.03, -0.73], and $t(17) = -0.34$, $p = .74$, $z_{CC} = -0.35$ [-0.82, 0.13], respectively, and ToM Session 1 and Session 2, $t(17) = -0.52$, $p = .61$, $z_{CC} = -0.53$ [-1.02, -0.03], and $t(17) = -0.52$, $p = .61$, $z_{CC} = -0.53$ [-1.01, -0.03]. Finally, as expected, H.C.'s ratings relating to the recollection of AM events were significantly lower than that of controls, $t(17) = -9.25$, $p < .00001$, $z_{CC} = -9.50$ [-12.69, -6.30].

Table 4.2

Phenomenological Qualities of the Generated pToM, ToM, and AM Events

	pToM	ToM	AM
Vividness (/4)			
H.C. session 1	2.14*	2.67	--
H.C. session 2	2.87	2.50	2.83*
Controls	3.22 (0.42)	3.11 (0.39)	3.56 (0.23)
Remember/Know (/3)			
H.C. session 1	--	--	--
H.C. session 2	--	--	2.61*
Controls	--	--	2.99 (0.04)
Similar to a Memory (/4)			
H.C. session 1	2.71	3.3	--
H.C. session 2	3.27	3.3	--
Controls	3.46 (0.54)	3.56 (0.49)	--

The number in parentheses in the left-hand column indicates the maximum score for each rating scale. Standard deviations are given in parentheses; pToM, personal theory of mind; ToM, theory of mind; AM, autobiographical memory.
*$p < .05$

Adapted Autobiographical Interview Results

Given the use of visually rich photos as cues, I was most interested in the elaborative details that participants generated. I analyzed the data in two ways. First, I compared the average number of elaborative details H.C. and controls produced in response to each pToM, ToM, and AM event. These absolute numbers, however, are confounded by participants' total verbal output. In order to overcome this issue, I also calculated the proportion of elaborative-to-total internal details, which provides an unbiased quantification of details. It also serves as an index of the weight given to descriptive versus elaborative details.

The average number of elaborative details produced by participants in response to each pToM, ToM, and AM event is shown in Figure 4.1. Due to the small number of elaborative

details produced for each narrative, I was unable to make meaningful comparisons when the details were further divided into the internal detail categories (i.e., event, place, time, perceptual, thought/emotion). In response to the pToM events, H.C. produced significantly fewer elaborative details than controls during Session 1, $t(17) = -3.10$, $p = .007$, $z_{CC} = -3.18$ [-4.33, -2.02], and there was a trend towards impaired performance during Session 2, $t(17) = -1.84$, $p = .083$, $z_{CC} = -1.89$ [-2.6, -1.10]. In terms of the ToM events, no significant differences emerged for Session 1, $t(17) = -1.60$, $p = .13$, $z_{CC} = -1.64$ [-2.35, -0.92], or Session 2, $t(17) = -0.97$, $p = .35$, $z_{CC} = -0.99$ [-1.55, -0.42]. With respect to the AM events, as expected, H.C. produced significantly fewer elaborative details than did controls, $t(17) = -1.76$, $p = .049$, $z_{CC} = -1.80$ [-2.55, -1.04].

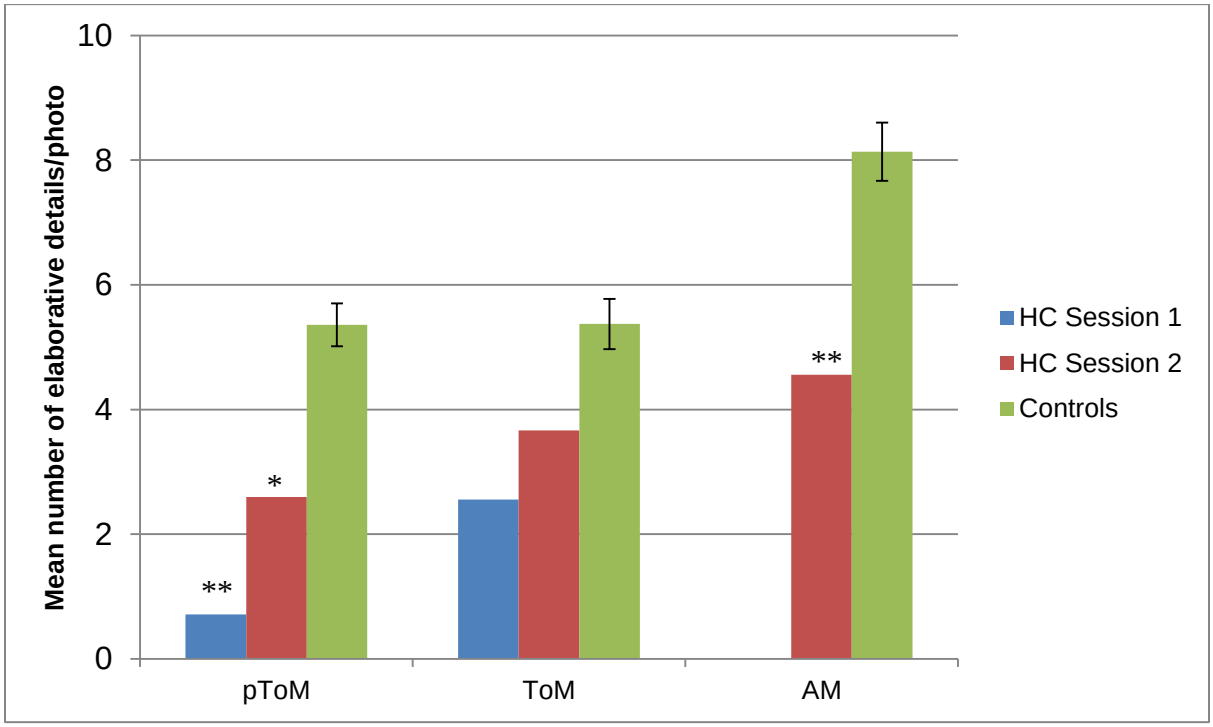


Figure 4.1. The Mean Number of Elaborative Details Generated in Response to Each pToM, ToM, and AM Event. Error bars indicate standard error of the mean.
*$p < .08$; **$p < .05$.

The proportion of elaborative-to-total-internal details produced by participants in response to each pToM, ToM, and AM event is presented in Figure 4.2. Analyses revealed that H.C. produced a lower proportion of elaborative details (and therefore more descriptive details) than controls in response to the pToM events during both Session 1, $t(17) = -7.08$, $p < .00001$, $z_{CC} = -7.27$ [-9.73, -4.80], and Session 2, $t(17) = -5.03$, $p = .0001$, $z_{CC} = -5.18$ [-6.95, -3.39]. In contrast, H.C. and controls produced an equivalent proportion of elaborative details in response to the ToM events during both Session 1, $t(17) = 0.78$, $p = .45$, $z_{CC} = 0.80$ [0.26, 1.33] and Session 2, $t(17) = -0.31$, $p = .76$, $z_{CC} = -0.32$ [-0.79, 0.16] . As predicted, H.C. generated a lower proportion of elaborative details relative to controls in response to the AM events, $t(17) = -2.66$, $p = .008$, $z_{CC} = -2.70$ [-3.70, -1.70].

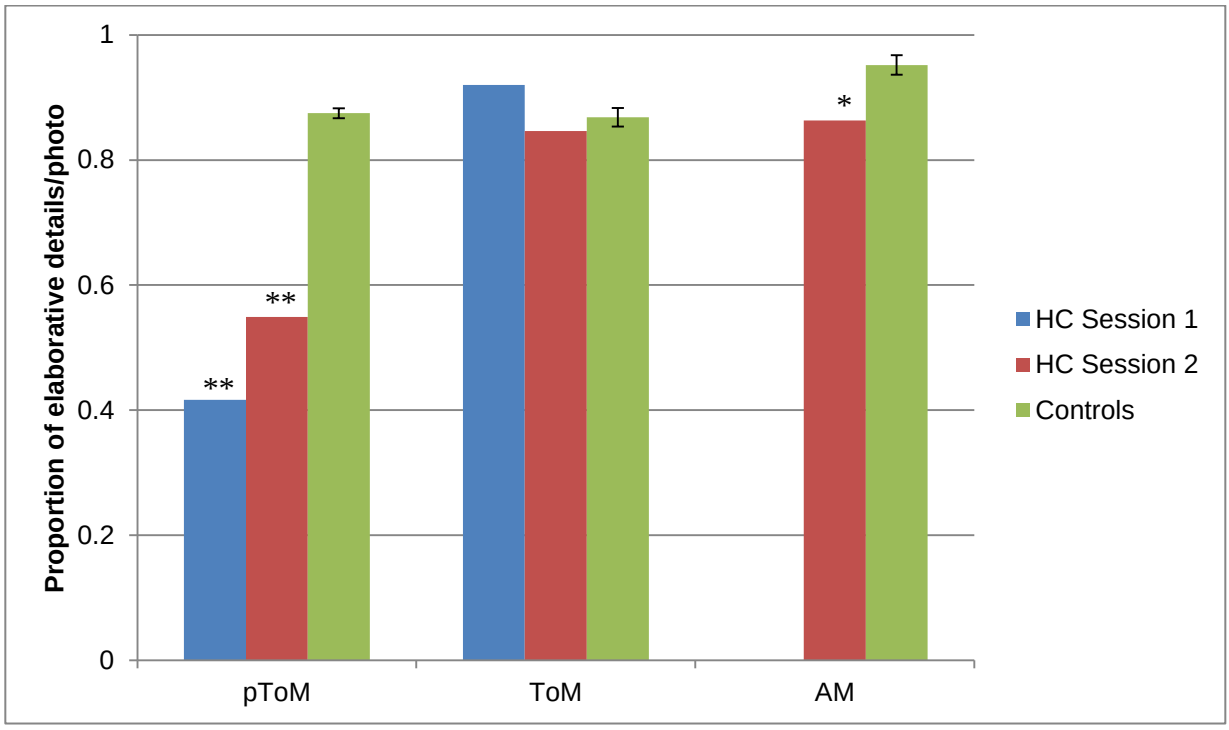


Figure 4.2. The Mean Proportion of Elaborative-to-Total Internal Details Generated in Response to Each pToM, ToM, and AM Event. Error bars indicate standard error of the mean.
*$p < .01$; **$p < .0001$.

pToM involving familiar others

H.C.: That is my cousin and my uncle, so her dad, and I would assume that they went on a big marathon and they had just finished, and that's why my uncle looks really tired and he looks really happy.

Representative Control: Aunty Debra just drove Michelle to school in Kingston, and she's really sad to see Michelle go because Michelle's growing up now, and she said 'You're so grown up'. And Michelle's like, 'Don't worry, I'll be fine' and Auntie Debra says, 'I know, but this is a huge change for me' and all that stuff. And then she says bye and then when Michelle turns around, she's secretly happy that she's leaving her mother.

ToM involving unfamiliar others

H.C.: I imagined they were in Australia because I think that's where koala bears are from and she was trying to convince her mother who was the one was taking the photo. And I was imagining she was trying to convince her mother to let her take the koala bear home. It looks like she really wants it.

Representative Control: This dad and his two sons went apple picking and he's like 'Okay follow me guys'. Then they go on a path less traveled. The dad ends up losing his bearings and getting lost a little bit, and his sons realize that they're lost and they're like 'Oh no, we're lost'. The dad finds his way back and the kids keep on asking 'Dad are you lost?' and he's like 'Of course not'. And then the dad finally finds his way back and he's like 'phew'.

AM

H.C.: That's in Florida. That was at my Aunt Jill's… my Aunt Jill and Uncle Bill had a place in Florida so that was in the pool at their like resort condo sort of place, and that was the second pool I went to because that one was warmer because it was a little shallower.

Control: That is my grandparents' wedding anniversary. I was thinking about the fact that it was also my 18th birthday. I wasn't particularly pleased to be there, but my Aunt turned up. I hadn't realized that she was going to be coming all the way from Germany. So at that point when the photo was taken, she had just come in and I was really relieved. She had turned up, and I was glad that I came. I also thought about saying a ridiculously long speech about my grandparents that I had to have memorized. And yeah, that was their wedding anniversary.

Figure 4.3. Representative Samples of the pToM, ToM, and AM Narratives Provided by H.C. and a Control Participant.

Discussion

H.C., a developmental amnesic person with bilateral hippocampal damage, was impaired at imagining the experiences of personally known others, which resembles her compromised ability to recall past experiences via AM. These impairments stand in contrast to her preserved ability to imagine the experiences of unknown others. This pattern of results held whether we analyzed the average number of elaborative details (i.e., details that go beyond what is visually depicted in the photo) or the proportion of elaborative-to-total-internal details in order to control for verbal output. These results bolster the finding that different neural and cognitive mechanisms support thinking about personally known versus unknown others and that the former may depend on processes mediated by the hippocampus and AM.

The idea that individuals rely on past personal experiences to infer and simulate another person's mental state has been suggested by philosophers and cognitive neuroscientists alike (Buckner & Carroll, 2007; Corcoran, 2000, 2001; Gallagher & Frith, 2003; Spreng & Mar, 2012). However, the current findings indicate that reliance on past personal experiences may be pivotal only when imagining the experiences and mental states of personally known others. Indeed, knowing an individual for a long period of time and observing that person's behaviour in different situations provides a rich source of information from which one can draw when imagining that person's mental states in various situations. Consistent with this interpretation, Krienen and colleagues (2010) showed that participants reported that they relied on a specific memory or anecdote significantly more often when making judgments relating to friends relative to strangers. In another study, Ciaramelli and colleagues (2013) found that participants' level of empathy for a familiar character was modulated by the retrieval of previous episodes involving that character. Additional support for this idea is provided by the neuroimaging results in

Experiment 2, which revealed that the pattern of neural activity supporting pToM shares more in common with AM than with ToM. Notably, the greatest degree of neural overlap between pToM and AM was observed within midline regions, particularly within the hippocampus and related MTL structures.

Reliance on past personal experiences to infer personally familiar others' mental states may occur with or without one's intention or awareness. Indeed, there is accumulating evidence that AM supported by the hippocampus can rapidly and automatically influence one's performance on non-mnemonic tasks (Greenberg et al., 2009; Sheldon & Moscovitch, 2010; Westmacott, Black, Freedman, & Moscovitch, 2004; Westmacott & Moscovitch, 2003). Gobbini and Haxby (2007) suggest that the mere perception of a familiar individual is associated with the spontaneous retrieval of personal knowledge about that individual (i.e., personal traits, attitudes, biographical facts, and AMs), which may then help to better understand and predict what that person is thinking and/or feeling. These automatic processes may have been at play in the current study given that participants were instructed not to refer to past episodes when generating the pToM and ToM events. It is possible that participants engaged in inhibitory processes to help overcome the prepotent tendency to rely on past memories. Alternatively, other memory regulation processes such as thought substitution (Benoit & Anderson, 2012) may have been employed.

Another possible explanation for H.C.'s corresponding impairment in both AM and pToM may relate to a deficit in (re)constructing specific episodes. Accumulating evidence from neuroimaging studies suggests that imagining specific versus general past and future events elicits greater activity within the hippocampus (Addis, Cheng, Roberts, & Schacter, 2011; Henessy Ford, Addis, & Giovanello, 2011; Holland, Addis, & Kensinger, 2011), likely due to the

greater relational processing that is required for the former (Addis et al., 2011). Several theories propose that individuals are more likely to imagine close others with greater specificity relative to unknown others, which are typically represented in more generic and abstract terms (Lieberman, 2012; Liviatan, Trope, & Liberman, 2008). This may be because individuals possess idiosyncratic theories about close others' personalities that enable one to richly imagine how well-known others would respond in various scenarios and situations (Lieberman, 2012). Therefore H.C.'s difficulty in generating specific details may account for her poor performance on the AM and pToM conditions.

It may be the case that for the pToM events H.C. attempted to rely on a strategy that is optimal for people who are able to conjure up contextual and specific details rather than relying on a strategy that would be advantageous for her. Like controls, H.C. may have been engaging in inhibitory processes of past events when generating the pToM and ToM events. However, because her autobiographical recollection is impaired, she may have generalized this instruction to personal semantic information, which would have likely helped her to generate additional details for the pToM events. Perhaps, if she had been probed in a manner that enabled her to draw more effectively on her intact personal or social semantic memory, she may have performed better on the pToM task. Indeed, different methods of cuing can differentially affect task performance. H.C., for instance, was impaired at imagining herself in future episodes when provided with a specific cue word (e.g., "coffee"; Kwan et al., 2010) but showed intact performance when a more general and nonspecific cue was provided (e.g., "Imagine something you will be doing this weekend"; Hurley et al., 2011; for similar findings in developmental amnesia see Cooper et al., 2011).

The corresponding deficit that emerged during AM and pToM is unlikely to be due to a deficit in narrative construction, given that H.C. had no difficulty constructing narratives in response to the ToM photos. This pattern of results is consistent with those from a recent study showing that the ability to generate a detailed narrative is preserved in adult-onset amnesia (Race et al., 2011; Race, Keane, & Verfaellie, 2013; cf. Rosenbaum et al., 2009). Although the patients in the study by Race and colleagues (2011) produced impoverished descriptions of past and future events, they showed intact performance when asked to tell a story in response to pictures depicting fictional characters. It is important to note that while the participants were instructed to generate a story rather than to report what was literally depicted in the picture, to our knowledge, the authors did not examine whether participants adhered to this instruction. In the current study, when examining the extent to which participants relied on the visual content of the photos to generate details, approximately half of the details H.C. produced for the pToM events consisted of descriptive details (vs. 12.5% for controls). The current findings highlight the importance of examining descriptive versus elaborative details when rich visual cues are used.

H.C.'s impairment in AM and pToM contrasts with her preserved ability to imagine the experiences of unknown others during ToM. The latter finding is consistent with her intact performance on a wide range of standard ToM tests that employ strangers or fictional characters as targets (See Experiment 1 and Rosenbaum et al., 2007). Imagining the experiences of unfamiliar others may be achieved by relying on social semantic memory, which remains relatively intact in H.C. This might include reliance on generic representations about how the average person is expected to think and feel in a given situation (Lieberman, 2012). Generic representations are likely based on routines or schemas that are already bound together and therefore require minimal relational processing. The fMRI findings from Experiment 2 support

this interpretation. Using the same family photos paradigm employed here, I showed that relative to pToM, ToM involving unfamiliar others elicited greater activity in lateral regions known to be associated with accessing semantic knowledge (Martin & Chao, 2001). Taken together, these data further corroborate the notion that AM may be needed for social cognition, but that its role may be specific to imagining the experiences of personally known others, and may not be necessary for imagining the experiences of unknown others.

The use of an open-ended ToM task allowed us to gain insight into possible compensatory strategies that H.C. employed when taking the perspective of another person. H.C. generated a significantly greater proportion of descriptive details in response to the pToM photos than did controls, suggesting that she relied more heavily on the visual information depicted in the photos to imagine the experiences of personally known others. This may have included relying on the familiar others' facial expressions, body language, and/or the relative spatial relations between people. This strategy may serve her well in social settings when external cues are readily available but may fail when external cues are absent or when situations are complex and require the integration of information from the past and present. For example, H.C. may have difficulty considering the mental states of people who are not currently present or predicting a person's reaction to a situation that has not yet occurred.

H.C.'s performance on the pToM condition was not at floor which indicates that her ability to imagine the experiences of personally familiar others is impaired but not entirely absent. In fact, approximately 50% of the details she generated in response to the pToM events were elaborative details (i.e., details that go beyond what is literally depicted in the photo). However, upon closer examination, even the qualitative nature of the elaborative details she generated differed from that of controls. Specifically, H.C.'s responses tended to reflect more

basic emotional states that could be inferred from the visual features of the photo, such as "they're both really excited" or "she looks really happy." In contrast, control participants typically provided more complex mental state inferences such as "they were probably afraid but they are trying to look cool" and "her mother was pleased that her daughter was having so much fun" (see Figure 4.3 for narrative samples).

H.C. generated a greater number of elaborative details in response to the pToM and ToM events during Session 2 relative to Session 1. It is important to note, however, that the overall pattern remained consistent over the two testing sessions in that H.C. produced fewer elaborative details for the pToM versus ToM events within each session. It is possible that the difference across testing sessions reflects a practice effect resulting from experience with narrative generation. Although our two testing sessions took place three years apart, H.C. participated in several other studies during that time that required her to generate detailed narratives (Hurley et al., 2011; Kwan et al., 2010). In fact, within these other studies, H.C. showed improved performance on tests of future imagining over testing sessions (Hurley et al., 2011; Kwan et al. 2010). A related explanation for H.C.'s higher scores during Session 2 may be due to the fact that she learned to use a more effective strategy that enabled her to generate a greater number of details.

It should be noted that I did not confirm the accuracy of participants' reported memories. However, anecdotal evidence provided by H.C.'s family suggests that she tends to fill in memory gaps. Therefore, H.C.'s AM scores are likely an overestimate of her true AM capabilities. Furthermore, the Autobiographical Interview scoring procedure (Levine et al., 2002) states that any detail that could reasonably reflect episodic re-experiencing should be classified as internal. Levine and colleagues (2009) acknowledge that although this practice helps avoid subjective

judgments in scoring, it results in "episodic-like" details being classified as internal when episodic re-experiencing does not occur (Brewer, 1988). The authors recognize that this may occur in patients with impaired AM, who recall 'episodic-like' details that may be part of their personal semantic memory, and may also be the case with H.C.

In the current study, I attempted to control for vividness by including only the pToM, ToM, and AM events with the highest vividness ratings in the analyses. Nevertheless, the analyses revealed that H.C. rated the pToM events in Session 1 and the AM events in Session 2 as less vivid than controls. Several other factors, such as personal significance, may have differed between H.C. and controls. It should be noted, however, that several researchers have argued that individuals with developmental amnesia likely do not know what it is like to truly remember or imagine an event in great detail. As a result, developmental amnesic individuals likely assign these types of ratings in a qualitatively different way compared to healthy individuals (Cooper et al., 2011; Mullally, Vargha-Khadem, & Maguire, 2014).

In conclusion, using an ecologically valid and naturalistic test of ToM, I formally show that AM supported by the hippocampus may be pivotal for imagining the experiences of personally familiar, but not unfamiliar others. The current findings complement the fMRI data reported in Experiment 2 and suggest that individuals are more likely to rely on AM when the target is personally familiar and on general social semantic memory when the target person is unknown. However, both types of memory are likely at play when healthy individuals engage in ToM. Continued research with H.C. and other amnesic individuals, particularly those that acquire damage later in life, is needed to better understand the role that AM plays in this and other aspects of social cognition.

CHAPTER 5

Experiment 4: Activation of Hippocampal Tissue in Developmental Amnesia During Remembering and Imagining

As noted previously, a recent topic of interest is whether the hippocampus, known for its role in AM, is also critical for imagining novel events (for reviews on this topic see Schacter, 2012; Schacter et al., 2012). Evidence supporting this idea comes from a variety of empirical approaches. For instance, neuroimaging studies show that both remembering and imagining rely on an overlapping set of brain regions that includes the hippocampus (Addis et al., 2007; Rabin et al., 2010; Spreng & Grady, 2010; Spreng et al., 2009). Similarly, neuropsychological studies demonstrate that amnesic patients with damage to the hippocampus show a parallel deficit in remembering the past and imagining novel events (Hassabis, Kumaran, Vann, et al., 2007; Klein et al., 2002; Kwan et al., 2010; Race et al., 2011; Tulving, 1985). For example, Hassabis and colleagues (2007) found that four out of five amnesic individuals with bilateral hippocampal damage were significantly impaired at recalling past episodes and imagining new experiences. Specifically, the patients' descriptions of past and novel events lacked spatial coherence, contained less content, and were more fragmented relative to control participants' descriptions.

Although previous work has shown that hippocampal amnesic patients are impaired at imagining episodes, there are some patients who retain these abilities despite hippocampal damage and impaired remembering. For example, in the study by Hassabis and colleagues (2007) reported above, one of the patients (P01) could construct spatially coherent scenes and events. Similar findings of intact imagining have also been reported in a group of amnesic patients with bilateral hippocampal damage but spared remote memory (Squire, Horst, Mcduff,

Frascino, & Hopkins, 2010), and several developmental amnesic individuals, including the well-known case Jon (Cooper et al., 2010; Maguire, Vargha-Khadem, & Hassabis, 2010).

A question that has recently received a great deal of attention is how these seemingly inconsistent patient findings can be resolved (Mullally, Hassabis, & Maguire, 2012; Mullally et al., 2014; Schacter et al., 2012). Two possible explanations have been put forth. One possibility is that intact imagining in these amnesic patients may be due to reliance on compensatory strategies that are supported by extrahippocampal regions. This idea has been proposed in several studies (Cooper et al., 2011; Maguire et al., 2010); however, the most direct evidence for this idea comes from a recent fMRI study with the developmental case, Jon (Mullally et al., 2014). In that study, Jon was scanned with fMRI as he constructed and imagined various scenes (e.g., standing on a crowded platform of a train station). The authors found that Jon activated many of the regions known to be associated with scene construction, such as the ventromedial PFC, posterior cingulate cortex, retrosplenial cortex, and posterior parietal regions. Critically, however, Jon did not activate his remaining hippocampal tissue. Based on these findings, the authors suggested that in order to imagine scenes Jon is likely relying on his preserved semantic memory and intact reasoning abilities.

Another possible explanation for preserved imagining abilities in some amnesic individuals is that there may be residual hippocampal tissue that is functional and sufficient to support imagining but not remembering. Evidence in favour of this hypothesis comes from the adult-onset amnesic patient, P01, who retained the ability to construct novel scenes despite suffering from a dense amnesia and 50% hippocampal volume loss bilaterally. P01's intact scene construction was accompanied by activation in his remaining right hippocampal tissue (Mullally et al., 2012). Additional evidence supporting this idea is provided by Jon who showed bilateral

hippocampal activation during the retrieval of a few detailed memories (Maguire et al., 2001). In addition to activating hippocampal regions, Jon showed a different pattern of functional connectivity compared with controls. Specifically, Jon failed to exhibit connectivity between the parahippocampal cortex and the hippocampus, but elicited greater connectivity between the retrosplenial cortex and hippocampus and between the retrosplenial cortex and medial frontal regions. These findings suggest that intact imagining abilities and even isolated instances of remembering in hippocampal amnesia may be attributed to functional remnant hippocampal tissue and possibly altered functional connectivity.

To test between these possibilities, what is needed is a paradigm with closely matched conditions in which both intact and impaired imagining can be demonstrated in an amnesic person. The study described in Experiment 3 presents such an instance. In the present study, fMRI was used to examine the brain activation patterns and functional connectivity of H.C. during intact performance on the ToM condition and impaired performance on the AM and pToM conditions.

If H.C. shows selective hippocampal activation during ToM, but not during AM and pToM, it would indicate that the hippocampus is functional and sufficient to support ToM. Alternatively, if H.C. does not activate the hippocampus across any of the three conditions, it would suggest that extrahippocampal regions are sufficient for supporting ToM, but not AM and pToM. A final possibility is that H.C. would demonstrate hippocampal activation across all three conditions despite dissociations in behavioural performance, which would indicate that her hippocampal activation is nonspecific and likely does not represent functionally beneficial activity. In addition, it is well established that brain regions do not operate in isolation, but rather

as coherent networks. Therefore, I also examined whether different patterns of functional connectivity support H.C.'s intact versus impaired performance.

Method

Participants

A detailed description of H.C. is provided earlier in this dissertation (see Experiment 3) and elsewhere (Kwan et al., 2010; Olsen et al., 2013; Rosenbaum et al., 2011). H.C.'s performance was compared with that of the same sample used in Experiment 3 (i.e., 18-demographically matched women). As mentioned previously, all participants gave informed written consent in accordance with the ethics committees at York University and Baycrest. Participants received monetary compensation for their time.

Task

In the current experiment, I employed the same family photos test used in Experiment 2 and therefore the task is only briefly described here (see Experiment 2 for a full description of the task). Participants were scanned with fMRI as they recollected past experiences in response to personal photos (AM condition) and imagined others' experiences in response to photos of personally known others (pToM condition) and unknown others (ToM condition). All photos were presented for 20 seconds. Two control conditions were included in this study. One control condition consisted of luminance judgments made in response to scrambled photos, and the second consisted of an odd–even number judgment task. In the current study, only the latter control condition was used for the analyses, as this task does not elicit hippocampal activity (Stark & Squire, 2001).

Following the presentation of each photo, participants rated the event they recollected/imagined on a number of dimensions known to influence neural activity. Three rating

scales were presented after each photo. For the first rating scale, AM events were rated on the extent to which events were recollected or familiar (Gardiner et al., 1998; Tulving, 1985), whereas imagined pToM and ToM events were rated for likeness to an actual memory. The other two rating scales were the same for all conditions. One assessed the amount of detail retrieved or imagined for each event and the other assessed the spatial coherence of each event (Hassabis, Kumaran, & Maguire, 2007; Hassabis, Kumaran, Vann, et al., 2007). The responses from the spatial coherence scale are not reported in the current study, as participants had difficulty making these judgments.

Postscan Interview

Immediately following the scan, participants took part in an interview in which they viewed the same photos that had been presented in the scanner. Participants were asked to think back to the events they had generated in the scanner and to rate each event on the same three scales that had been presented in the scanner. The photos with the highest vividness ratings (approximately two-thirds of all photos) were selected for a semistructured interview in which participants described the events as they had been recollected or imagined in the scanner. The events were recorded and then transcribed for scoring. Narratives were scored using an adapted Autobiographical Interview scoring procedure (Levine et al., 2002). Given the use of visually rich photos as cues, we wanted to ensure that participants' performance was not inflated due to merely describing the details depicted in the photos. Therefore, internal details were further classified as either descriptive (i.e., details that describe the visual content of the photo) or elaborative (i.e., details that go beyond what is literally depicted in the photo). The criteria developed to classify details as either descriptive or elaborative are presented in Table 4.1.

Control participants were tested on the family photos paradigm once, whereas H.C was tested on the paradigm on two separate occasions for reliability purposes. The two testing sessions took place three years apart. The AM events that were included during H.C.'s first testing session were excluded because it was subsequently learned that she frequently views and rehearses the events depicted in these photos.

The results from the postscan interview are reported in Experiment 3.

Data Acquisition and Preprocessing

Brain imaging data were acquired with a Siemens Trio 3T magnet with a 12-channel head coil. Anatomical scans were acquired using a T1-weighted volumetric MRI (TR=2000 ms, TE=2.63 ms, 160 oblique axial slices, 1.0mm thick, FOV=256 mm). Functional scans were acquired with a whole-head T2*-weighted EPI pulse sequence (TR=2000 ms, TE=30 ms, flip angle=70°, FOV=200 mm, 64×64 acquisition matrix), consisting of 30 contiguous, 5-mm-thick axial slices. Physiological data (heart and respiration rate) were acquired during the scanning session. Stimuli were presented visually through a mirror mounted on a coil that reflected images from a projector located at the bottom of the scanner. Images were reconstructed and preprocessed with AFNI (Cox, 1996). The initial 10 time points of each run, in which transient signal changes occur as brain magnetization reaches a steady state, were excluded. The data were first corrected for respiration and heart rate. Next, slice-timing was corrected to the first slice. Motion correction was then performed by co-registering volumes to a reference EPI volume. The next several steps differed for the percent signal change analyses and the functional connectivity analyses.

For the percent signal change analysis, volumes were normalized by the mean signal intensity in each voxel to reflect percent signal change. Time series were detrended to correct for

possible constant baseline drifts using a cubic polynomial. Events were modeled with a gamma hemodynamic response function that was applied when each photo appeared on the screen. Maps of brain activity were produced by fitting a general linear model to the measured fMRI time series at each voxel using the AFNI program 3dDeconvolve. Prior to group analyses, the activation maps for each participant were transformed into standardized spaces (Talairach & Tournoux, 1988), resampled at 2 mm × 2 mm × 2 mm, and spatially smoothed with an 8-mm FWHM Gaussian kernel.

With respect to the functional connectivity analyses, following coregistration, the data were spatially smoothed with an 8-mm FWHM Gaussian kernel, transformed into standardized space (Talairach & Tournoux, 1988), and resampled at 2 mm × 2 mm × 2 mm. Time series were detrended to correct for possible constant baseline drifts using a cubic polynomial.

Data Analysis

Given that H.C. frequently forgot to make a button press demarcating the end of the construction phase and the beginning of the elaboration phase, events were collapsed across all time points for all participants. Data were analyzed using a modified *t*-test procedure, which compares test scores of a single patient to that of a small control sample (Crawford & Howell, 1998). Following the rationale described in Experiment 3, two-tailed *t* tests were used to compare H.C.'s behavioural performance with that of controls on the pToM and ToM conditions, whereas a one-tailed *t*-test was used for the AM condition. In contrast, for the fMRI data, two-tailed *t* tests were used to compare the neural activity between H.C. and that of controls across all three conditions. Like other case studies reported in the literature, values associated with $p < .05$ were considered to be significant (Bowles et al., 2007; Hassabis, Kumaran, Vann, & Maguire,

2007; Hurley et al., 2011; Levine et al., 2009; Maguire et al., 2010; Rosenbaum et al., 2008, 2009) and values associated with $p < .09$ were considered to be trends (Rosenbaum et al., 2009). Given the low statistical power associated with case studies, this level of correction provide a desirable balance between type I and type II error rates. Effect sizes (z_{cc}) and 95% confidence intervals on the effect sizes are reported (Crawford, Garthwaite, & Porter, 2010).

Percent signal change.

For the data analysis, all AM, pToM, and ToM events were included, with the exception of two ToM events from one participant because she recognized the people in the photo and two pToM events from another participant due to technical difficulties. In addition, one AM event was excluded from two participants because the participants did not experience the events depicted in those AM photos.

To determine whether there were significant differences in the pattern of activation supporting AM, pToM, and ToM in H.C. versus controls, a region of interest (ROI) analysis was performed. Percent signal change was calculated in relation to the control task (odd-even number judgment task). To ensure that regional measurements were made in an unbiased manner, the ROIs were selected from a conjunction analysis reported in a separate dataset examining AM and ToM (Rabin et al., 2010). The selected ROIs included the left medial PFC (-2 46 2), left ventrolateral PFC (-43 29 -1), left posterior cingulate cortex (PCC; -5 -56 21), right temporal pole (44 14 -26), and left temporal pole (-50 13 12). These ROIs were created by placing a sphere with an 8mm radius at the point of the peak activation.

In addition to examining the above ROIs, I was also interested in examining differences in hippocampal activation between H.C. and controls. To do so, left and right hippocampal ROIs were created for each participant by manually tracing the hippocampus based on published

standardized guidelines (Pruessner et al., 2000). The tracings were performed by a trained rater (R. Olsen).

Mean BOLD percent signal change was extracted from the ROIs for the AM, pToM, and ToM events for each participant. Only voxels that elicited percent signal change in a positive direction when compared with the control task (i.e., odd/even number judgments) were included. Differences in percent signal change between H.C. and the control group were calculated using a two-tailed modified *t*-test procedure (Crawford & Howell, 1998).

fMRI analyses within H.C.

To further explore the hippocampal activity observed in H.C. (see Results) and to determine whether this activation represents functionally relevant activity (Maguire et al, 2001), I carried out two analyses. The first analysis compared the BOLD signal associated with the AM events that H.C. rated as "remember" (9 AM events) with those she rated as "familiar" or "don't know" (6 AM events). The second analysis compared the BOLD signal associated with the AM events that H.C. rated as vividly remembered (a vividness rating of 3 or 4, for a total of 7 AM events) versus the AM events she rated as vaguely remembered (a vividness rating of 1 or 2, for a total of 8 AM events). It was not possible to carry out the vivid versus vague contrast for the pToM and ToM events given that H.C. rated all of these events as vividly imagined (i.e., a vividness rating of 3 or 4). Because these analyses were computed on a single participant, a liberal threshold was employed, $p < .01$ (uncorrected) for the hippocampus (Maguire et al., 2001). The rationale behind these analyses is that if the hippocampal activation observed in H.C. is functionally relevant then the activation should be greater for AM events that are "remembered" relative to those that are familiar/unknown (Maguire et al, 2001) and greater for AM events rated as vividly recollected versus those that are only vaguely recollected.

Functional connectivity analyses.

In addition to examining percent signal change, functional connectivity was explored and the regional temporal correlations were compared between groups. Correlations were computed between the PCC (seed region) and other brain regions within the common core network for each of the three conditions. The PCC was selected as the seed region because: (a) it is considered the primary "hub" of both the AM and ToM networks (Andrews-Hanna et al., 2010) and (b) it not known to be damaged in H.C. The same PCC ROI defined above (selected from Rabin et al., 2010) was used as the seed region for the connectivity analyses (coordinate -5 -56 21). Note that this PCC ROI used here is very similar to the ROI employed by Andrews-Hanna and colleagues to examine default mode network connectivity.

For each participant, the mean time course (i.e., collapsing across all time points) within the PCC seed region was extracted and Pearson's correlation coefficients were calculated between the PCC seed and all voxels in the brain. Individual r-maps were transformed using Fisher's *z* to yield normally distributed values. The mean correlation coefficients were then extracted for each defined ROI. The ROIs used here were the same as those used in the percent signal change analysis and included the left medial PFC, left ventrolateral PFC, left and right hippocampus, as well as left and right temporal poles.

Results

Phenomenology of the AM, pToM, and ToM Events

As mentioned above, all AM, pToM and ToM events were included in the analyses. Within-scanner ratings were compared between H.C. and control participants to assess differences in the phenomenological quality of the AM, pToM, and ToM events. Table 5.1 presents participants' ratings.

Table 5.1

Phenomenological Qualities of the Generated AM, pToM, and ToM Events

	AM	pToM	ToM
Remember/Know (/3)			
H.C. session 1	--	--	--
H.C. session 2	2.53**	--	--
Controls	2.90(0.09)	--	--
Similar to a Memory (/4)			
H.C. session 1	--	3.2	3.33
H.C. session 2	--	3.47	3.53
Controls	--	3.51(0.34)	3.60(0.32)
Vividness (/4)			
H.C. session 1	--	2.73	2.2*
H.C. session 2	2.53*	3.4	3.2
Controls	3.34(0.37)	3.06 (0.43)	3.13 (0.42)

The number in parentheses in the left-hand column indicates the maximum score for each rating scale.
Standard deviations are given in parentheses; AM, autobiographical memory pToM, personal theory of mind; ToM, theory of mind.
*$p < .05$, **$p < .0005$

With respect to the AM events (in Session 2), as expected H.C.'s ratings relating to the recollection of AM events were significantly lower compared to those of controls, $t = -4.22$, $p = .0005$), $z_{CC} = -4.11$ [-5.55, -2.66]. In terms of the ratings assessing likeness to an actual memory, no significant differences emerged between H.C. and controls for the pToM and ToM events in Session 1 or Session 2 (pToM Session 1 and Session 2, $t = -0.90$, $p = .39$, $z_{CC} = -0.91$ [1.46, -0.35), and $t = -0.12$, $p = .90$, $z_{CC} = -0.12$ [-0.58, 0.35], respectively, and ToM Session 1 and Session 2, $t = -0.82$, $p = .42$, $z_{CC} = -0.84$[-1.38, -0.29], and $t = -0.21$, $p = .83$, $z_{CC} = -0.22$ [-0.68, 0.25], respectively).

With respect to vividness, H.C.'s ratings for the AM events were significantly lower than that of controls, $t = -2.13$, $p = .02$; $z_{CC} = -2.19$ [-3.04, -1.32], whereas no significant differences

emerged for the pToM and ToM events across both testing sessions (pToM Session 1: t = -0.75, p = .47; z_{CC} = -0.77 [-1.29, -0.23]; pToM Session 2: t = 0.77, p = .45, z_{CC} = 0.79 [0.25, 1.31]; ToM Session 1: t = -2.16, p = .046; z_{CC} = 2.21[-3.08, -1.30], and ToM Session 2: t = 0.17, p = .87, z_{CC} = 0.17 [-0.30, 0.63]).

Percent Signal Change

In order to investigate differences in activation between H.C. and controls, percent signal change was examined within bilateral hippocampus[1] (Figure 5.1) and extrahippocampal regions (Figure 5.2) for the AM, pToM, and ToM events.

AM.

Relative to controls, H.C. exhibited significantly greater percent signal change within the left hippocampus, t = 2.86, p = .01, z_{CC} = 2.94 [1.85, 4.01], and left PCC, t = 2.84, p = .01, z_{CC} = 2.91 [1.83, 3.98]. A trend in the same direction was observed within the left ventrolateral PFC, t = 1.82, p = .09, z_{CC} = 1.87 [1.08, 2.63]. In contrast, no significant differences were observed within the right hippocampus, t = 0.68, p = .51, z_{CC} = 0.69 [0.17, 1.20], left medial PFC, t = -0.47, p = .64, z_{CC} = -0.48 [-0.97, 0.01], left temporal pole, t = 1.70, p = .11, z_{CC} = 1.74 [0.99, 2.47], and right temporal pole, t = -0.61, p = .55, z_{CC} = -0.63 [-1.12, -0.11].

pToM.

For Session 1, comparisons between H.C. and controls revealed no differences in percent signal change for any of the regions examined, including the left hippocampus, t = -0.19, p = 0.85, z_{CC} = -0.19 [-0.66, 0.28], right hippocampus, t = -0.61, p = .55, z_{CC} = -0.63 [-1.12, -0.11], left medial PFC, t = -1.43, p = .17, z_{CC} = -1.46 [-2.13, -0.78], left ventrolateral PFC, t = 1.52, p = .15, z_{CC} = 1.56 [0.85, 2.24], left PCC, t = 1.58, p = 0.13, z_{CC} = 1.62 [0.90, 2.33], left temporal

[1] Note that when the hippocampus was divided into anterior (head) and posterior (body and tail) segments, the same pattern of results was generally observed across AM, pToM, and ToM events.

pole, t = -1.02, p = 0.32, z_{CC} = -1.05 [-1.62, -0.46], and right temporal pole, t = -0.86, p = .40, z_{CC} = -0.89 [-1.42, -0.33].

For Session 2, H.C. showed significantly greater percent signal change within the left PCC, t = 3.93, p = .001, z_{CC} = 4.04 [2.61, 5.46], and a trend in the same direction within the left ventrolateral PFC, t = 1.83, p = .09, z_{CC} = 1.88 [1.09, 2.65]. However, no group differences were observed within the left hippocampus, t = 1.73, p = .10, z_{CC} = 1.78 [1.02, 2.52], right hippocampus, t = 0.83 p = .42, z_{CC} = 0.85 [0.30, 1.39], left medial PFC, t = -0.04, p = .97, z_{CC} = -0.04 [-0.50, 0.43], left temporal pole, t = 1.54, p = .14, z_{CC} = 1.58 [0.87, 2.27], and right temporal pole, t = -0.87, p = .40, z_{CC} = -0.89 [-1.43, -0.3].

ToM.

For Session 1, no group differences in percent signal change were observed for any of the regions examined, including the left hippocampus, t = 0.01, p = .99, z_{CC} = 0.01[-0.45, 0.47], right hippocampus, t = -0.07, p = .94, z_{CC} = -0.08 [-0.54, 0.39], left medial PFC, t = -0.90, p = .38, z_{CC} = -0.93 [-1.48, -0.37], left PCC, t = 0.92, p = .37, z_{CC} = 0.95 [0.38, 1.50], left ventrolateral PFC, t = 0.93, p = .36, z_{CC} = 0.96 [0.39, 1.51], left temporal pole, t = -0.31, p = .76, z_{CC} = -0.32 [-0.78, 0.16], and right temporal pole, t = -0.88, p = .39, z_{CC} = -0.90 [-1.44, -0.34].

For Session 2, relative to controls, H.C. exhibited greater percent signal change within the PCC, t = 2.6, p = .02, z_{CC} = 2.67 [1.66 to 3.67]; no group differences were observed within the left hippocampus, t = 0.75, p = .46, z_{CC} = 0.77 [0.23, 1.29], right hippocampus, t = 0.43, p = .67, z_{CC} = 0.45 [-0.05, 0.93], left medial PFC, t = .08, p = .94, z_{CC} = 0.083 [-0.38, 0.55], left ventrolateral PFC (t = 1.51, p = .15, z_{CC} = 1.55 [0.85, 2.24], left temporal pole, t = 0.43, p = .67, z_{CC} = 0.45 [-0.05, 0.93], and right temporal pole, t = -0.91, p = .37, z_{CC} = -0.94 [-1.48, -0.37].

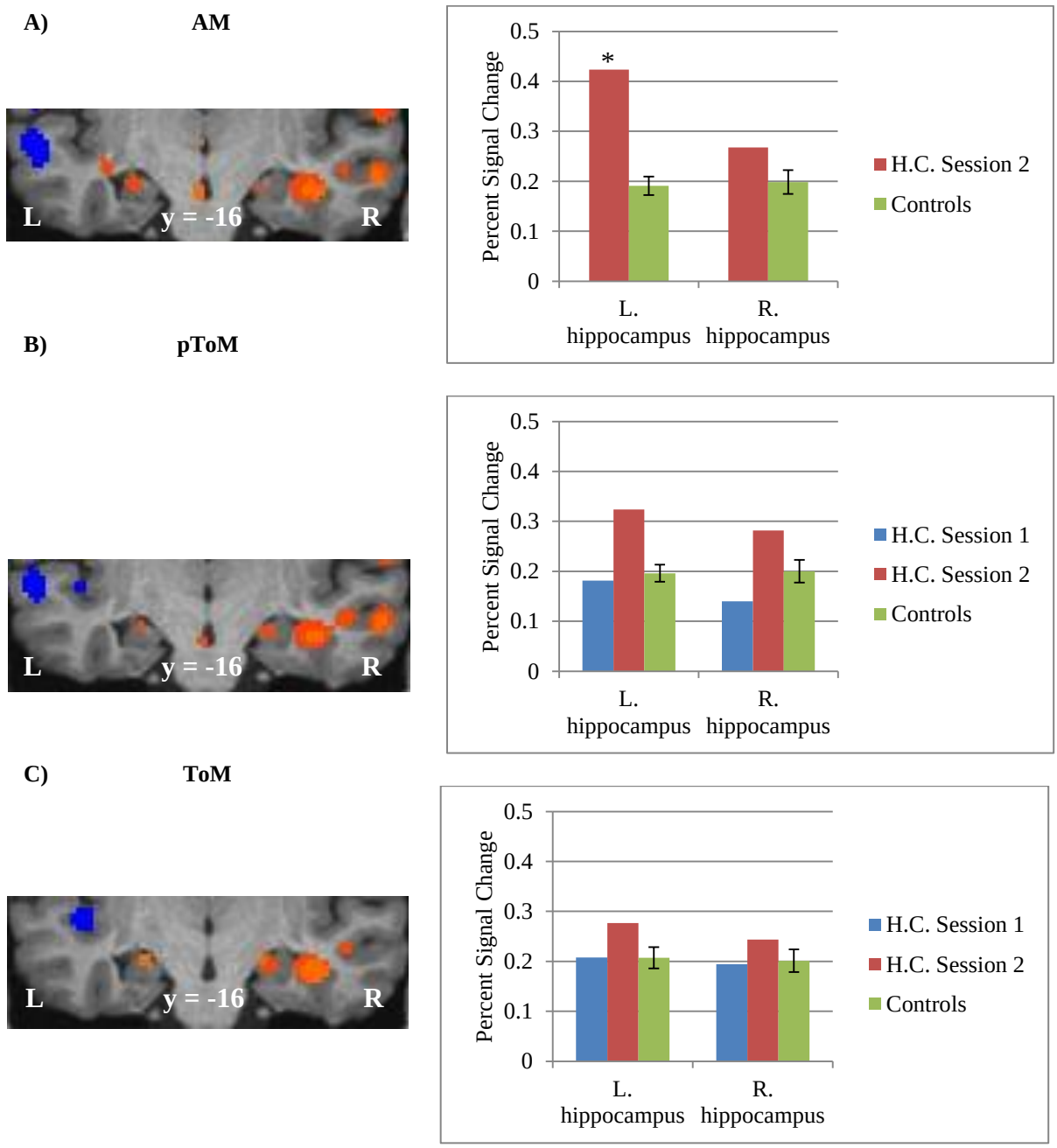
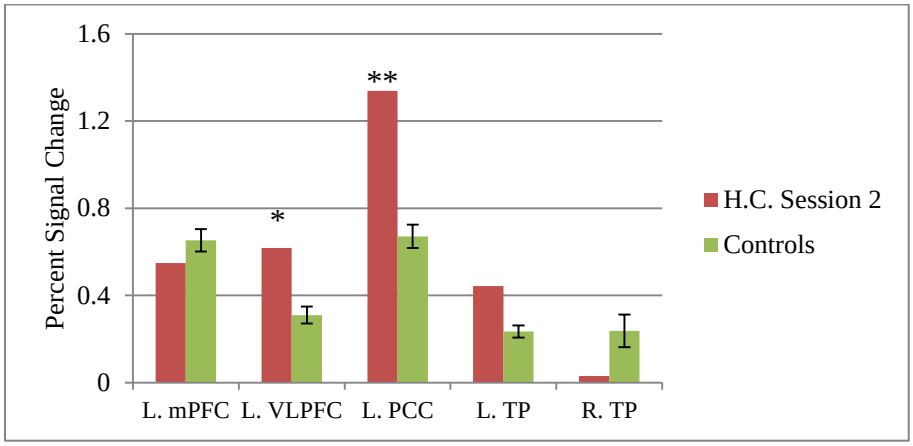
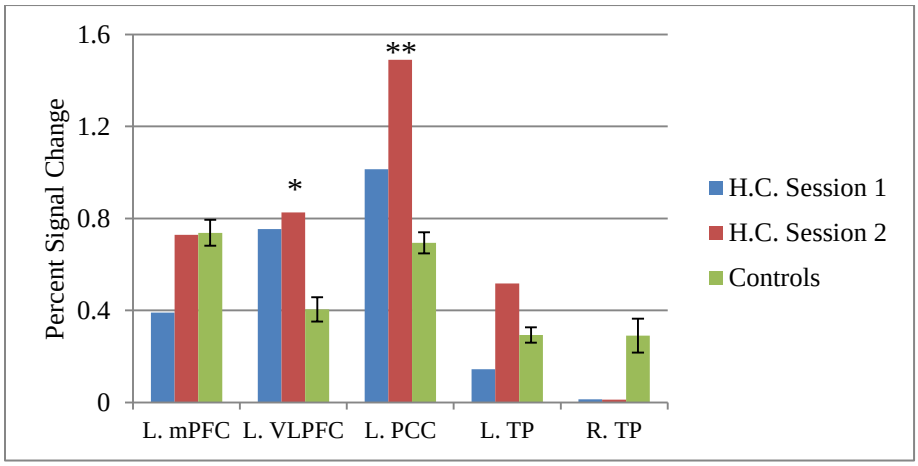


Figure 5.1. Coronal Slices Showing Hippocampal Activation in H.C. in Response to the (A) AM (B) pToM, and C) ToM. The images are thresholded at $p < .05$, uncorrected. The bar graphs depict mean percent signal change in left and right hippocampus. Error bars indicate standard error of the mean.
* $p < .05$

A) AM



B) pToM



C) ToM

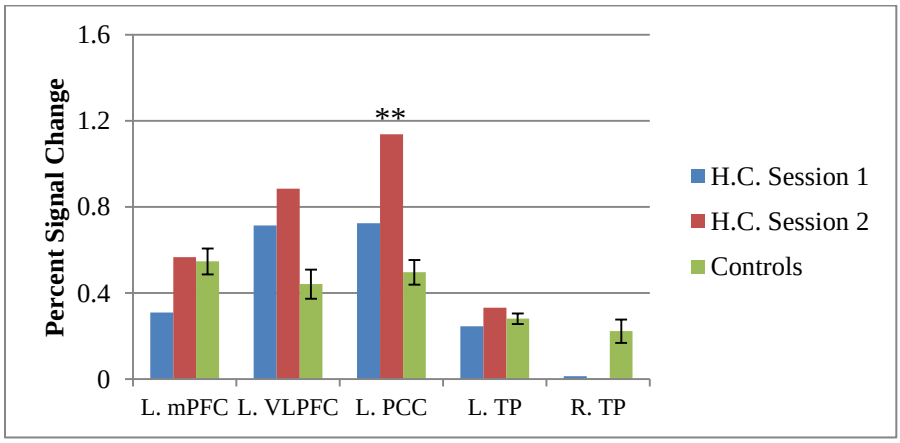
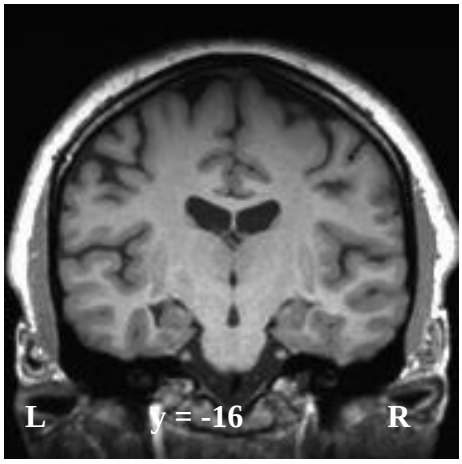


Figure 5.2. The Bar Graphs Depict the Mean Percent Signal Change in H.C. and Controls for (A) AM (B) pToM, and (C) ToM Events. Regions include the left medial prefrontal cortex (mPFC), left ventrolateral PFC (VLPFC), left posterior cingulate cortex (PCC), and bilateral temporal pole (TP). Error bars indicate standard error of the mean. *$p < .09$, ** $p < .05$

fMRI Analyses Within in H.C.

A contrast between the BOLD signal associated with the AM events that H.C. rated as "remember" versus those she rated as "familiar" or "don't know" revealed no differential activity within the hippocampus (see Figure 5.3). Similarly, a contrast between the AM events H.C. rated as vividly recollected versus those rated as vaguely recollected also revealed no differential activity within the hippocampus (see Figure 5.3). Even at a more relaxed threshold ($p < .05$), no differences emerged within the hippocampus.

A) 

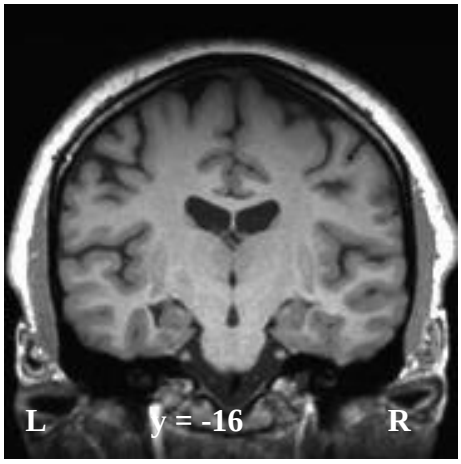
B) 

Figure 5.3. Differential fMRI Activity in H.C. (A) AM events H.C. remembered versus those she rated as familiar or was unable to recall and (B) AM events H.C. rated as vividly recollected versus those she rated as vaguely recollected. Both coronal images are at a threshold of $p < .01$, uncorrected, voxel size > 5).

Functional Connectivity Between the PCC and ROIs

In order to investigate differences in functional connectivity between H.C. and controls, regional temporal correlations between the PCC (seed region) and other brain regions within the common core network were examined for all three conditions[2] (Table 5.2).

[2] Functional connectivity analyses were also computed using the hippocampus as a seed region. These analyses also revealed no differences in connectivity between H.C. and the control group across AM, pToM, and ToM events.

AM.

With respect to AM, comparisons between H.C. and controls revealed no differences in functional connectivity between the PCC and the following regions: left hippocampus, $t = 1.71$, $p = .10$), $z_{CC} = 1.76$ [1.00, 2.50], right hippocampus, $t = 0.81$, $p = .43$, $z_{CC} = 0.833$ [0.29, 1.36], left medial PFC, $t = -0.48$, $p = .64$, $z_{CC} = -0.49$ [-0.98, 0.01], left ventrolateral PFC, $t = -0.18$, $p = .86$, $z_{CC} = -0.19$ [-0.65, 0.28], left temporal pole, $t = 0.32$, $p = .75$, $z_{CC} = 0.33$ [-0.15, 0.81], and right temporal pole, $t = 0.40$, $p = .70$, $z_{CC} = 0.41$ [-0.08, 0.88].

pToM.

For both pToM Session 1 and Session 2, comparisons between H.C. and controls revealed no differences in functional connectivity between the PCC and the following regions: left hippocampus (Session 1: $t = 0.64$, $p = .53$, $z_{CC} = 0.66$ [0.14, 1.16], Session 2: $t = 0.96$, $p = .35$, $z_{CC} = 0.99$ [0.41, 1.55]), right hippocampus (Session 1: $t = 0.25$, $p = .80$, $z_{CC} = 0.26$ [-0.22, 0.72], Session 2: $t = -1.70$, $p = .11$, $z_{CC} = -1.75$ [-2.48, -0.99]), left medial PFC (Session 1: $t = 0.62$, $p = .54$, $z_{CC} = 0.64$ [0.12, 1.14], Session 2: $t = -1.03$, $p = .32$, $z_{CC} = -1.06$ [-1.63, -0.47]), left ventrolateral PFC (Session1: $t = 1.75$, $p = .10$, $z_{CC} = 1.80$ [1.03, 2.55], Session 2: $t = 1.60$, $p = .13$, $z_{CC} = 1.64$ [0.91, 2.35]), left temporal pole (Session1: $t = -0.76$, $p = .46$, $z_{CC} = -0.78$ [-1.30, -0.24], Session 2: $t = 0.77$, $p = .45$, $z_{CC} = 0.792$ [0.25, 1.32]), and right temporal pole (Session 1: $t = -0.91$, $p = .38$; $z_{CC} = -0.94$ [-1.48, -0.37], Session 2: $t = 0.36$, $p = .72$, $z_{CC} = 0.37$ [-0.11, 0.84]).

ToM.

For both Session 1 and Session 2 comparisons between H.C. and controls revealed no differences in functional connectivity between the PCC and the following regions: left hippocampus (Session 1: $t = 0.02$, $p = .98$, $z_{CC} = 0.03$ [-0.44, 0.49], Session 2: $t = 0.06$, $p = .96$, $z_{CC} = 0.06$ [-0.41, 0.52]), right hippocampus (Session 1: $t = 0.24$, $p = .82$, $z_{CC} = -0.244$ [-0.71,

0.23], Session 2: t = -0.41, p = .70, z_{CC} = -0.42 [-0.89, 0.07]), left medial PFC (Session1: t = -0.70, p = .50, z_{CC} = -0.72 [-1.23, -0.19], Session 2: t = -0.70, p = .49, z_{CC} = -0.722 [-1.23, -0.192]), left ventrolateral PFC (Session 1: t = 0.61, p = .55, z_{CC} = 0.62 [0.11, 1.12], Session 2: t = -0.14, p = .89, z_{CC} = -0.14 [-0.60, 0.33]), left temporal pole (Session 1: t = -0.90, p = .38, z_{CC} = -0.92 [-1.47, -0.36], Session 2: t = 0.01, p = .99, z_{CC} = 0.007 [-0.46, 0.47]), and right temporal pole (Session 1: t = -0.82, p = .42, z_{CC} = -0.84 [-1.37, -0.29], Session 2: t = 0.02, p = .98, z_{CC} = 0.02 [-0.44, 0.48]).

Table 5.2

The Mean Correlation Coefficients Between the PCC and Other Brain Regions Within the Common Core Network for AM, pToM, and ToM.

AM

	L. mPFC	L. VLPFC	L. Hippo	R. Hippo	L. TP	R. TP
H.C. Session 2	.556	.244	.504	.395	.272	.230
Controls	.637	.272	.335	.300	.221	.174
SD	.165	.150	.096	.114	.154	.137

pToM

	L. mPFC	L. VLPFC	L. Hippo	R. Hippo	L. TP	R. TP
H.C Session 1	.758	.533	.373	.326	.109	.055
H.C. Session 2	.381	.511	.408	.122	.313	.196
Controls	.616	.288	.303	.300	.210	.156
SD	.222	.136	.106	.102	.130	.108

ToM

	L. mPFC	L. VLPFC	L. Hippo	R. Hippo	L. TP	R. TP
H.C Session 1	.433	.401	.298	.220	.071	-.011
H.C. Session 2	.432	.259	.302	.198	.211	.157
Controls	.572	.285	.295	.251	.210	.153
SD	.194	.186	.120	.127	.151	.195

Note. No differences emerged for any of the comparisons between H.C. and controls.

AM = autobiographical memory condition; pToM = theory of mind condition involving personally known others; ToM = theory of mind condition involving unknown others; L = left; R = right; mPFC = medial prefrontal cortex; PCC = posterior cingulate cortex; VLPFC = ventrolateral PFC; Hippo = hippocampus; TP = temporal pole; SD = standard deviation.

Discussion

In the current study, the neural basis of recollection and imagining abilities were examined in the developmental amnesic patient H.C., who experienced 30% hippocampal volume loss bilaterally. Behaviourally, H.C. was shown to be impaired in generating details relating to AM events and pToM events involving personally familiar others, but was indistinguishable from controls when generating details of ToM events involving unfamiliar others. Despite dissociations in behavioural performance, ROI analyses revealed that H.C. activated the same brain regions as healthy controls, including bilateral hippocampus, left medial PFC, left PCC, left ventrolateral PFC, and bilateral temporal poles. Similarly, H.C. showed the same functional connectivity pattern as controls across all three conditions. These findings suggest that hippocampal activation and preserved functional connectivity may not necessarily differentiate preserved versus impaired behavioural performance on closely matched conditions.

Hippocampal Activation

The most intriguing finding of the present study was the observation of robust bilateral hippocampal activation by H.C. across AM, pToM, and ToM conditions despite dissociations in behavioural performance and bilateral hippocampal volume loss. To further determine whether this hippocampal activation represents functionally relevant activity, events that H.C. "remembered" were compared with those that she merely knew about or was unable to recall. A similar analysis was also conducted for the AM events H.C. rated as vividly recollected versus those she rated as vague. The logic here is that if the activation is functionally relevant, then greater hippocampal activation should be evident during the "remembered" and vividly rated

events (Maguire et al., 2001). Interestingly, no differences in hippocampal activation emerged; instead, H.C. showed equivalent activation across these AM events, further suggesting that her hippocampal activity is not fully functional.

There is some evidence in the literature that hippocampal activation does not always correlate with behavioural performance (Dickerson et al., 2005; Protzner, Kovacevic, Cohn, & McAndrews, 2013; Westmacott, Silver, & McAndrews, 2008). For example, in an fMRI study that required participants to learn and remember face-name pairs, low-performing older adults showed greater hippocampal activation compared with high-performing older adults (Miller et al., 2008). The authors suggested that the hyperactivation observed in the low-performing older adults may serve as a compensatory mechanism. In another study, Zamboni and colleagues examined memory performance in individuals with amnestic mild cognitive impairment (aMCI) and demographically matched controls and found that the aMCI group demonstrated greater hippocampal activation compared with controls for both successful and unsuccessful memory recognition trials (Zamboni et al., 2013). These findings led the authors to suggest that hippocampal activation in aMCI is nonspecific and is not reflective of behavioural performance. Similarly, Westmacott and colleagues (2008) reported robust hippocampal activation during unsuccessful memory recognition trials in an individual experiencing an episode of transient global amnesia (she rated 95% of the trials as ‘‘new”) in contrast to a baseline condition. The authors speculated that the pattern of results reflects processes based on attempts to retrieve the studied material. Finally, there is evidence that healthy older adults show hyperactivity in the CA3 region of the hippocampus when performance is impaired on a pattern separation task (Yassa, Lacy, Stark, Albert, & Stark, 2011). Given the spatial resolution used in the current

study, it was not possible to determine if H.C.'s hippocampal activation was restricted to a particular subfield or subfields, and this remains to be probed further.

The possibility that H.C.'s remaining hippocampal tissue is contributing to task performance cannot be ruled out. In fact, this may account for why H.C.'s behavioural performance on the family photos task is not at floor on any of the conditions examined (see Experiment 3). It is possible that H.C.'s damaged hippocampus is less efficient at remembering/imagining, and as a result the increased activity reflects compensatory recruitment of additional resources (even to achieve suboptimal performance). That H.C.'s remaining hippocampal tissue may be functional is in line with neuroimaging findings reported in the developmental case Jon (Maguire et al., 2001). However, unlike H.C., Jon exhibited greater hippocampal activity only during events he clearly remembered versus those he merely knew about. Differences in hippocampal activation between H.C. and Jon may be due to differences in hippocampal pathology. Even though they are both developmental amnesic individuals, Jon's selective bilateral hippocampal pathology was induced by perinatal hypoxic–ischemic episodes (Maguire et al., 2001), whereas there is evidence that H.C.'s hippocampal damage occurred in the early stages of fetal development (Rosenbaum et al., in preparation; see also Olsen et al., 2013). Anoxia typically results in relatively selective cell loss in the CA1 region of the hippocampus (Zola-Morgan, Squire, & Amaral, 1986), which is likely the case in Jon. In contrast, a recent high resolution MRI analysis of H.C.'s hippocampus showed reduced volume bilaterally across all hippocampal subfields and that H.C.'s damage may have been less extensive compare to that of Jon (Olsen et al., 2013).

Another possibility is that H.C. may be engaging in a similar strategy as controls, however due to damage to the extended hippocampal system, the information cannot be

outputted by the hippocampus. Qualitative analysis of H.C.'s MRI scans indicates bilateral atrophy of the fornix (Olsen et al., 2013; Rosenbaum et al., in preparation), the major output pathway of the hippocampus. Thus, H.C.'s hippocampal activation may reflect task involvement, however given that the information cannot be sent to other brain structures, tasks dependent on the hippocampus are consequently affected (i.e., AM and pToM).

Extrahippocampal Activations

In Experiment 3, I showed that H.C.'s performance was intact on the ToM condition involving unfamiliar others and suggested that this is likely due to her relatively preserved semantic knowledge. Unlike AM, semantic memory is not dependent on the hippocampus but rather is supported by the left ventrolateral PFC and posterior temporal regions (Martin & Chao, 2001). Of note, in the current study H.C. showed strong left ventrolateral PFC activity during ToM for both Session 1 and Session 2, which may reflect her reliance on semantic memory. However, it should be mentioned that robust activation was observed in this region across all three conditions. Therefore, it may be the involvement of the left ventrolateral PFC region, and not the hippocampus, that contributed to H.C's ability to produce some details in response to the AM and pToM events in Experiment 3.

It is notable that during Session 2 (but not Session 1) H.C. elicited greater PCC activation than controls during the pToM and ToM conditions. It is possible that this increased activation reflects H.C.'s improved performance over time in that she generated a greater number of details in response to these events during the second testing session. This interpretation is consistent with the hypothesis that the PCC plays a central role in supporting internally directed cognition (Buckner et al., 2008; Raichle et al., 2001). Therefore, during Session 2 H.C. may have engaged

in greater internally directed thinking, which allowed her to produce more details in response to the pToM and ToM events.

Functional Connectivity

Not only were regional activations in H.C. equivalent to what was observed in controls (and in some cases greater than controls) across all three conditions but so were measures of functional connectivity. These findings are at odds with other studies examining functional connectivity during autobiographical remembering, which show alterations in the AM network in individuals with hippocampal amnesia. For example, Maguire and colleagues (2001) found that relative to controls, for the few memories that were described by Jon as recollected, connectivity was relatively weak or absent between the parahippocampal cortex and the hippocampus but greater between the retrosplenial cortex and hippocampus, and between the retrosplenial cortex and medial frontal regions. Similarly, Addis and colleagues (2007) found that patients with left mesial temporal lobe epilepsy showed a significant change in connectivity throughout the AM network, such that they exhibited reduced connectivity with the hippocampus and enhanced connectivity among anterior and posterior midline regions.

It is also useful reviewing studies examining DMN connectivity in hippocampal amnesia, given that this network overlaps closely with the AM network. Such studies have produced mixed findings, with some work showing aberrant DMN connectivity (Hayes et al., 2012) and other studies demonstrating intact connectivity in patients with lesions restricted to the hippocampus (Rudebeck, Filippini, & Lee, 2013). Of note, these studies were carried out in individuals with adult-onset amnesia, and it is possible that normal resting-state networks are more likely to be observed when structural damage occurs early in life (Tyszka, Kennedy, Adolphs, & Paul, 2011). It remains unknown whether DMN connectivity is intact in H.C.

The failure to find altered neural activity in H.C. does not necessarily indicate that such alterations do not exist. However, it is important to note that they were not detectable using a comprehensive approach that employed the most commonly used fMRI methods (i.e., brain activation and functional connectivity). It is possible that functional alterations in H.C. are more subtle and not measurable with BOLD fMRI approaches.

In conclusion, the current results suggest that measures of activation and functional connectivity do not necessarily distinguish between preserved and impaired behavioural performance on closely matched conditions in developmental amnesia. The present study highlights the importance of scanning patients with fMRI while completing cognitive tasks, particularly when performance is impaired. If not, researchers may mistakenly assume that the hippocampus is not activated during instances of impaired performance.

CHAPTER 6

General Discussion

The purpose of the present set of experiments was to examine if, and under what conditions, AM supported by the hippocampus is related to, and benefits, ToM and imagining of other people's experiences. To this end, I attempted to address two main research questions:

1. Are AM difficulties caused by early-onset hippocampal damage associated with impaired performance on standard measures of ToM (Experiment 1)?
2. Is AM and the brain regions that support it involved to a greater extent in imagining the experiences of personally known others compared to unknown others (Experiments 2, 3, and 4)?

In this general discussion, I first summarize the key findings from each of the four experiments. I then discuss the theoretical and clinical implications of these findings, and finally demonstrate how these results set the stage for future research examining AM and ToM.

Summary of the Experiments

In Experiment 1, I tested whether the development of AM is critical for the development of ToM. To do so, ToM abilities were examined in H.C., a young woman with impaired AM development due to early hippocampal damage. In this study, I showed that H.C. performed at the same level as controls on a wide range of commonly used ToM tests. These findings provide convincing evidence that the normal development of AM is not critical for the development of ToM, at least as measured by standard ToM tests. These results suggest caution be used when interpreting correlations in neuroimaging or behavioural data as causal.

In Experiment 2, I scanned healthy individuals with fMRI to test whether different neural and cognitive mechanisms support imagining the mental experiences of personally known others (pToM) versus unknown others (ToM) and how these abilities relate to AM. I showed that the brain regions supporting AM and pToM showed greater neural overlap compared to those supporting pToM and ToM. Of note, the greatest degree of overlap between AM and pToM was within midline regions. A complementary finding was striking neural differences between pToM and ToM, such that midline regions associated with AM predominated during pToM, whereas more lateral regions associated with social semantic memory predominated during ToM. These findings suggest that there are multiple routes to ToM and the extent to which each memory system is recruited during ToM depends, at least in part, on whether the target person is personally known or unknown.

Experiment 3 corroborated the neuroimaging results from Experiment 2 by showing that H.C., a developmental amnesic case, was impaired at producing detailed descriptions of events relating to her own past as well as events relating to personally known others. In contrast, she had no difficulty describing events relating to unknown others. These findings, therefore, suggest that hippocampally mediated AM and the processes that support it may be more essential when imagining the experiences of personally known others and that extrahippocampal regions are sufficient to support imagining events from the perspective of unknown others.

Finally, in Experiment 4, I used fMRI to explore the neural basis of the results reported in Experiment 3. In that experiment H.C. was shown to be impaired in generating details relating to AM events and pToM events involving personally familiar others, but showed intact performance when generating details relating to ToM events involving unfamiliar others. Despite dissociations in behavioural performance, ROI and functional connectivity analyses revealed no

neural differences between H.C. and controls across AM, pToM, and ToM events. These finding suggest that measures of activation and functional connectivity do not necessarily distinguish between preserved and impaired behavioural performance in developmental amnesia.

Taken together, using standard tests of ToM and the family photos task, these studies collectively demonstrate that AM and hippocampal function are more strongly related to imagining the mental experiences of personally known others relative to unknown others. Furthermore, in the face of hippocampal damage and impaired AM, regions outside the MTL are sufficient to support ToM but not pToM. I have speculated throughout this dissertation that ToM involving unfamiliar others can likely be achieved via reliance on social semantic memory supported by lateral frontal and temporal regions.

The Role of the Common Core Network and the Hippocampus

The current dissertation adds to the accumulating evidence that the network of regions traditionally associated with AM also plays a crucial role in other high-level, non-mnemonic cognitive processes. The majority of research in this area has focused on the relationship between AM and future thinking (Addis et al., 2009, 2007; Schacter et al., 2008; Schacter et al., 2012; Szpunar et al., 2007). fMRI and patient work examining these two abilities consistently show that they are intimately related. Without the current research, a similar relationship between AM and ToM might have been assumed based on qualitative and quantitative reviews of the neuroimaging literature (Buckner & Carroll, 2007; Hassabis & Maguire, 2007; Spreng et al., 2009). Importantly, the present set of studies highlight that even though AM, pToM, and ToM engage a common set of regions, AM and ToM (but not pToM) are dissociable. Taken together, this work underscores the importance exploring commonalities based on neuroimaging studies in patient populations. For instance, recent work has shown that at least some aspects of

future thinking and spatial memory are spared in episodic amnesia despite studies showing overlap in the brain regions that they recruit (Kwan, Craver, Green, Myerson, & Rosenbaum, 2013; Rosenbaum et al., 2000).

A number of theories have been proposed to account for the neural correspondence observed across AM, ToM, future thinking, and spatial navigation. Buckner and Carroll (2007) proposed that "self-projection" is the common process linking these diverse abilities together, which they define as the ability to mentally project oneself from the present moment into other times, places, and perspectives. This theory emphasizes the role of the MTL memory system and suggests that past memories enable one to build mental models and simulations of what might happen in the future or what another person might be thinking and/or feeling.

By contrast, building on cognitive map theory (O'keefe & Nadel, 1978), Hassabis and Maguire (2007) proposed that scene construction (i.e., the retrieval and integration of relevant spatial information to produce a coherent context) is the common element driving the core pattern of activity. The authors posited that the hippocampus is central to this process which in turn supports AM, spatial navigation, imagining new experiences, future thinking, and ToM. Evidence supporting their theory was based on (a) the observation that the core network is engaged when individuals imagine fictitious scenes that have no relationship to the self or time and (b) the finding that individuals with amnesia are impaired at imagining atemporal fictitious scenes that do not involve the self (Hassabis, Kumaran, & Maguire, 2007; Hassabis, Kumaran, Vann, et al., 2007).

A third theory proposed to account for the neural correspondence across these diverse cognitive abilities is the constructive episodic simulation hypothesis, which highlights that personal memories are not literal representations of the past, but instead, involve reassembling

and binding together event details from stored memories (Schacter & Addis, 2007). This hypothesis was put forth to account for the neural overlap observed between past and future thinking, although it can easily be extended to include ToM (Rabin et al., 2010). That is, individuals may recombine details stored in memory to imagine and simulate the experiences of other people.

Although I did not directly test any of these theories, the present results bear relevance to the theories as they relate to AM and ToM. All three theories emphasize the role of the MTL/hippocampus and suggest that AM is crucial for the expression of ToM, among other abilities. Thus according to these theories, damage to this memory system should impair ToM. For example, if self-projection is driving the common core network then we would expect H.C, a person with hippocampal damage, to be equally impaired at projecting herself into the perspective of a personally known other as well as an unknown other. Similarly, if the retrieval and recombination of details is critical to imagining events from other people's perspectives then we would once again expect H.C. to perform poorly on both pToM and ToM conditions. Critically, this was not observed in the present set of studies, but rather H.C. performed well on ToM tasks involving unfamiliar others and poorly on tasks involving personally known others (Experiment 1 and Experiment 3). Therefore, in order to accommodate the present results, a more flexible theory that draws on multiple processes is needed.

The results from the current dissertation, therefore, appear to be more consistent with a recent proposal put forth by Spreng and Mar (2012). These authors suggest that the neural overlap observed across AM and ToM may facilitate the integration of personal and interpersonal information, which provides a means for personal experiences to become social conceptual knowledge that in turn guides one's social behaviour. The integration of this

knowledge may also support the generation of personality models that enable individuals to accurately predict other people's behaviour (Hassabis et al., 2013).

Building on these ideas and taking the current findings into account, I suggest that in healthy individuals, ToM can be achieved by relying on an interplay between AM and semantic memory, and that in the face of AM impairment, semantic memory is sufficient to support some types of ToM abilities. These ideas are further discussed below.

How is ToM Achieved?

Based on the results of the current dissertation, I propose that in healthy individuals there are at least two routes to inferring and imagining what another person is thinking and/or feeling. One route involves access to past experiences mediated by the hippocampus and a second route relies on semantic memory and general reasoning abilities supported by extrahippocampal regions. Importantly, however, these strategies are not viewed as mutually exclusive, but rather AM and semantic memory are believed to interact during ToM. This idea is similar to the transformation theory, which posits that there is a dynamic interaction between AM supported by the hippocampus and semanticized versions of the original memory supported by the neocortex. Importantly, both types of memories can co-exist in the brain, and situational demands will influence which memory type predominates at retrieval (Winocur & Moscovitch, 2011; Winocur et al., 2010; see also Moscovitch et al., 2005, 2006; Rosenbaum et al., 2001).

The idea that AM and semantic memory interact is consistent with recent empirical studies suggesting that the DMN is composed of at least two distinct yet interacting subsystems: a medial temporal subsystem and a dorsal medial subsystem, both of which converge on midline regions (Andrews-Hanna et al., 2010). The medial temporal subsystem closely resembles the brain regions that support AM, whereas the latter network closely resembles the regions that

support semantic memory. Thus, these interacting subsystems may be responsible for retrieving and combining information stored in AM and semantic memory in order to infer other people's thoughts and feelings during ToM, and the extent to which each memory system is involved will depend, at least in part, on who the target person is.

Based on the current findings, I propose that reliance on AM may be the preferred strategy for imagining the experiences of personally known others, whereas reliance on semantic memory may predominate during ToM involving unfamiliar others. Indeed, knowing someone for a long period of time and observing that person's behaviour in different situations provides a rich source of information on which one can draw when imagining that person's mental states and experiences. In contrast, reliance on semantic memory, such as social semantic scripts, may be beneficial when imagining how an unknown person would think and act in a given situation. In such instances, we may rely on scripts of how the average person would likely respond in a given situation. For example, on would probably expect the average individual to feel depressed after losing his/her job and overjoyed after learning he/she won the lottery.

In the face of AM impairment, the semantic memory system is likely sufficient to support some types of ToM abilities, such as those tapped by standard ToM tests and ToM tasks involving imagining the experiences of unknown others. Indeed, this type of ToM is likely based on schemas or generic information that is already bound together and does not require access to past episodes. In contrast, access to AM appears to be necessary for relating to experiences involving personally known others. It remains to be determined, however, whether semantic memory is also necessary for pToM, such that imagining the experiences of personally familiar others requires access to both AM and semantic memory (see future directions for further discussion on this topic). Indeed, recent patient work has demonstrated that both AM and

semantic memory are crucial for future imagining abilities (Irish, Addis, Hodges, & Piguet, 2012).

It is possible that other variables, in addition to one's relationship with the target person, play a role in mediating the relationship between AM and ToM. For example, a recent study showed that participants recounted more semantic memories when responding to narratives relating to the protagonists' physical actions, and recalled more AMs when responding to narratives about the protagonists' mental qualities, predicaments, and accomplishments (Yang, Bossmann, Schiffhauer, Jordan, & Immordino-Yang, 2012). Personality factors and social-perceptual cues may also play a role in the extent to which AM versus semantic memory is involved during ToM. However, it remains for future research to determine how these different variables interact to influence the predominant strategy employed to infer or imagine another person's experience during ToM.

Clinical Implications

The present findings have important implications for how we understand and define amnesia. Amnesia is currently defined as an isolated deficit in AM in the context of preserved cognitive abilities including spared intelligence, working memory, semantic memory, attention, executive functioning, and visuospatial abilities. However, based on the current set of results along with other recent data (Andelman et al., 2010; Hassabis, Kumaran, Vann, et al., 2007; Kwan et al., 2010; Race et al., 2011), it appears that amnesia results in deficits that extend beyond autobiographical remembering, including impairments in imagining the perspectives of personally known others, imagining the future, and constructing detailed scenes. Such findings have important implications for health-care professionals who diagnose and treat individuals with hippocampal amnesia, which can arise from a number of different etiologies, including

hypoxic-ischemic injury (e.g., due to cardiac arrest, asphyxiation, carbon monoxide poisoning), infectious disease (e.g., herpes encephalitis), stroke (particularly involving the posterior cerebral artery), traumatic brain injury, and Alzheimer's disease.

In Experiment 3, if it is the case that H.C. relied on her relatively preserved semantic memory of situations relating to unknown others, it is interesting that she did not employ this strategy for events relating to personally known others. As mentioned in the discussion of that experiment, it would be interesting to investigate whether H.C. could be probed in a manner that would promote reliance on semantic memory when imagining personally known others' experiences. If so, this idea may serve as an important starting point for research aimed at developing new strategies to help improve AM and pToM abilities in individuals with hippocampal damage.

Future Directions

Although the current dissertation provides critical insight into the neural and functional relationship between AM, pToM, and ToM, several important questions remain unanswered. As mentioned previously, it will be important to replicate the present results in other developmental amnesic individuals and to investigate whether the current findings extend to those who sustain damage in adulthood. Currently, there is only one other study that supports the finding that AM development is not necessary for the development or expression of ToM. In a recent study, Staniloiu and colleagues tested a young male with developmental amnesia due to perinatal hypoxia on standard measures of ToM as well as tests of social perception, empathy, social judgment, and social regulation (cognitive control, emotion regulation, monitoring/error correction, self-reflection, deception; Staniloiu, Borsutzky, Woermann, & Markowitsch, 2013). Consistent with the results reported in Experiment 1, the patient showed largely preserved

performance on standard ToM measures, but was impaired on tasks tapping more complex social judgment and perception (e.g., incongruent affective prosody processing, performance on the Ultimatum Game). The authors suggested that these impairments may relate to the patient's reduced amygdala and basal ganglia volume or alternatively to deficits in relational processing that are likely needed to perform well on these complex tasks. Future studies are needed to discern among these possibilities. Furthermore, although no other study has formally assessed amnesic individuals' performance on ToM measures involving personally known others, there is some anecdotal evidence supporting this idea. For example, it was reported that M.L., the same amnesic patient who performed well on the standard ToM tests (Rosenbaum et al. 2007), had difficulty in knowing how to behave around family members and friends following his injury (Spreng & Mar, 2012).

Further neuroimaging research might also help to further understand the nature of H.C.'s hippocampal activation during instances of preserved and impaired behavioural performance. One way to further investigate this finding is to employ high-resolution BOLD fMRI while she completes the family photos task. This would allow us to investigate neural activity within the different hippocampal subfields. It may be the case that like other studies (Yassa et al., 2011), H.C.'s robust hippocampal activation is associated with the CA3 region of the hippocampus. Structural techniques, such as diffusion tensor imaging may also prove to be useful in helping us understand H.C.'s robust hippocampal activation.

Further investigations should also examine the role of semantic memory in ToM. In the current dissertation, I speculated that H.C. is likely relying on her relatively intact semantic memory in order to perform well on the standard ToM tests (Experiment 1) and to imagine the experiences of unfamiliar others on the family photos task (Experiment 3). However, this idea

was not formally tested in the current set of experiments. As mentioned earlier, previous work assessing individuals with semantic dementia have demonstrated that these patients are impaired on a wide range of standard ToM tests. However, it remains unknown whether semantic memory is also necessary for imagining the experiences of personally familiar others. Indeed, AM and semantic memory are both necessary for future imagining future events (Irish et al., 2012). Thus, an important next step is to examine how individuals with semantic dementia perform on the family photos task or other ToM tasks that employ personally familiar others.

A final question worthy of future investigation is exactly how AM contributes to pToM and ToM in healthy individuals. For example, do past episodes implicitly influence current social processing? Are specific episodes brought to mind in order to better understand what another person is thinking and/or feeling? Alternatively, are details from past episodes recombined in novel ways during pToM and ToM, as suggested by the constructive episodic simulation theory (Schacter & Addis, 2007)?

Conclusion

The purpose of the present set of experiments was to examine if, and under what conditions, AM supported by the hippocampus benefits ToM. Using a combination of behavioural and neuroimaging methods, I demonstrated that AM and the hippocampus are more essential for ToM tasks that involve personally familiar others compared with unknown others. In contrast, regions outside the MTL are likely sufficient to support ToM involving unfamiliar others. These results suggest that ToM is not dependent on a single process, but rather comprises a rich set of mechanisms for understanding other people's experiences. Overall, these results contribute substantially to our current understanding of the functional and neural relationship between AM and ToM, and add to the literature suggesting that the hippocampus plays a broader

role in cognition beyond that of recalling past events. It is my hope that these studies stimulate new avenues of research that help us better understand the role of the hippocampus in mnemonic and non-mnemonic cognitive abilities.

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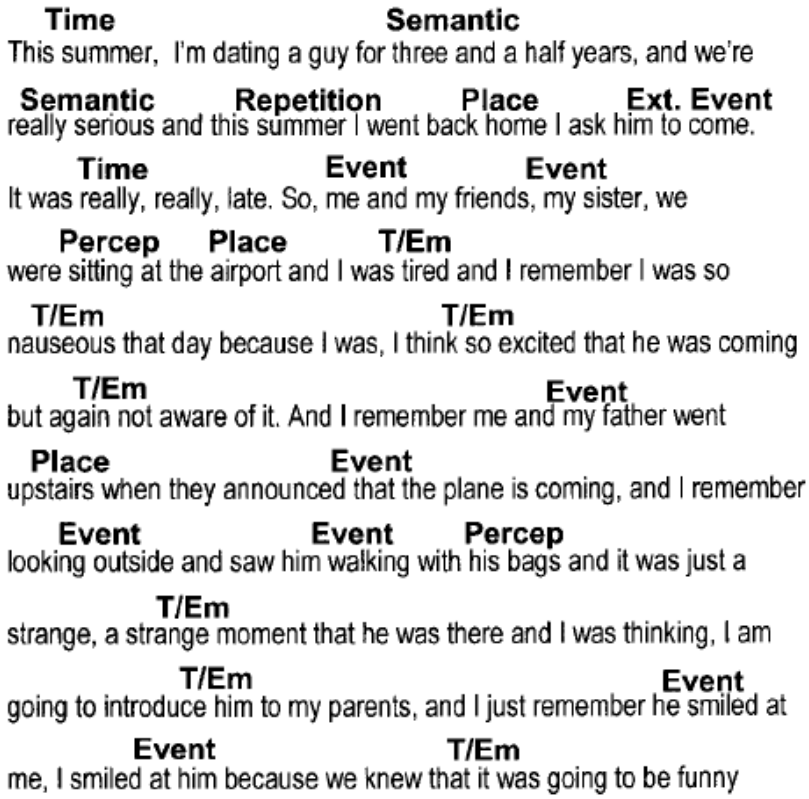

Figure A.1. Narrative Sample from Levine et al. (2002) Illustrating the Autobiographical Interview Scoring Procedure. Internal details include event, place, perception (percep), time, thought/emotion (T/Em) and External details include external events (ext. event), semantic, and repetitions.

Appendix B

Neuropsychological profile of H.C.

Table B.1

Test	Normed Score
General Intellectual Function	
WASI Verbal IQ (percentile)	61st
WASI Performance IQ (percentile)	66th
WASI Full Scale IQ (percentile)	66th
AM-NART (standard score)	101 (estimated FSIQ)
Semantic Knowledge and Academic Attainment	
WASI Vocabulary (T-score)	55
WAIS-III Information (scaled score)	12
WAIS-III Arithmetic (scaled score)	8
Language Production	
Boston Naming Test (z-score)[1]	0.75
Semantic Fluency (animals) (percentile)	> 90th
Anterograde Memory	
WMS-III*	
Logical Memory I – immediate recall (scaled score)	4
Logical Memory II – delayed recall (scaled score)	1
California Verbal Learning Test-II	
total trials 1–5 (T-score)	38
short delay free recall (z-score)	-4
long delay free recall (z-score)	-3
recognition (z-score)	-2
Rey Osterrieth complex figure[2]*	
immediate recall (T-score)	<20
delayed recall (T-score)	<20
delayed recognition – total correct (T-score)	22
Visuospatial Function	
WASI Block Design (T-score)	54
Rey-Osterrieth Complex Figure – Copy (percentile)	> 16th
Judgement of Line Orientation (percentile)	56th
Benton Facial Recognition (percentile)	33–59th

Table B.1 cont.

Test	Normed Score
Attention and Executive Function	
Stroop[3]	
Word full (seconds) (z-score)	3.65
Colour full (seconds) (z-score)	−0.03
Interference full (seconds) (z-score)	−0.57
Word errors (z-score)	0
Colour errors (z-score)	−0.5
Interference errors (z-score)	−0.13
Word self-corrections (z-score)	−0.5
Colour self-corrections (z-score)	−0.71
Interference self-corrections	1.44
Trail Making Test[1]	
Part A (sec) (z-score)	0.69
Part B (sec) (z-score)	−0.23
Phonemic Fluency (FAS) (percentile)[4]	70–80th
WASI Similarities (T-score)	50
WASI Matrix Reasoning (T-score)	55
Wisconsin Card Sorting Task – categories (T-score)[5]	57
Processing Speed	
WAIS-III Digit Symbol (scaled score)	13
WAIS-III Symbol Search (scaled score)	14
Mood	
CES-D[6]	no indication of depression
PANAS	
Positive Affect (z-score)	1.06
Negative Affect (z-score)	0.21

Note: AM-NART, American National Adult Reading Test; WASI, Wechsler Abbreviated Scale of Intelligence; WAIS-III, Wechsler Adult Intelligence Scale–III; CES-D, Center for Epidemiological Studies Depression Scale; PANAS, Positive and Negative Affectivity Scale
[1]Spreen & Strauss (1998) [2]Meyers & Meyers (1996) [3]in-house unpublished normative data
[4]Tombaugh, Kozak, & Rees (1996) [5]Heaton et al. (1993) [6]McDowell & Newell (1996) *17.8 years old at time of testing