Spatial Information Modulates the Neurocognitive Dynamics of Episodic Autobiographical Memory Retrieval

by

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A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy
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Abstract

Episodic autobiographical memory (EAM) enables reliving past experiences, recalling the sensory information associated with that event. Spatial information is thought to play an early and important role in EAM, contributing to the dynamics of retrieval. Using a combination of behavioural, neuroimaging, and neurostimulation approaches, this dissertation aimed to examine the temporal dynamics of EAM and the role spatial information plays in its retrieval. Chapter 2 demonstrated a temporal precedence for spatial information at the behavioural level, but importantly found high individual variability in early recall of spatial information. Further, individual differences in spatial aspects of EAM were reflected in hippocampal and precuneus grey matter volumes. Chapter 3 examined the temporal dynamics of EAM at the neural level using magnetoencephalography (MEG). While cueing individuals with familiar locations altered the dynamics of retrieval, it did not confer an early neural advantage. Together with the findings from Chapter 2, these results indicate that early spatial information alters the dynamics of EAM retrieval, but does not play a ubiquitous or automatic role in EAM. This study also found that spatial perspective during EAM retrieval was associated with a well-established neural component of episodic memory recollection. Transcranial magnetic stimulation (TMS) administered to the precuneus disrupted this association, demonstrating that this region is crucially involved in neural processing of spatial perspective during EAM. In Chapter 4, I
assessed how regions representing spatial information, such as the precuneus and medial temporal lobe (MTL), interact dynamically during EAM retrieval. Using MEG to measure oscillatory activity, this study found that theta (3-7 Hz) and high gamma (65-85 Hz) oscillations underlie MTL-parietal communication, demonstrating the importance of coupling between theta and gamma oscillations in EAM. TMS to the precuneus disrupted this oscillatory activity, suggesting that this region plays a causal role in network-wide theta and gamma oscillatory activity. Together, these studies elucidate the behavioural and neural dynamics of EAM retrieval, as well as spatial contributions to EAM. Future research is needed to further clarify the key contributions of specific regions and the dynamic activity underlying widespread neural communication during EAM.
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Chapter 1
General Introduction

1.1 Overview

Episodic memory is a unique cognitive function that allows us to relive events from our past, recalling rich sensory information. Tulving (2002) identified autonoetic consciousness, the self-conscious awareness of prior experiences, as a crucial aspect of episodic recollection. Autonoetic consciousness enables rich recollection, allowing individuals to mentally time travel, re-experiencing past events in detail. Recalling personal events from one’s past is referred to as autobiographical memory and may entail a form of episodic memory (Kopelman & Kapur, 2001). One prominent view is that this type of memory is distinct from experimental recall of stimuli (Gilboa, 2004), and also from semantic autobiographical memory, which includes knowledge of one’s personal past (Levine, 2004). Here I refer to episodic autobiographical memory (EAM) as the conscious remembering of specific events from one’s past involving vivid recollection of events and sensory-perceptual details.

It is important to note that some alternative accounts do not hold this view. One view is that episodic memory is representative of an original experience rather than a vivid record of it (Conway, 2009) Conway argues that a single episodic memory is comprised of more specific representations (episodic elements) and a contextualizing knowledge that organizes it (conceptual frame). One or more single episodic memories associated with a conceptual frame are organized into complex episodic memories. Many episodic memories are lost after a few days, although they may last longer if they become integrated with a conceptual system representing autobiographical knowledge. By this view, memory for a list of words and memory for what you had for dinner last week fall under the same, although hierarchically organized, overall memory system. Another view proposes that ‘event memory’ is the basis of memories for personally experienced past events and for events learned in laboratory episodic memory tasks (Rubin & Umanath, 2015). Event memory is a mental construction of a scene, with or without a sense of reliving. Rubin and Umanath argue for the use of event memory in part because it provides a clearer distinction from semantic memory. According to this framework, episodic
memories are a type of event memory that include a sense of reliving, involve the self, are recalled voluntarily, and are for unique experiences. In this dissertation I take the view that autobiographical memory contains within it a distinct form of episodic memory.

This dissertation will examine the neural underpinnings of EAM, the role that spatial context plays in its retrieval, and the temporal dynamics of retrieval at the behavioural and neural level. In this chapter I will review the relevant literature and outline details of the studies designed to address the aims of this dissertation.

1.2 Medial temporal lobes and memory

EAM recruits a distributed network of brain regions including medial and ventrolateral prefrontal cortices, medial and lateral temporal cortices, temporoparietal junction, posterior cingulate cortex, and cerebellum (For review see Svoboda, McKinnon, & Levine, 2006). The hippocampus and surrounding medial temporal lobe (MTL) regions play a particularly crucial role in EAM (Scoville & Milner, 1957), and also in spatial memory and navigation (Eichenbaum & Cohen, 2004; Morris, Garrud, Rawlins, & O’Keefe, 1982; O’Keefe & Nadel, 1979). The MTL is comprised of the perirhinal cortex, the parahippocampal region (including the parahippocampal cortex and entorhinal cortex), and the hippocampus. The perirhinal cortex receives input from a variety of areas including the MTL itself as well as unimodal and polymodal cortical association areas, while the parahippocampal cortex receives mostly polymodal input from neocortical regions. Information from these two areas converge within the hippocampus and reverse projections follow the same pathway backwards (For review, see Eichenbaum, Yonelinas, & Ranganath, 2007). At encoding, the hippocampus is thought to bind MTL and neocortical neural elements into a multimodal episodic memory trace, consisting of an ensemble of hippocampal-neocortical neurons (Moscovitch, Cabeza, Winocur, & Nadel, 2016). Hippocampal-neocortical ensembles are reinstated at retrieval, although the nature of this reinstatement changes as memories become more remote (Moscovitch et al., 2016). The multiple trace theory posits that there is a distinction between detailed episodic memories, which always rely on the hippocampus, and gist-like or semantic memories, which rely more on the neocortex (Nadel & Moscovitch, 1997). When memories are retrieved frequently they are re-encoded by the hippocampus many times and neocortical regions can extract the gist of the memory independent
of its context. Building on the multiple trace theory, the trace transformation hypothesis proposes that memories are transformed from detailed episodic memories to gist-like memories without many details (Winocur & Moscovitch, 2011). Such schematic memories do not depend on the hippocampus, but detailed, context-specific memories will depend on the hippocampus regardless of their age. Crucially, a detailed hippocampal-based memory may co-exist and interact with a schematic extra-hippocampal-based memory. Others have suggested that both types of memories are created in parallel and semanticization begins at the outset of encoding. Which representation is more prominent and expressed during recall depends on time and the purpose of recall (Gilboa & Marlatte, 2017).

In addition to its established role in EAM, a long line of animal research supports the MTLs crucial role in spatial memory and navigation (Eichenbaum & Cohen, 2004; Morris et al., 1982; O’Keefe & Nadel, 1978). The discovery of place cells in the rodent hippocampus that exhibit location-specific firing gave rise to the cognitive map theory, which argues that the hippocampus is fundamental to the construction and maintenance of spatial maps of the environment (O’Keefe & Nadel, 1978). According to this theory, the hippocampus plays a distinct role in supporting viewpoint independent (allocentric) processing, while other regions such as the parietal lobe support viewer-centered (egocentric) processing. Extending the cognitive map theory, others found that posterior parietal cortex neurons support translations between allocentric and egocentric frames (Snyder, Batista, & Andersen, 1998), and between different egocentric frames (Andersen, Essick, & Siegel, 1985).

An influential computational model of spatial memory and imagery, the BBB model, attempts to explain the involvement of the human hippocampus in spatial memory (Becker & Burgess, 2000; Byrne, Becker, & Burgess, 2007). This model suggests that long-term spatial memories are stored allocentrically by the hippocampus and egocentric images are created during perception or recall by the parietal cortex. In this model based on established anatomical connections, the hippocampal formation is represented by a layer of place cells that are specific to fixed spatial configurations. These place cells receive input on object location from the parahippocampal cortex, and on the textural features of an object from the perirhinal cortex. Medial parietal areas receive information on egocentric representations of object location from the dorsal visual stream, and connections allow for bidirectional translation from allocentric to egocentric
representations via posterior parietal areas. Support for this model has come from its ability to simulate normal recall and imagery, to replicate neglect following a simulated parietal lesion, and from a functional magnetic resonance imaging (fMRI) study. Burgess et al (2001) had participants navigate through a virtual reality town, receiving objects from characters during different encounters. During a later fMRI scan, participants made judgments about the places, people, and objects they encountered while navigating. A continuous strip of activation was found between the precuneus, parieto-occipital sulcus and hippocampus via the retrosplenial cortex for place judgments compared to non-place judgments. Burgess et al (2002) posit that these patterns of results reflect the interactions proposed in the BBB model, suggesting that the hippocampus stores index-like information about events in the task, and the parahippocampal gyrus uses this information to create an allocentric representation of the scene. To allow for visual imagery, the right posterior parietal cortex and precuneus translate this representation from allocentric to body-centered to head-centred.

The scene construction theory (Hassabis & Maguire, 2007) attempted to reconcile the role of the hippocampus described by episodic memory theories and space-based theories (i.e. the cognitive map theory). According to this theory, the hippocampus facilitates scene construction by retrieving and integrating multimodal information from neocortical areas, reconstructing them into a coherent spatial context (Hassabis and Maguire, 2007). Many researchers consider scene construction fundamental to the vivid recollection of memories (Burgess et al., 2001; Hassabis and Maguire, 2007; Robin et al., 2015), and some view it as the central process underlying cognitive processes such as future thinking, navigation, and imagination. Scene construction accounts view spatial context as a scaffold for EAM (Hassabis and Maguire, 2007; Robin et al., 2015), implying that spatial context is reinstated before other information. According to these theories, spatial context reinstatement is believed to be an early and ubiquitous process associated with the hippocampus. Neuropsychological evidence has provided support for the scene construction theory, demonstrating that patients with bilateral hippocampal damage have deficits in constructing spatially coherent fictitious scenes (Hassabis, Kumaran, Vann, & Maguire, 2007; Mullally, Vargha-Khadem, & Maguire, 2014), and in boundary extension (Mullally, Intraub, & Maguire, 2012). In addition to the hippocampus, several studies have shown that posterior parietal regions including retrosplenial cortex, posterior cingulate cortex,
and precuneus are also fundamental to scene construction (Hassabis, Kumaran, & Maguire, 2007; Irish et al., 2015; Mullally et al., 2014).

### 1.3 Retrieval dynamics of EAM

Functional neuroimaging studies of EAM consistently report activation of a number of widespread brain regions, but few have examined the dynamics of activations at different time points of retrieval. A small number of fMRI studies have demonstrated different patterns of activation and functional connectivity differences during memory construction, which involves the search and reconstruction of a past event, and elaboration, which involves retrieving details and recollecting the past event (Addis, Wong, & Schacter, 2007; McCormick, St-Laurent, Ty, Valiante, & McAndrews, 2015). These studies delineate the stages by asking participants to press a button once they have accessed a specific incident, and then to continue elaborating the memory by retrieving details of the event. McCormick et al (2013) found that EAM construction is associated with interactions between the anterior hippocampus and a frontotemporal network, and elaboration with a posterior hippocampus-temporoparietooccipital network. Using structural equation modelling, they demonstrated that the anterior hippocampus influences activity in the dorsal medial prefrontal cortex (mPFC) during construction, which may represent an early self-guided search through memory. During elaboration, posterior hippocampal activity influenced activity in visual perceptual areas, possibly reflecting the retrieval of perceptual episodic elements needed for re-experiencing. Weiler et al (2010) similarly examined differences in fMRI activity during construction and elaboration phases during EAM and episodic future thinking. Compared to episodic future thinking, EAM construction was associated with right posterior hippocampal activity, somewhat contrasting findings from McCormick et al (2013). Elaboration was differentially associated with activity in the precuneus, anterior cingulate cortex, and inferior occipital gyrus. Addis et al (2007) and Daselaar et al (2008) found similar patterns of early hippocampal and later parietal activity, suggesting that the hippocampus plays an important role early in EAM construction, while parietal areas play a role in later elaboration. These findings are in line with the BBB model and scene construction theories, which suggest an order to EAM recall such that the MTL initially represents allocentric spatial information, and the retrosplenial cortex translates this into egocentric spatial information supported by the precuneus for mental
imagery and re-experiencing. While these findings provide important insights into the dynamics of EAM retrieval, limitations exist due to the poor temporal resolution of fMRI.

Consistent with scene construction theories as well as with cognitive map interpretations of memory and the hippocampus (Burgess, Becker, King, & O’Keefe, 2001; Nadel & Hardt, 2004), one study found that spatial context during encoding in a navigational task is reinstated by the hippocampus very early during memory recall (Miller et al., 2013). In this study, place-responsive cells in the hippocampus and entorhinal cortex were recorded in human patients with depth electrodes implanted due to drug-resistant epilepsy. Participants navigated through a virtual reality town visiting different stores and delivering items at each store, and later verbally recalled as many items as possible. The environment was split into regions based on the distance to where that item was delivered, and place cell activity during retrieval was compared to activity in each navigational region for each item. Neural similarity between navigation and recall was found to occur prior to vocalization of a delivered item and continued into item vocalization. This suggests that spatial context reinstatement occurred very early during memory recall, prior to the onset of verbalization. However, this study specifically tapped memory for locations and navigational ability and does not directly examine retrieval dynamics and the role of early spatial representations in EAM retrieval.

1.4 Parietal cortex and EAM

Although most early studies focused on the MTL’s contributions to memory, functional neuroimaging studies consistently reported activation of the parietal lobe during EAM retrieval (Addis, Knapp, Roberts, & Schacter, 2012; Addis, McIntosh, Moscovitch, Crawley, & McAndrews, 2004; Svoboda et al., 2006). However, much remains unclear about the contribution of the parietal lobe to episodic memory. Contrary to MTL lesions, lateral parietal lesions do not produce severe amnesia, but are associated with more subtle memory deficits such as reduced vividness and amount of detail in freely recalled autobiographical memories (Berryhill, Phuong, Picasso, Cabeza, & Olson, 2007), and decreased confidence in memories (Davidson et al., 2008). Lateral parietal lobe activity has been associated with retrieval-success effects (McDermott, Jones, Petersen, Lageman, & Roediger, 2000), recollected versus familiar items (Henson, Rugg, Shallice, Josephs, & Dolan, 1999), more confidently retrieved items
(Yonelinas, Otten, Shaw, & Rugg, 2005), and contextually richly recalled items (Raposo, Han, & Dobbins, 2009). Medial parietal activation including the precuneus is more robustly reported in autobiographical memory studies (Cabeza & St Jacques, 2007; Fuentemilla, Barnes, Duzel, & Levine, 2014; Svoboda et al., 2006).

Different patterns of results may be due to the functional heterogeneity of the parietal lobe. The parietal cortex contains several functionally distinct subregions which are highly connected with many brain regions. The posterior parietal cortex has reciprocal anatomical connections with the MTL, including entorhinal, parahippocampal, and hippocampal subregions (for review, see Cabeza, Ciaramelli, Olson, & Moscovitch, 2008), and displays high fMRI connectivity with the hippocampus (Buckner, Andrews-Hanna, & Schacter, 2008). The posterior medial parietal lobe largely corresponds with the precuneus (BA7), a region often thought of as an association area (Cavanna & Trimble, 2006). The precuneus has reciprocal connections with neighboring posterior cingulate and retrosplenial cortices, inferior and superior lobules, as well as with the frontal cortex and numerous widespread regions (for review, see Cavanna and Trimble, 2006). Parietal subregions have been attributed various roles in episodic memory. One recent study found that fMRI activity in the precuneus was associated with vividness judgments in an episodic memory task, while angular gyrus activity in the same task was associated with retrieval precision (Richter, Cooper, Bays, & Simons, 2016), although others have found angular gyrus activity to be associated with vividness ratings (Bonnici, Richter, Yazar, & Simons, 2016; Kuhl & Chun, 2014). Other studies have found a relationship between precuneus activity and vividness (cf. Gilboa, Winocur, Grady, Hevenor, & Moscovitch, 2004; Sheldon & Levine, 2013) or specificity (Addis et al., 2004) of autobiographical memories. The precuneus has also been attributed a wide array of functions including visuo-spatial imagery, episodic memory retrieval, and self-related processing. A number of studies have associated the precuneus with adopting a first-person (egocentric) perspective during spatial processing and navigation (Spiers & Maguire, 2008; Zaehle et al., 2007), autobiographical memory (Freton et al., 2014), and even story telling (Vogeley et al., 2001).

As described above, the BBB model of spatial memory and imagery argues that the precuneus is responsible for representing, manipulating, and updating egocentric spatial information generated from allocentric long-term spatial memory (Burgess, Becker, et al., 2001; Byrne et al.,
According to this model, during spatial memory retrieval, the retrosplenial cortex translates long-term allocentric scene information provided by the MTL into short-term egocentric information which is supported by the medial parietal lobe. This model posits that a parietal window, a population of neurons likely within the precuneus, represents egocentric information which is manipulated and updated for the purposes of navigation, planning, and mental exploration. Theta oscillations (3-7 Hz) are thought to coordinate MTL-parietal translations and interactions (Byrne, Becker & Burgess, 2007; Becker and Burgess, 2001). A number of studies have supported this role for the precuneus and extended it beyond spatial memory and imagery, showing that precuneus activity is associated with manipulating egocentric information during spatial navigation (Wolbers, Hegarty, Büchel, & Loomis, 2008), and in shifting egocentric perspectives during autobiographical memory (St. Jacques, Szpunar, & Schacter, 2016). A recent structural MRI study found that precuneus grey matter volume was positively associated with the tendency to recall autobiographical memories from an egocentric, or first-person perspective (Freton et al., 2014). Thus, some recent studies suggest that a primary function of the precuneus is to represent, manipulate, and update egocentric information during spatial navigation and memory.

Animal research has further supported the role of the posterior parietal cortex in egocentric spatial processing, with the primate posterior parietal cortex containing cells that egocentrically represent visual information in head and body-centered reference frames (Andersen & Buneo, 2002). A direct link between the parietal lobe and hippocampal place cells during spatial processing has also been observed. In a combination lesion and electrode recording study, rats were given associative parietal cortex lesions, an area thought to be analogous to the posterior parietal cortex in humans. Hippocampal place cells were then recorded during a spatial memory task. Lesioned rats had altered place cell firing, suggesting that the parietal cortex may be needed to convert egocentric coordinates into allocentric ones used by the hippocampus (Save, Paz-Villagran, Alexinsky, & Poucet, 2005). While this study is unable to point to the precuneus specifically, it suggests that the posterior parietal cortex is involved in the elaboration of hippocampal maps in rats.

Despite a number of recent studies examining the parietal lobe’s contribution to memory, much remains unclear about the functions of parietal subregions. As I will discuss below (section 1.6),
transcranial magnetic stimulation (TMS) provides an opportunity to elucidate the roles of different parietal subregions in memory using a causal approach.

1.5 Individual differences in EAM

Behavioural and neural individual differences in EAM ability can present challenges to using a group-level approach to study memory. Individuals have been found to differ on many aspects of EAM including subjective ratings of vividness (D’Argembeau and Van der Linden, 2006), self-reported trait mnemonics (Palombo, Williams, Abdi, & Levine, 2013), and perspective-taking tendencies (Rice & Rubin, 2011). Extreme cases of highly superior and highly deficient EAM have been identified in healthy individuals with otherwise normal cognitive functions. In highly superior autobiographical memory (HSAM; LePort et al. 2012), individuals are able to recall in great detail even the most mundane events from their past given a randomly selected date. Individuals with Severely Deficient Autobiographical Memory (SDAM), on the other hand, are unable to vividly recollect personally experienced events and notably, report difficulty remembering events from an egocentric perspective (Palombo, Alain, Söderlund, Khuu, & Levine, 2015). Functional and structural brain differences between HSAM/SDAM individuals and control participants have been reported. One HSAM individual, who was also blind, demonstrated greater amygdala-hippocampal functional connectivity during resting state fMRI (Ally, Hussey, & Donahue, 2013). Structurally, HSAM has been associated with increased grey and white matter in the parahippocampal gyrus and lateral temporal lobes, increased uncinate fasciculus volume, and hypertrophy of the right amygdala (Ally et al., 2013; LePort et al., 2012). On the other end of the spectrum, one study of SDAM individuals reported reduced right hippocampal volume, reduced activation of midline regions including medial PFC and precuneus during EAM retrieval, and attenuated event related potential (ERP) signatures of recollection compared to matched controls (Palombo et al., 2015). A subsequent study from the same group found that gamma phase synchrony during EAM retrieval was absent in one SDAM individual, suggesting a mechanism for the inability to re-experience past events (Fuentemilla, Palombo, & Levine, 2017).

Differences in EAM ability have also been associated with functional and structural MRI in individuals within the normal range of memory ability. Sheldon et al (2015) found that trait-like
differences in episodic and semantic remembering are related to intrinsic functional connectivity patterns. Endorsement of EAM ability was associated with connectivity between the MTL and posterior occipital/parietal regions (Sheldon, Farb, Palombo, & Levine, 2015), suggesting that accessing visual-perceptual information may allow individuals to re-experience memories more vividly (Greenberg and Rubin, 2003). On the other hand, endorsement of semantic memory ability was related to MTL–middle prefrontal connectivity (Sheldon et al., 2015), suggesting that higher-order control and organization are involved in a semantic memory style. Structurally, the tendency to recall EAMs from an egocentric perspective has been associated with greater precuneus grey matter volume in healthy young participants (Freton et al, 2014). Structural differences in the hippocampus have been associated with EAM performance among patient groups (Gilboa et al., 2005; Herold et al., 2013), and recently, among healthy individuals (Palombo et al., 2017). A few studies have related hippocampal volume in healthy individuals to episodic memory although the strength and direction of the relationship depends on many factors including age of participants (Chadwick, Bonnici, & Maguire, 2014; Van Petten, 2004 for review). Hippocampal volume has been found to relate more clearly to spatial memory (Erickson et al., 2009; Maguire, Woollett, & Spiers, 2006; Maguire et al., 2000) and to scene construction of fictitious events in healthy individuals (Irish et al., 2015). While these studies provide important insights into the neural correlates of individual differences in memory ability, relatively little is known about the association between EAM performance and structural differences in the brains of healthy individuals. Studying the neural correlates of such individual differences is a crucial step in understanding the complexities of EAM.

## 1.6 Transcranial magnetic stimulation

TMS is a form of noninvasive brain stimulation that uses magnetic fields to induce electrical currents that can depolarize small regions of the cortex. The frequency, intensity, and localization of stimulation determine the neural effects of TMS. Single pulse TMS is generally excitatory and is used on-line due to short-lasting effects, while repetitive TMS (rTMS), may be used off-line due to longer-lasting effects. Lower frequency rTMS (sending TMS pulses at 1 Hz or lower) is typically inhibitory, while the effects of higher frequency rTMS can be either inhibitory or excitatory partly depending on the intensity of stimulation (Parkin, Ekhtiari, & Walsh, 2015). Theta burst stimulation is a form of repetitive TMS using short bursts of low
intensity, high frequency (50 Hz) pulses repeated at 5 Hz (the theta rhythm) in different patterns. Continuous theta burst stimulation (cTBS) repeats these pulses continuously for 20-40 seconds and has been shown to have longer lasting inhibitory effects (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). Intermittent theta burst stimulation (iTBS) applies each burst for 2 seconds, repeated every 10 seconds, and is thought to have excitatory effects (Parkin et al., 2015). Theta burst stimulation has been shown to alter the amplitudes of motor evoked potentials measured from hand muscles (Di Lazzaro et al., 2005, 2008; Huang, Chen, Rothwell, & Wen, 2007). A slightly modified version of cTBS in which three 30 Hz pulses are repeated at 6 Hz at a higher intensity has been found to induce even greater suppression of motor evoked potentials than the standard version of cTBS (Goldsworthy, Pitcher, & Ridding, 2012).

1.6.1 Mechanisms of action

It is difficult to directly study the physiological mechanisms by which TMS works. Long-lasting effects of rTMS have been likened to long term potentiation (LTP) and depression (LTD) of synapses reported in animal studies using electrical stimulation (Huang, Chen, Rothwell, & Wen, 2007). Huang and colleagues demonstrated that the effects of theta burst stimulation are dependent on N-methyl-D-aspartate (NMDA) receptors in humans, which suggests the involvement of LTP and LTD. They administered memantine, a drug that acts on NMDA receptors involved in the induction of LTP and LTD, and then measured the effect of theta burst stimulation on the amplitude of motor evoked potentials. Huang and colleagues found that memantine blocked the inhibitory effect of cTBS and the excitatory effect of iTBS on motor evoked potentials. These results demonstrate that the after effects of theta burst stimulation are dependent on NMDA receptors, thereby suggesting that these effects likely involve plasticity-like changes similar to LTP and LTD (Huang, Chen, Rothwell, & Wen, 2007). Several additional studies have supported the idea that rTMS alters synaptic strength through mechanisms similar to LTP and LTD (for review, see Hoogendam, Ramakers, & Di Lazzaro, 2010).

TMS can also induce long-lasting effects beyond the site of stimulation, perhaps via neural oscillations. One study found that cTBS to the primary motor cortex led to 20 minute suppression of MEPs, and at least 30 minute alteration of cortical neural oscillations, primarily in the beta and theta band (Noh, Fuggetta, Manganotti, & Fiaschi, 2012). It has been suggested that
rTMS, being delivered at regular intervals, interacts with neural oscillations in a way that affects cognitive processes (Klimesch, Sauseng, & Gerloff, 2003). Neural oscillations may in fact be a more sensitive measure of TMS effects than behavioural measures, given that several studies have found oscillatory changes following TMS without finding behavioural changes (Hansenne, Laloyaux, Mardaga, & Anseaux, 2004; Holler, Siebner, Cunnington, & Gerschlager, 2006; Ortu, Ruge, Deriu, & Rothwell, 2009; Rossi et al., 2000). These studies and others, which will be described in greater detail below (Section 1.7.1), suggest that TMS can have widespread effects on the brain through the alteration of neural oscillations.

1.6.2 TMS investigation of the parietal cortex

A number of studies have successfully used TMS to alter cognitive performance, including working memory, perceptual discrimination, motor learning, object identification, attention, language, and visual imagery (For reviews, see Pascual-Leone, Walsh, & Rothwell, 2000; Luber & Lisanby, 2014). The parietal cortex is a common target due to its involvement in a wide array of functions. rTMS has been found to result in neglect-like spatial bias in a line bisection task when applied to the right precuneus (Mahayana, Tcheang, Chen, Juan, & Muggleton, 2014), and to disrupt self-other face discriminations when applied to the right inferior parietal lobe (Uddin, Molnar-Szakacs, Zaidel, & Iacoboni, 2006). Several recent studies have used TMS to examine parietal contributions to episodic memory. Yazar et al (2014) found that cTBS applied to the angular gyrus reduced source memory confidence judgments while sparing overall accuracy. Five consecutive days of rTMS to lateral parietal regions demonstrating high functional connectivity with the hippocampus has been shown to enhance associative memory and hippocampal-cortical connectivity (Wang et al., 2014), with effects lasting up to 15 days (Wang & Voss, 2015), and also to enhance precision of memory recollection (Nilakantan, Bridge, Gagnon, Vanhaerents, & Voss, 2017). A small number of studies have also used rTMS to examine the involvement of the precuneus in episodic memory. In one study, Bonni and colleagues found that cTBS to the precuneus led to enhanced context-dependent memory as indicated by fewer source memory errors, while no effect was found with posterior parietal or vertex stimulation (Bonni et al., 2015). The same group found that rTMS to the precuneus modestly enhanced episodic memory in patients with Alzheimer’s disease (Koch et al., 2017). In a third study, this group used graph theoretical measures to determine the effects of precuneus
cTBS on resting state functional connectivity (Mancini et al., 2017). Precuneus cTBS decreased both intra- and inter-modular functional connectivity of the left temporal pole at 5 minutes post-stimulation, and led to an increased number of nodes within the precuneus module at 15 minutes post-stimulation. The authors propose that the effects at 15 minutes post-stimulation reflect a compensatory mechanism in which temporary functional connections increase the centrality of the precuneus (Mancini et al., 2017). Together, these findings (Wang et al, 2014; Wang and Voss, 2015; Mancini et al., 2017) demonstrate that applying TMS to highly connected regions significantly alters widespread activity.

Only two studies to date have used TMS to investigate parietal contributions to EAM. Thakral et al (2017) used inhibitory TMS to examine the role of the left angular gyrus in EAM and episodic simulation. Following rTMS to either the left angular gyrus or a control region, participants saw cue words and were asked to either recall a past event (EAM task), imagine a future event (episodic simulation task), or generate related words (control task). Episodic memory and simulation responses were scored for internal and external details using a version of the Autobiographical Interview (Levine, Svoboda, Hay, Winocur, & Moscovitch, 2002), providing a measure of primarily episodic or semantic details, respectively. TMS to the left angular gyrus reduced the number of internal details in both episodic tasks, but did not affect performance on the control task, suggesting that the left angular gyrus plays a crucial role in both episodic memory and simulation (Thakral, Madore, & Schacter, 2017). Bonnici et al (2018) similarly found that angular gyrus stimulation reduced the number of internal details recalled, and additionally found that it reduced the number of autobiographical memories experienced from a first-person perspective. Based on these findings, the authors argue that the angular gyrus is crucial for integrating memory features within an egocentric framework, which enables the subjective experience of remembering. Although these studies are important first steps, more research is needed to understand the contributions of different parietal subregions to EAM.

1.6.3 Challenges to using TMS

While TMS can be a useful tool to study parietal contributions to memory, its effects on neurocognitive functions generally, and memory in particular are complex and often inconsistent. For example, while Thakral et al (2017) found that TMS to the angular gyrus
reduced the number of internal details as a group, closer inspection of the pattern of results reveals high variability in individual responses to TMS, with some participants showing the opposite pattern of results. Yazar et al (2014) used one-tailed t-tests to find a medium effect of angular gyrus stimulation on memory confidence ratings, although variability in the angular gyrus stimulation group was high relative to the mean (M = 0.55, SD = 0.22). fMRI-guided selection of stimulation site and multiple days of TMS seem to yield more consistent results (Wang et al, 2014), but even these methods lead to a small effect of parietal stimulation relative to sham stimulation. Combining TMS with neuroimaging techniques may offer some insight into the neural underpinnings of such variable effects.

Inconsistent results also exist when using TMS to alter basic measures of motor cortical excitability. One study examined the reproducibility of such TMS effects through an anonymous online survey of researchers and found that 50% of researchers were unable to reproduce published TMS effects (Héroux, Taylor, & Gandevia, 2015). 44% of respondents reported that they knew researchers who engaged in questionable research practices such as using selective screening techniques, rejecting data based on a ‘gut feeling’, and reporting only selective results. Thus, studies reporting weak or variable effects of TMS on behaviour should be interpreted cautiously.

### 1.7 Neural oscillations

Most accounts of episodic memory agree that coordination between widespread regions is necessary for retrieval, particularly between the MTL and various neocortical regions. Brain oscillations may be a mechanism by which this coordination takes place during memory retrieval. Neural oscillations represent synchronized, rhythmic, or repetitive activity allowing for interactions between regions (Nyhus & Curran, 2010). Specifically, communication between brain regions may occur through oscillatory synchrony. Neuronal assemblies phase synchronize within frequency bands, where two oscillations of the same frequency have the same phase angles (phase coupling), and also across frequency bands, where one frequency band modulates the activity of another frequency (cross-frequency coupling). Oscillations in the theta (3-7 Hz) and gamma (30-85 Hz) frequency bands may play a particularly important role in MTL-neocortical coordination.
Insights into the functions of neural oscillations originated from animal studies using single or multi-unit recordings and local field potentials (LFPs). Theta oscillations were first recorded from the rodent hippocampus during voluntary movement (Vanderwolf, 1969), and were later shown to be associated with successful spatial (Olvera-Cortés, Cervantes, & Gonzalez-Burgos, 2002) and recognition memory (Wiebe & Stäubli, 2001). Hippocampal theta oscillations were further found to modulate local gamma oscillations in the neocortex during navigation (Chrobak & Buzsáki, 1998; Sirota et al., 2008). This form of cross-frequency coupling, phase-amplitude coupling (PAC), refers to the relationship between the phase of low-frequency oscillations and the amplitude of high-frequency activity, which allows activity to be integrated across different spatial and temporal scales (Canolty & Knight, 2010). Theta-gamma PAC is likely involved in the formation and recall of long-term memories (for review, see Lisman & Buzsáki, 2008).

Taken together, these animal studies provide important insights but are limited in their ability to associate oscillatory activity with different types of memory. Human studies have similarly linked theta and gamma oscillations to memory using intracranial recordings in patients, electroencephalography (EEG), and magnetoencephalography (MEG). Note however that differences in recording methodologies between animal studies and non-invasive human studies make direct comparison difficult.

In humans, theta oscillations have been shown to mediate MTL-neocortical orchestration during memory retrieval and have been implicated in working (Payne & Kounios, 2009), episodic (Sederberg, Kahana, Howard, Donner, & Madsen, 2003), spatial (Kaplan et al., 2014) and autobiographical memory (Fuentemilla, Barnes, Duzel, & Levine, 2014; Steinworth, Wang, Ulbert, Schomer, & Halgren, 2010). During virtual spatial navigation, theta oscillations have been observed in MTL and neocortical regions including the mPFC, parietal lobes, and retrosplenial cortex (Kaplan et al., 2012; Ekstrom et al., 2005; Kahana et al., 1999). Theta phase coupling between these regions also occurs during spatial memory (Kaplan et al., 2014; Watrous et al., 2013) and autobiographical memory (Fuentemilla et al., 2014; Foster et al., 2013). Fuentemilla et al (2014) used MEG to measure oscillatory activity during recall of autobiographical memory, cued by personal recordings. Participants mentally re-experienced autobiographical memories, which were recorded prospectively, as they were played back to them for 30 seconds during recall. Theta power within the MTL was phase-synchronized with
both mPFC and precuneus theta, and greater synchrony predicted higher visual imagery ratings. Using implanted electrodes, Foster et al. (2013) also demonstrated theta phase locking during autobiographical memory retrieval between the retrosplenial cortex and MTL. It has further been suggested that the theta rhythm mediates the translation of MTL-allocentric to parietal-egocentric spatial information during spatial navigation and memory. The BBB model posits that the hippocampus receives input from parietal structures during troughs in the rhythm and transmits information to these structures during peaks (Byrne et al., 2007). Although phase coupling between the MTL, retrosplenial cortex, and parietal regions have been demonstrated, no studies have directly tested this proposed function of theta rhythms.

Gamma oscillations are associated with visual perception in humans (Hall et al., 2005; Hoogenboom, Schoffelen, Oostenveld, Parkes, & Fries, 2006; Tallon-Baudry & Bertrand, 1999), and may bind stimulus features together for perception (Nyhus & Curran, 2010 for review). Increases in gamma power have also been associated with successful memory encoding, but interestingly such power increases were associated with decreased global gamma synchrony (Burke et al., 2013). In contrast, one recent study found that EAM but not general semantic memory retrieval was associated with gamma phase synchrony (Fuentemilla et al., 2017). As in animals, the interplay between theta and gamma oscillations in humans may play an important role in memory. Kaplan et al. (2014) found that theta power in the mPFC was phase coupled with MTL theta as well as medial parietal gamma during spatial memory retrieval. Interestingly, MTL-parietal theta-gamma PAC has also been proposed as a mechanism for spatial information transfer between allocentric and egocentric perspectives during navigation (White et al., 2013), although experimental support for this claim is lacking. Using EEG during a virtual navigation task, White et al (2013) identified increased theta and gamma power within a medial-temporal-parietal source, which was associated with more efficient navigation. The authors speculate that these theta and gamma oscillations are coherent and represent the integration of egocentric and allocentric spatial representations needed for navigation, although it is important to note that they did not measure coherence or perspective integration directly.

These studies suggest that theta and gamma oscillations coordinate the activation of MTL and neocortical regions, allowing for communication between regions needed for memory recollection and spatial navigation. Few studies to date have examined theta and gamma
oscillations during EAM, however it seems likely that similar mechanisms underlie spatial memory, navigation, and EAM. Accordingly, it is possible that such oscillatory activity also plays a role in representing space during EAM recollection. Specifically, theta and gamma oscillations may play a role in coordinating activity between the hippocampus and precuneus during EAM retrieval. Such activity could allow allocentric representations in the hippocampus to be translated to egocentric representations in the precuneus.

1.7.1 Altering neural oscillations

Neural oscillations can be altered using direct brain stimulation in humans. One recent study used direct brain stimulation to alter neural oscillations and performance on a free recall task in patients based on multivariate classifiers (Ezzyat et al., 2016). Intracranially implanted electrodes were used to record activity while epilepsy patients were performing a free recall task, and a multivariate classifier identified oscillatory activity states associated with high and low encoding states which predicted remembered and forgotten information, respectively. When stimulation was delivered during a low encoding state (associated with later forgotten words), memory recall improved, but when stimulation was delivered during a high encoding state (associated with later remembered words), recall was inhibited. Furthermore, stimulation delivered during low encoding states led to increased evidence for high encoding states post stimulation, while the reverse pattern occurred when stimulation was delivered during high encoding states. This study demonstrates that neural oscillations and memory can be altered using direct brain stimulation and that these effects depend on neural activity at the time of stimulation. It further highlights the complex interactions between brain state and stimulation, and the difficulty of predicting exact effects of stimulation.

Recent studies have found that neural oscillations can also be altered non-invasively using TMS and that these alterations can be long-lasting (30-70 minutes), even after a single stimulation session. One study found that cTBS to the frontal eye field in four subjects led to higher synchronization across all frequency bands when comparing the stimulated hemisphere to the non-stimulated hemisphere, for up to one hour (Schindler et al., 2008). cTBS has also been shown to induce at least 30 minute alteration of beta and theta oscillations when applied to the primary motor cortex (Noh et al., 2012). Another study found that applying rTMS to the superior
parietal lobule induced changes in alpha power and alpha-gamma cross-frequency synchrony across parietal and frontal regions that predicted changes in visual working memory (Hamidi, Slagter, Tononi, & Postle, 2009). Repetitive TMS to the lateral parietal lobe has further been shown to reduce theta-alpha power and late-positive evoked potential amplitude during an object-location task, in conjunction with enhanced memory precision on this task (Nilakantan et al., 2017). Thus, it appears that the effects of TMS on neural oscillations are variable and likely depend on stimulation parameters as well as task demands. A review examining combined EEG-TMS studies found that rTMS and cTBS produced similar effect sizes on oscillatory activity (30-35% change relative to pre-TMS or sham), but that the after effects of cTBS (70 minutes) lasted longer than those of rTMS (29.5 minutes) (Thut & Pascual-Leone, 2010).

Evidence from invasive and non-invasive brain stimulation studies highlight the complexity of stimulation’s effects on behaviour and neural oscillations. Nonetheless, TMS provides a unique opportunity to casually examine the role of neural oscillations in memory non-invasively. As described above, theta and gamma oscillations originating from the MTL and neocortical regions are believed to play a crucial role in memory retrieval and recollection. Applying TMS to such neocortical regions may affect activity within a region and alter neural oscillations involved in memory, therefore altering memory retrieval.

1.8 Present research

This thesis aims to address unresolved questions about the temporal dynamics and the role spatial information plays in EAM retrieval. The primary goals of this thesis are twofold: First, I aim to explore how spatial information is represented during EAM both behaviourally and at the neural level. Scene construction theories argue that spatial information is represented early and ubiquitously by the hippocampus during EAM retrieval, but no studies have demonstrated this. The BBB model further suggests that spatial information is initially represented from an MTL-based allocentric perspective and later translated into a parietal-based egocentric perspective for mental imagery, navigation, and spatial memory. Whether this can be applied to EAM remains unclear. A second, related, overarching aim of this thesis is to examine the temporal dynamics of EAM recollection. Specifically, how do regions representing spatial information interact during retrieval? While computational models and fMRI studies have shed some light on this question,
much remains unclear. These questions will be addressed using a combination of behavioural, neuroimaging, and neurostimulation approaches.

Chapter 2 attempts to address these questions using a behavioural task that assesses the role of spatial information during memory retrieval and allows us to examine early spatial representations from a behavioural perspective, providing some insight into the temporal dynamics of EAM. An individual differences approach was taken to better understand the large variability in EAM tendencies and how these tendencies may relate to structural brain difference. By relating behavioural measures to brain volumes, we are able to obtain a general idea of how variations in the way individuals use spatial information to construct EAM are reflected at the neural level.

Chapters 3 and 4 use MEG to examine the dynamics of EAM recollection at the neural level, and TMS to enable causal inference about the roles of regions involved in EAM. Previous studies have shown that rTMS to the parietal lobe leads to long lasting changes in hippocampal-cortical functional connectivity. Based on these findings, I use TMS to directly alter the activity of the precuneus in order to observe system-level changes in activity, specifically in the MTL and other structures that comprise the autobiographical memory network. Activity following TMS is measured using MEG, allowing us to observe how altering precuneus activity alters EAM at the neural level. Specifically, Chapter 3 examines the temporal dynamics of EAM recollection at the neural level by assessing ERPs at different stages of memory retrieval across the brain. ERPs following a control TMS session (vertex stimulation) are compared to those following precuneus stimulation to assess how altering precuneus activity changes the temporal dynamics of EAM. Chapter 4 examines the power spectrum and measures of phase and phase amplitude coupling during memory retrieval to assess how regions representing spatial information interact dynamically, with a focus on theta and gamma oscillations. Again, control TMS is compared to precuneus TMS in order to observe how altering precuneus activity affects cross-brain connectivity.
2.1 Introduction

EAM enables reliving personally experienced past events, recalling the sensory information associated with that event (Greenberg and Rubin, 2003). Spatial information is a central aspect of EAM and may be represented from both allocentric (third-person) and egocentric (first-person) perspectives. As outlined in the Introduction, an extensive network of cortical and subcortical structures allows for flexible transformations across different viewpoints. Two key structures according to influential theories are the hippocampus, supporting allocentric spatial processing (O’Keefe and Nadel, 1978; Nadel & Hardt, 2004; Zaehle et al., 2007), and the posterior parietal neocortex, supporting egocentric processing during spatial memory and navigation (Committeri et al., 2004; Galati et al., 2000; Zaehle et al., 2007), and also during EAM (Freton et al., 2014).

Individuals can use both allocentric and egocentric strategies during navigation and spatial memory and may favour one strategy over the other (Bohbot, Iaria, & Petrides, 2004; Iglói, Zaoui, Berthoz, & Rondi-Reig, 2009). Similarly, individuals differ in their perspective-taking tendencies during autobiographical remembering (Rice & Rubin, 2011), with egocentric strategies being used more commonly than allocentric, although most use a combination of both (Freton et al., 2014; Sutin & Robins, 2008). The ability to experience events from an egocentric perspective is fundamental to vivid re-experiencing of EAMs (Bergouignan et al., 2014; Vogeley et al., 2004). Similarly, the type of perspective taken during recall can influence the conscious experience during remembering. Memories re-experienced from egocentric perspectives tend to include greater affective and sensory details compared to those recalled from allocentric perspectives (Berntsen & Rubin, 2006; McIsaac & Eich, 2002; Robinson & Swanson, 1993). The

1 A version of Chapter 2 was accepted for publication on March 28, 2017
relationship between egocentric perspective and vivid recall may be mediated by the precuneus, perhaps via its involvement in mental imagery (Gardini, Cornoldi, De Beni, & Venneri, 2006). Interestingly, the tendency to recall EAMs from an egocentric perspective has been associated with greater precuneus grey matter volume (Freton et al, 2014).

Beyond differences in perspective-taking, individuals vary greatly in their overall ability to recall EAMs. Cases of highly superior and severely deficient EAM have been identified in healthy individuals with otherwise normal cognitive functions (LePort et al., 2012; Palombo et al., 2015). Even among individuals within the normal range of EAM, there is variability between subjective ratings of vividness and the use of different memory strategies (D’Argembeau and Van der Linden, 2006; Palombo et al., 2013). Trait-like differences in episodic and semantic remembering are further related to intrinsic functional connectivity patterns (Sheldon et al., 2015). Furthermore, differences in autobiographical and episodic memory ability have been related to variability in hippocampal volumes in patients (Gilboa et al., 2005; Herold et al., 2013) and healthy individuals (Chadwick et al., 2014), although the nature of this relationship is complex (Van Petten, 2004). Hippocampal volume has also been related to spatial memory, with larger hippocampi predicting greater spatial memory in healthy individuals (Erickson et al., 2009; Maguire et al., 2006; Maguire et al., 2000), and to scene construction of fictitious events in healthy older adults (Irish et al., 2015). Thus, structural differences in the hippocampus appear to be related to spatial memory and scene construction, and possibly to autobiographical and episodic memory abilities.

These studies demonstrate that the subjective experience of remembering in EAM varies across healthy individuals, that these differences pertain to spatial representations (Rice and Rubin, 2011; Bohbot et al., 2004), and may be represented in the brain structurally (Freton et al, 2014; Chadwick et al., 2014) and functionally (Sheldon et al. 2015). Structural differences may reflect more stable recollection tendencies and consistent reliance on certain strategies (Kanai & Rees, 2011).

In the present study, we cued participants with familiar locations and non-locations and related behavioural performance to regional brain volumes. As described in the Introduction, space-based theories of memory view spatial context reinstatement as an early, crucial process
associated with the hippocampus (Hassabis and Maguire, 2007; Burgess et al., 2001; Robin et al., 2015). Thus, we hypothesized that cueing participants with familiar locations would serve as a shortcut to scene construction, allowing them to access memories more easily and recollect them more vividly. This ability to benefit from spatial cues may vary depending on hippocampal volume, in line with the established relationship between hippocampal volume and spatial memory (Maguire et al., 2000; Maguire et al., 2006; Erickson et al., 2009) and scene construction (Irish et al., 2015). Based on the proposed early function of spatial context reinstatement, we further expected that participants would demonstrate a tendency to recall locations before other information regardless of cue type, and that this may also vary depending on hippocampal volume. Finally, we predicted that egocentric over allocentric remembering would be associated with greater vividness and re-experiencing of memories (McIsaac and Eich, 2002; Robinson and Swanson, 1993; Berntsen and Rubin, 2006), and that the tendency to recall events from an egocentric perspective would be associated with precuneus volume.

2.2 Materials and Methods

2.2.1 Participants

63 healthy young adults (21 males, mean age = 24.3, SD = 3.5, range = 19-35) participated in the experiment. Participants were recruited from the Rotman Research Institute’s healthy volunteer pool. Participants had completed an average of 16.7 years of formal education (SD = 2.0), were all native or fluent English speakers, had normal or corrected-to-normal vision, and were free from a history of neurological illness or injury, psychiatric condition, substance abuse, or serious medical conditions. All participants provided informed consent prior to participating in the experiment in accordance with the Rotman Research Institute/Baycrest Hospital ethical guidelines.

2.2.2 Episodic autobiographical memory

2.2.2.1 Pre-study stimulus collection interview

At least 48 hours prior to the study, participants provided the names of familiar places, objects, people, and fruits and/or vegetables in a telephone interview. Locations, people and objects were used as cues because they are elements that commonly make up an event (Addis et al., 2009; Burgess et al., 2001). Fruits and vegetables were used as a comparison as they are less
commonly a central element of events. Participants were instructed to name the first fifteen items that came to mind and to limit items to those encountered within the past year. For the places category, participants were allowed to name multiple locations in the same building (i.e. my office, the cafeteria), so long as these were distinct enough to serve as independent cues for personal memories. Participants could also name public places, but could not name places tied exclusively to a particular person (e.g. could not use “my friend’s house”). For objects, participants were told to provide objects that were unique and personally meaningful, but that were not tied exclusively to a particular location (e.g. could not use “my TV chair”). To disguise the purpose of this interview, participants were led to believe that this was a study aimed at collecting norms of familiar items. Cue length was equated within less than 3 characters on average across all categories.

2.2.2.2 Computerized task

Based on the telephone interview, sixty cue words were created for each participant, 15 per category. E-Prime 1.2 software was used to display the items and collect response data. Items were presented in a randomized order, with a break after every 15 items. Participants were instructed to use the words as cues in order to recall personal events that are specific in time that had occurred in approximately the last year, not including the past week. Specific events were defined as “past events from a specific time and place for which you were personally involved. Events are defined as occurring within a day or less. For example, a three-week vacation is not considered a specific event, but something that happened on one day during your vacation is considered a specific event.” Cue words were displayed for a maximum of 20 seconds and participants were instructed to retrieve a specific past event related to the cue as quickly as possible. Participants were asked to press the spacebar as soon as a memory came to mind. Trials in which no memory was retrieved were discarded. The retrieval phase was terminated when the spacebar was pressed, and an elaboration phase followed in which participants were prompted to imagine the event in as much detail as possible for 15 seconds. Following the elaboration phase, participants saw a slide asking “What was the very first thing that came to mind”, and had to choose one of the following five options: object, person, place, action, other. They next typed a brief description of the first thing that came to mind when recalling the event. Next, participants rated the memory on eight scales aimed at measuring different phenomenological characteristics of the memory. They were given a maximum of 6.5 seconds
Participants were asked to estimate the date of the event (1 = less than 1 month, 2 = 1 month, 3 = 1-3 months, 4 = 3-6 months, 5 = 6 months to 1 year), effort required to bring the event to mind (1 = very easy, 6 = very effortful), feelings of re-experiencing the event (1 = not at all, 6 = completely), emotionality (1 = detached, 6 = intense emotional experience), recall of setting (1 = not at all, 6 = distinctly), visual details (1 = a little, 6 = a lot), sound details (1 = little, 6 = a lot), and perspective (1 = saw event through my own eyes, 6 = saw myself from an external perspective) (Scales adapted from Addis et al., 2007; Arnold, McDermott, & Szpunar, 2011).

Participants were instructed to rate the experience of remembering and not the event itself. Participants completed practice trials to familiarize themselves with the task before moving on to the test trials. See Figure 2.1 for a depiction of the episodic autobiographical memory task.

Figure 2.1. Episodic autobiographical memory paradigm. There were no time limits for the “first thing that came to mind” selection or the written description. All rating scales were limited to 6.5 seconds. Recall of setting rating scale is shown here as an example.

### 2.2.3 Survey of Autobiographical Memory (SAM)

61 participants completed the SAM prior to completing the episodic autobiographical memory task to assess self-reported episodic autobiographical, semantic, and spatial memory, in addition to future prospection (Palombo et al., 2013). SAM data were not collected for 2 participants due to time constraints. Participants rated the strength of their agreement with a total of 26 statements using a 5-point Likert scale (1 = strongly disagree, 2 = disagree somewhat, 3 = neither agree not disagree, 4 = agree somewhat, 5 = completely agree). Instructions were given for each set of questions.
2.2.4 MRI data acquisition

MRIs from 42 participants were obtained following completion of the behavioural portion of the study. MRIs from 21 participants were not collected due to feasibility and because a priori power analysis based on Freton et al. (2014) indicated a minimum sample size of 27 was required to obtain power of 95% for the parietal lobe. All anatomical scans were acquired using the same 3.0 Tesla Siemens full-body MRI machine. Structural images were acquired using whole-brain magnetization prepared rapid gradient-echo (MP-RAGE) 3-D T1-weighted scans (TR = 2000 msec, TE = 2.63 msec, TI = 1100, 1.0 mm thick, FOV = 256 x 192 mm for 37 participants; TR = 2400 msec, TE = 2.43 msec, TI = 1000, 1.0 mm thick, FOV = 256 x 256 mm for 5 participants). Independent samples t-tests confirmed that the use of different scan parameters did not influence the consistency of FreeSurfer volumes (precuneus volume: t(40) = .174, p = .863); hippocampal volume: t(40) = .145, p = .885; total intracranial volume: t(40) = .837, p = .407).

2.2.5 Behavioural data analysis

2.2.5.1 Reaction time and rating scales

Repeated-measures analyses of variance (ANOVAs) were used to compare reaction time and rating scales for place, person, object, and fruit/vegetable-cued memories to determine the effect of location cues on the subjective experience of remembering. To address the hypothesis that location cues would lead to less effortful recall and more vivid recollection, we examined rating scales for reaction time, re-experiencing rating, effort rating, setting details, visual details, and perspective rating. Perspective ratings were log transformed as they violated normality. Post hoc comparisons were Bonferroni corrected. Based on these results, person cued memories were chosen as a comparison for future individual differences analyses as they were most similar to place cued memories in terms of overall vividness (re-experiencing, setting, visual details), thus allowing for a more conservative analysis.

Cue-based difference scores were calculated to assess variability in the way individuals respond to location cues. Person-place difference scores were calculated by subtracting mean person- and place-cued ratings for each participant. We limited calculation of person-place difference scores to rating scales that directly addressed a priori hypotheses. Difference scores were calculated for ratings for effort, re-experiencing, setting, and visual details such that a higher value indicated
that place-cued memories were recalled with less effort, more highly re-experienced, with greater setting and visual details. For re-experiencing, setting, and visual details, person-cued ratings were subtracted from place-cued ratings. For effort, place-cued ratings were subtracted from person-cued scores to compensate for the fact that low ratings indicate less effort. These difference scores were used in the anatomical analyses described below to determine whether hippocampal volume is associated with the ability to benefit from spatial cues.

To examine how spatial perspective during recollection influences the subjective experience of remembering, partial correlations between average rating scales were performed (FDR corrected for multiple comparisons, p < .05). Log perspective ratings were reversed such that higher values indicated greater egocentric remembering and lower values indicated greater allocentric remembering. Age and gender were entered as covariates for all behavioural partial correlations as previous studies have found age- and gender-related differences in both autobiographical memory (for review, see Piefke and Fink, 2005; Grysman and Hudson, 2013) and spatial processing (for review, see Coluccia & Louse, 2004; Wolbers & Hegarty, 2010). To test the hypothesis that egocentric over allocentric remembering would be associated with greater vividness and re-experiencing of memories, we examined the association between perspective rating and re-experiencing, setting, and visual details.

2.2.5.2 First to mind forced choice odds ratios

56 participants completed the forced choice selection indicating the first thing that came to mind when recalling the event. Six participants only completed the free description and not the forced choice selection of first to mind, as it was added to the experimental design after they had participated. To determine the likelihood of selecting place over other categories as the first thing that came to mind, we first excluded responses that matched the cue (e.g. location-cued memories where participants selected place as the first thing that came to mind). This resulted in the inclusion of 71.1% of place responses and 66.5% of person responses for subsequent analyses. Each response type was then tallied across all other cue-types, allowing for calculation of likelihood ratios for each participant. To form a ratio of place responses versus person responses, the proportion of place responses for person, object, and fruit/vegetables cues, and the proportion of person responses for object, place, and fruit/vegetable cues were computed. The place proportion was then divided by the person proportion. This ratio represented the overall
likelihood of a participant to select place as the first thing that came to mind when they were not cued with a location, compared to their likelihood of selecting person when not cued with a person (place-person ratio). In other words, it represented the likelihood of spontaneously reporting a location when not cued with one. The ratio for one participant was dropped from further analyses due to being over 4 standard deviations above the group mean. To test the hypothesis that the tendency to recall location information first would be associated with faster recall of memories, a partial correlation was calculated between place-person ratio and reaction time.

2.2.6 Anatomical analyses

2.2.6.1 Freesurfer reconstruction and segmentation

MRIs from 42 participants were analyzed using FreeSurfer’s automated brain segmentation software (FreeSurfer version 5.3, http://surfer.nmr.mgh.harvard.edu), described in detail elsewhere (Fischl et al., 2004; Fischl & Dale, 2000). Briefly, this analysis involves skull stripping, registration to Talairach space, subcortical gray and white matter segmentation, intensity normalization, gray and white matter boundary identification, topology correction, and registration to spherical atlas. Previous studies comparing FreeSurfer’s automatic segmentation of cortical and subcortical volumes to other segmentation methods such as manual tracing have demonstrated high reliability in healthy adults (Wonderlick et al., 2009), specifically for whole hippocampal volumes in young adults (Wenger et al., 2014).

Final FreeSurfer outputs were visually inspected for accuracy or processing errors. Volumes for the precuneus, the hippocampus, and a measure of total intracranial volume (TIV) were used for statistical analyses. Figure 2.2 illustrates the output of the Freesurfer segmentation.
2.2.6.2 Statistical analyses

A series of partial correlations were performed to examine a priori relationships between inter-subject volumetric variations of the hippocampus/precuneus and behavioural performance. As we did not have specific laterality hypotheses, volumes for the left and right hemispheres were summed in order to reduce the number of analyses performed. Age, gender, and estimated total intracranial volume were entered as covariates.

To test the hypothesis that hippocampal volume influences the ability to benefit from spatial cues, partial correlations between hippocampal volume and cue-based difference scores for effort, re-experiencing, setting, and visual details were performed. The partial correlation between hippocampal volume and place-person ratio was calculated to examine whether the tendency to recall location before other information would vary depending on hippocampal volume. Finally, the association between precuneus volume and perspective rating was examined to determine whether egocentric remembering is associated with precuneus volume. The reliability of all correlations (95% confidence intervals) was based on 1000 bootstrap resamples.
Where multiple comparisons were performed, results were corrected (False discovery rate (FDR) corrected, p < .05) and adjusted p-values are reported. All analyses were performed using SPSS.

2.2.7 Exploratory analyses

The present study tested a set of a priori hypotheses about the roles of the hippocampus and precuneus in spatial aspects of EAM. However, a wider set of brain regions are involved in EAM, spatial memory, and scene construction more generally. Neuroimaging and neuropsychological studies have identified the parahippocampal and retrosplenial cortices as important scene-related areas. In the context of spatial navigation, the parahippocampal cortex is important for encoding a representation of the local scene which can later be remembered, while the retrosplenial cortex is involved in orienting oneself in a broader spatial environment (for review, see Epstein, 2008). Specifically, it has been proposed that the retrosplenial cortex plays a role in translating between allocentric and egocentric representations during spatial memory and navigation (Epstein, 2008), and possibly episodic autobiographical memory (Burgess et al, 2001; Byrne et al, 2007). A distributed network of regions are also involved in scene construction, including the hippocampus, parahippocampal gyrus, retrosplenial and posterior parietal cortices, middle temporal cortices, and medial prefrontal cortex (Hassabis et al., 2007). Notably, construction of fictitious scenes is related to the structural integrity of regions within the frontal and parietal lobes as well as the parahippocampal gyrus and posterior hippocampus (Irish et al., 2015). Specifically, Brodmann area 7 both medially (precuneus) and laterally (superior parietal lobe), and the medial prefrontal cortex have been implicated in scene construction (Irish et al., 2015) and EAM (Svoboda, McKinnon, Levine, 2006; Addis et al., 2012), with the later possibly providing schematic support for retrieval (Gilboa & Moscovitch, 2017; Hebscher & Gilboa, 2016) and monitoring (Hebscher, Barkan-Abramski, Goldsmith, Aharon-Peretz, & Gilboa, 2016; Hebscher & Gilboa, 2016) of personally relevant information. Thus, it is possible that structural differences within these regions may also relate to behavioural measures in the current study.

To determine the possible contributions of a wider set of regions to spatial aspects of EAM, a series of exploratory multiple regressions were performed. Behavioural measures used in a priori analyses (perspective rating, place-person ratio, cue-based difference scores for effort rating, re-experiencing, setting, and visual details) were used as dependent variables, while controlling for age, gender, and total intracranial volume. Freesurfer derived volumes for the precuneus,
hippocampus, superior parietal lobe, isthmus cingulate (corresponding to the retrosplenial cortex), parahippocampal cortex, and the medial orbitofrontal cortex were entered as predictors. The superior parietal lobe, retrosplenial, parahippocampal and medial orbitofrontal (corresponding to the medial prefrontal cortex) cortices were chosen based on their established roles in spatial memory, scene construction, and EAM, as described above. Multiple regressions using averaged behavioural measures of effort, re-experiencing, setting, and visual details as dependent variables were also performed. As in previous analyses, volumes for left and right hemispheres were combined.

2.3 Results

2.3.1 Behavioural results

2.3.1.1 Results by cue type

Rating scales for place, person, object, and fruit/vegetable cued memories were compared to determine the effect of location and non-location cues on the subjective experience of remembering. Repeated measures ANOVAs revealed significant differences based on cue type for effort rating (F(3,186) = 25.16, p < .001, \(\eta^2 = .29\)), re-experiencing (F(3,186) = 28.65, p < .001, \(\eta^2 = .32\)), setting (F(3,186) = 22.46, p < .001, \(\eta^2 = .27\)), visual details (F(3,186) = 20.49, p < .001, \(\eta^2 = .25\)), and perspective rating (F(3,186) = 2.96, p = .047, \(\eta^2 = .05\)), but not reaction time (F(3,186) = .89, p = .449, \(\eta^2 = .01\)). Posthoc pairwise t-test comparisons (Bonferroni corrected) revealed that place-cued memories were recalled with less effort than fruit/vegetable-cued memories (p = .0005). Compared to fruit/vegetable and object cued memories, place cued memories were re-experienced more vividly, and with greater setting and visual details (all p’s < .001; see Table 2.1). Place-cued memories were also recalled from more of an allocentric perspective compared to person-cued memories (p = .037). These results indicate that the use of location cues may influence the nature of autobiographical recall and recollection.

Notably, person-cued memories were recalled with similar or lower levels of effort, re-experiencing, setting, and visual details, than place-cued memories. Based on these findings, subsequent analyses examined place and person cued memories as they are most similar to one another and allow for a more conservative analysis. All values are reported in Table 2.1.
Table 2.1. Repeated measure ANOVA post-hoc comparisons and descriptive statistics

<table>
<thead>
<tr>
<th>Rating scale</th>
<th>Cue</th>
<th>M</th>
<th>SD</th>
<th>F</th>
<th>Post-hoc comparison t-statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fruit/Veg</td>
</tr>
<tr>
<td>Effort</td>
<td>Fruit/Veg</td>
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<td>0.94</td>
<td>25.16**</td>
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<td></td>
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<td>0.78</td>
<td>3.89*</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Person</td>
<td>2.07</td>
<td>0.80</td>
<td>6.62**</td>
<td>4.97**</td>
</tr>
<tr>
<td></td>
<td>Place</td>
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<td>0.86</td>
<td>5.29**</td>
<td>2.52</td>
</tr>
<tr>
<td>Re-experiencing</td>
<td>Fruit/Veg</td>
<td>3.35</td>
<td>0.85</td>
<td>28.65**</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Object</td>
<td>3.62</td>
<td>0.89</td>
<td>-3.09*</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Person</td>
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<td>-6.93**</td>
<td>-5.44**</td>
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<tr>
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<td>-6.45**</td>
<td>-4.30**</td>
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<td>-6.54**</td>
</tr>
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<td>0.90</td>
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<td>-5.75**</td>
</tr>
<tr>
<td>Perspective</td>
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<td>2.96*</td>
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</tr>
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<td>Object</td>
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<td>0.96</td>
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<td>-</td>
</tr>
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<td>0.30</td>
<td>1.07</td>
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<td>-2.13</td>
</tr>
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<td>0.89</td>
<td>-</td>
</tr>
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<td>5004.37</td>
<td>2196.59</td>
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<td>-</td>
</tr>
</tbody>
</table>

Note: Significant values are asterisked. Post-hoc comparisons reported only where overall ANOVA is significant. T-statistics for corresponding post-hoc comparisons are listed at column-row intersections. p-values Bonferroni corrected for multiple comparisons.

* p < .05 ** p < .001

M= Mean, SD = Standard deviation
2.3.1.2 Results collapsed across cue type

Mean place-person ratio across all participants was 2.22 (SD = 2.39), indicating that on average participants were over 2 times more likely to spontaneously select place over person as the first thing that came to mind. Higher ratios represent an increased likelihood of reporting a place over a person as the first thing that came to mind, when not cued with a location. Notably, this ratio was highly variable across participants, demonstrating individual differences in reporting the first content established during memory retrieval. See Figure 2.3.

![Figure 2.3](image)

Figure 2.3. Frequency distribution for place-person ratio, by participant. The majority (37 out of 55 participants) had ratios greater than 1, meaning they were more likely to report place over person as the first thing that came to mind when recalling a memory, when they were not cued with a location. Higher ratios represent an increased likelihood of spontaneously selecting place as the first thing that came to mind. The dotted line represents the point at which place and person responses were equal.

Reaction time and place-person ratio were significantly correlated ($r = -.40$, 95% CI [-.58, -.13], $p = .003$). See Figure 2.4a. After correction for multiple comparisons, perspective ratings were trending towards an association with setting ratings ($r = .29$, 95% CI [.05, .53], $p = .066$), such that the tendency to recall memories from an egocentric perspective was associated with higher recall of setting. Perspective rating was not associated with visual details ($r = .14$, 95% CI [-.08, .37], $p = .810$) or re-experiencing ratings ($r = -.08$, 95% CI [-.30, .21], $p = .566$). Notably, the correlation between perspective and setting was significantly greater than that of perspective and
visual details ($z = 1.7, p = .048$), as well as perspective and re-experiencing ($z = 2.6, p = .005$). See Figure 2.4b-d. While the association between perspective rating and setting did not remain significant after correction for multiple comparisons ($p = .032$, uncorrected), these findings may suggest a tentative relationship between egocentric recall and establishing a clear setting representation that may not necessarily hold true for other qualities of re-living a past event. Overall, these results indicate that individuals who more often spontaneously recalled location information first also tended to recall memories more quickly. Early spatial representations can be important for EAM recollection, possibly serving to reinforce EAM reconstruction, but are not a pre-condition for rich re-experiencing and recollection.

Figure 2.4. Partial correlations between behavioural measures holding age and gender constant. Log transformed perspective ratings were reversed such that higher values indicate egocentric ratings. (a) Participants with a higher place-person ratio (more likely to recall location before other information when not cued with locations) also recalled memories more quickly (faster reaction times). (b) Egocentric recall of memories was trending towards an association with greater recall of the setting of an event. The bottom panel shows non-significant partial correlations between perspective rating and (c) re-experiencing ratings, and (d) visual details ratings. Standardized residual scores are plotted, with 95% confidence intervals indicated by dashed lines.
2.3.1.3 Additional behavioural results

To assess whether subjective global ratings of memory traits can predict the extent of benefit from spatial cues, partial correlations were calculated between survey of autobiographical memory (SAM) scores and cue-based difference scores. None of the SAM subscales (episodic autobiographical memory, semantic memory, spatial memory, future prospection) were significantly correlated with person-place difference scores for perspective, effort, or re-experiencing ratings (all p’s > .096, FDR corrected for multiple comparisons). Note that the SAM episodic and spatial items may not correspond to the same constructs as measured by the EAM task, which may explain the lack of significant findings for these subscales. While the cue-based difference scores reported here measure the specific advantage for place over person cues, the SAM episodic subscale assesses subjective richness of autobiographical memory in general, and the SAM spatial subscale assesses navigational abilities.

2.3.2 Anatomical results

2.3.2.1 Results by cue type

The partial correlation between person-place effort rating and hippocampal volume revealed that participants who recalled place-cued memories with less effort than person-cued memories had larger hippocampal volumes (r = .35, 95% CI [.07, .58], p = .030, uncorrected), although this did not survive correction for multiple comparisons (p = .120, corrected). See Figure 2.5a. No significant associations were found between hippocampal volume and re-experiencing, setting, or visual details (see Table 2.2). These findings indicate a possible association between hippocampal volume and the ability to recall place-cued memories with less effort than person-cued memories that failed to survive correction for multiple comparisons.

To further examine the possible contributions of different hippocampal subfields to the ability to benefit from spatial cues, we subsequently performed an exploratory analysis using FreeSurfer version 6.0’s automated hippocampal segmentation. While whole hippocampal volume segmentation has been found to be reliable, subfield segmentations from previous versions of FreeSurfer’s hippocampal segmentation have been found to be inconsistent with anatomy (de Flores et al., 2015; Pluta, Yushkevich, Das, & Wolk, 2012; Wisse, Biessels, & Geerlings, 2014), raising questions about the validity and reliability of this tool. The most recent version of this
tool (FreeSurfer version 6.0) addresses many of the concerns from previous versions by using a new statistical atlas constructed from a combination of ultra-high resolution ex vivo MRI and manual annotations for neighbouring structures (Iglesias et al., 2015). This new algorithm provides reconstructions for the CA1, CA2/3, CA4, granule cell layer of dentate gyrus (GC-DG), parasubiculum, presubiculum, subiculum, hippocampus-amygdala-transition-area (HATA), fimbria, molecular layer, hippocampal fissure, and tail. To determine the contributions of different hippocampal subfield volumes to the ability to benefit from spatial cues, partial correlations between subfield volumes and cue-based difference scores for effort, re-experiencing, setting, and visual details were performed. Volumes for right and left CA1, CA2/CA3, and GC-DG were selected, in line with previous studies examining the association between episodic memory and these subfields (Chadwick et al., 2014). These analyses revealed that participants who recalled place-cued memories with less effort than person-cued memories had greater left CA1 (r = .38, 95% CI [.03, .65], p = .016, uncorrected), right GC-DG (r = .40, 95% CI [.06, .65], p = .012, uncorrected), and right CA2/CA3 (r = .47, 95% CI [.187, .69], p = .002, uncorrected) volumes. Only the association between person-place effort rating and right CA2/CA3 volume survived FDR correction for multiple comparisons (p = .048, corrected). No other person-place difference scores were significantly associated with any other subfield volume (all p’s > .128, corrected). These findings suggest that there may be an association between the ability to recall place-cued memories with less effort than person-cued memories and right CA2/CA3 hippocampal volume.

2.3.2.2 Results collapsed across cue type

Perspective ratings were significantly associated with precuneus volume (r = .40, 95% CI [.08, .67], p = .012), such that individuals who tended to recall memories from an egocentric perspective had larger precuneus volumes (Figure 2.5d). This finding supports our prediction that egocentric remembering relies on the parietal cortex, specifically the precuneus. Place-person ratio was not significantly correlated with hippocampal volume. (r = .10, 95% CI [-.24, .46], p = .552).
Figure 2.5. Partial correlations between behavioural measures and ROIs holding age, gender, and total intracranial volume constant. (a) Non-significant association between hippocampal volume and the tendency to recall place-cued memories with less effort than person-cued memories. (b) Participants who recalled memories more egocentrically had significantly larger precuneus volumes. Standardized residual scores are plotted, with 95% confidence intervals indicated by dashed lines.

Table 2.2. Partial correlations between behavioural measures and FreeSurfer volumes

<table>
<thead>
<tr>
<th>Volume</th>
<th>Effort Difference</th>
<th>Re-experiencing Difference</th>
<th>Visual Details Difference</th>
<th>Setting Difference</th>
<th>Place-person Ratio</th>
<th>Perspective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hippocampus</td>
<td>0.35</td>
<td>0.12</td>
<td>0.10</td>
<td>-0.06</td>
<td>0.10</td>
<td>-</td>
</tr>
<tr>
<td>Precuneus</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.40*</td>
</tr>
</tbody>
</table>

Note: Difference measures for effort, re-experiencing, visual, and setting details represent cue-based difference scores between place- and person-cued memories. One dash indicates a correlation that was not performed because it did not address a priori hypotheses.

* p < .05
Table 2.3. Descriptive statistics for brain regions used in a priori and post hoc analyses

<table>
<thead>
<tr>
<th>Volume</th>
<th>M</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precuneus</td>
<td>19796.19</td>
<td>2077.62</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>8766.93</td>
<td>726.47</td>
</tr>
<tr>
<td>PHC</td>
<td>4540.33</td>
<td>523.94</td>
</tr>
<tr>
<td>RSC</td>
<td>5148.98</td>
<td>727.03</td>
</tr>
<tr>
<td>mOFC</td>
<td>10895.24</td>
<td>1364.83</td>
</tr>
<tr>
<td>Superior parietal</td>
<td>26198.79</td>
<td>2761.13</td>
</tr>
</tbody>
</table>

Note: total volume for left and right hemispheres summed are listed (mm$^3$)

$PHC =$ parahippocampal cortex, $RSC =$ retrosplenial cortex, $mOFC =$ medial orbitofrontal cortex

2.3.2.3 Exploratory results

Exploratory analyses examining the association between a wider set of brain regions and behavioural performance revealed one significant regression. The results of this multiple regression indicated that the 6 predictors significantly explained the variance in perspective rating, after accounting for age, gender, and total intracranial volume ($F(9,32) = 2.80, p = .015$, $R^2 = .44$). Precuneus volume significantly predicted perspective rating ($\beta = .67, t = 2.28, p = .008$), while none of the other brain regions significantly predicted perspective rating (See Table 2.4). Interestingly, age ($\beta = .49, t = 3.14, p = .004$), and gender ($\beta = .52, t = 2.67, p = .012$) both predicted perspective rating, with older participants and females being more likely to experience memories from an egocentric perspective.

No other significant regression models were found (all $p$’s $> .306$), suggesting no other significant associations between the behavioural measures of interest and a wider set of brain regions involved in EAM. The results of these non-significant regression models are listed in Appendix A.
Table 2.4. Exploratory regression analysis on predictors of perspective rating scale

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Step 1</th>
<th></th>
<th>Step 2</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>t-value</td>
<td>$R^2$</td>
<td>β</td>
<td>t-value</td>
<td>$R^2$</td>
<td>$R^2$ change</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>.40</td>
<td>2.75*</td>
<td>.23*</td>
<td>.49</td>
<td>3.14**</td>
<td>.44*</td>
<td>.21</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>.39</td>
<td>2.27*</td>
<td></td>
<td>.52</td>
<td>2.67*</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>TIV</td>
<td>.14</td>
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<td></td>
<td>-.04</td>
<td>-0.13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precuneus</td>
<td></td>
<td></td>
<td>.67</td>
<td>2.83**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hippocampus</td>
<td></td>
<td></td>
<td>-.17</td>
<td>-0.92</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PHC</td>
<td></td>
<td></td>
<td>.03</td>
<td>0.20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RSC</td>
<td></td>
<td></td>
<td>-.33</td>
<td>-1.72</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mOFC</td>
<td></td>
<td></td>
<td>-.14</td>
<td>-0.64</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superior parietal</td>
<td></td>
<td></td>
<td>.18</td>
<td>0.98</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

$TIV = \text{total intracranial volume, PHC = parahippocampal cortex, RSC = retrosplenial cortex, mOFC = medial orbitofrontal cortex}$

* $p < .05$ ** $p < .01$

2.4 Discussion

The subjective experience of remembering personally experienced past events varies greatly from one individual to the next. The purpose of the current study was to determine how individuals differ in EAM recall tendencies, specifically those related to spatial information, and to identify neuroanatomical correlates of these differences. We found that while spatial information contributes to the efficiency and phenomenology of autobiographical remembering, there is significant variability in spatial aspects of EAM that is systematically related to select brain regions involved in memory and perception.

2.4.1 Behavioural findings

The majority of participants in the current study demonstrated an overall tendency to spontaneously recall location before other information, even when cues were non-spatial. These data are consistent with models that have emphasized the importance of spatial information in EAM (Hassabis and Maguire, 2007; Burgess et al., 2001). One recent study found that
individuals spontaneously generate a spatial context for imagined events and that events with spatial context are later recalled more vividly compared to events with no spatial context (Robin et al., 2015). Our results extend this finding to EAM, in line with recent conceptualizations that suggest similar processes underlie mental construction of a scene (Hassabis and Maguire, 2007) or an event (Rubin & Umanath, 2015), regardless of whether imagined or previously experienced. More importantly, here we demonstrate a temporal precedence for recall of spatial information during EAM recollection, with participants often reporting that location information came to mind first. Furthermore, individuals who more often displayed this tendency also recalled memories more quickly. Note that this finding may apply to individuals at extreme ends of the spectrum (those very likely to report location first and those very unlikely to report location first), but may not necessarily hold true for individuals with more moderate tendencies in either direction. These findings are in line with the proposed early role of spatial representations during memory retrieval (Miller et al., 2013), and suggest that some individuals are better able to capitalize on early spatial information and thus recall memories more quickly. However, our data also suggest that early scene construction is not obligatory and that EAMs can be accessed through other kinds of information, suggesting scene construction might better be viewed as facilitating autobiographical recall than as a critical scaffold for it.

While early spatial information appears to aid memory retrieval, egocentric remembering is thought to be crucial for later mental imagery and re-experiencing of memories (Bergouignan et al., 2014; Nigro & Neisser, 1983; Vogeley et al., 2004). In the current study we found tentative evidence that participants who tended to recall memories from an egocentric perspective recollected memories with higher setting ratings. This correlation did not survive correction for multiple comparisons (p = .069), although note that the association between perspective and setting was significantly greater than that of perspective and visual details or feelings of re-experiencing. This finding is interesting given that we expected to find a relationship between egocentric remembering and greater vividness and re-experiencing of memories. Participants in this study demonstrated flexibility in their perspective-taking such that they rarely reported memories from a purely allocentric perspective, and rated events as more egocentric on average. This could explain why we did not find an association between egocentric remembering and re-experiencing ratings or visual details, and also why we found a marginally significant relationship between egocentric remembering and setting ratings. The presence of at least some
egocentric information may have allowed participants to report high levels of re-experiencing, setting and visual details for the majority of memories. Future studies are needed to determine the reliability and strength of the relationship between egocentric remembering and spatial recall. Notably, the tentative pattern reported here is compatible with the ‘event memory’ framework recently proposed (Rubin and Umanath, 2015) that emphasizes the relationship between the mental construction of scenes as coherent wholes and the visual vantage point of the ‘self’, but suggests re-living may or may not result from these processes.

We also found that providing participants with different cues altered their recollection, in line with previous studies (Robin et al., 2015; Trinkler, King, Spiers, & Burgess, 2006). When cued with familiar locations, participants recalled memories more vividly compared to when cued with familiar fruit/vegetables and objects, and from more of an allocentric perspective than when cued with familiar people. Location-cued memories were recalled with less effort than fruit/vegetable-cued memories and with more effort than person-cued memories, although there were no differences in reaction time between cue types. While reaction times capture the initial effort needed to recall a memory, effort ratings may reflect the overall and ongoing effort of recalling and recollecting memories. Thus, place cued memories may alter recollection effort but not initial recall (represented by reaction times).

Importantly, both the dynamics and phenomenology of recollection differed greatly from one person to the next. As we will discuss below, these trait differences were related to volumetric differences in participants’ brains.

2.4.2 Anatomical findings

2.4.2.1 Spatial scaffold and the hippocampus

The tendency to spontaneously recall spatial information before other types of information was not significantly associated with hippocampal volume, contrary to our prediction based on the established role of the hippocampus in scene construction. One possible explanation for this finding is that accessing highly familiar locations early during retrieval does not depend on the hippocampus. Previous research suggests that, contrary to cognitive map and scene construction theories, well known locations are stored independent of the hippocampus (for review, see Moscovitch et al., 2005). Thus, participants who spontaneously relied on early spatial
information may have been accessing more schematic, semantic-like spatial representations stored outside the hippocampus.

Our findings may provide tentative evidence that the ability to benefit from spatial cues varies with hippocampal volume. The association between hippocampal volume and the tendency to recall place-cued memories less effortfully than person-cued memories failed to survive correction for multiple comparisons. This may reflect lack of statistical power, the age of participants, lack of precision in measuring hippocampal subfield volumes, or a combination of these. The relationship between hippocampal volume and memory tends to be more pronounced in healthy older adults and more so in the context of pathological populations (Irish et al., 2015; Van Petten, 2004). In young adults this relationship either does not exist or is reversed (Van Petten, 2004). Moreover, it could be that the volumes of specific subfields within the hippocampus are related to recall of space and EAM (Chadwick et al., 2014), but examining the whole hippocampus obscures contributions of specific subfields. Indeed, when individual subfields were examined in an exploratory analysis, right CA2/CA3 volume was significantly associated with the tendency to recall place-cued memories less effortfully. This is consistent with an autobiographical retrieval task that engages cue-related pattern completion processes, more heavily relying on CA3 computations through autoassociative network functions (Kesner, 2007). Therefore, while spatial cues may be more beneficial for individuals with larger hippocampi, further studies are needed to clarify this question.

2.4.2.2 The precuneus and egocentric remembering

We found a positive association between egocentric remembering and precuneus volume. The precuneus has previously been implicated in mental imagery (Fletcher et al., 1995; Spiers & Maguire, 2007), and in the elaboration of EAMs (Addis et al., 2007; Gilboa et al., 2004; Weiler et al., 2010). While parietal regions have long been associated with egocentric remembering (Bisiach & Luzzatti, 1978), one recent study demonstrated that the tendency to recall EAMs from an egocentric perspective is associated with increased precuneus volume (Freton et al., 2014). Our results replicate this finding, suggesting a relationship between the volume of the precuneus and egocentric remembering during EAM. We did not find an association between the retrosplenial cortex and perspective taken during recollection, as assessed in exploratory analyses. One possible explanation for this finding is that higher perspective ratings in our study
reflected the tendency to take an egocentric perspective rather than the ability to flexibly shift perspectives, a function thought to rely on the retrosplenial cortex (Epstein, 2008).

2.4.3 Limitations

One possible limitation of the current study is the design of the EAM behavioural task. It is conceivable that the use of spatial cues and setting ratings could bias participants’ responses towards locations, making them more likely to spontaneously recall locations before other information and to recall location-cued memories differently. We included non-spatial cues (people, objects, fruits/vegetables) and non-spatial rating scales (visual details, sound details, emotionality, etc.) in an attempt to reduce or eliminate this bias. These measures make it unlikely that performance would be influenced specifically towards spatial responses.

2.4.4 Conclusions

Our findings suggest that while spatial information may contribute to the efficiency and phenomenology of EAM, there is remarkable variability among individuals. Some individuals are better able to capitalize on early spatial information, while others may access memories through alternative routes. Thus, we suggest that early spatial information plays an important role in EAM recall, but argue against the notion that early scene construction is a prerequisite or universal feature of EAM, contrary to scene construction theories. That said, it could be that scene construction always occurs, but sometimes later in the re-constructive process.

We also found that individual differences in the tendency to recollect memories from an egocentric perspective were associated with larger precuneus volumes, in line with the established role for this region in egocentric representations. Taken together, our results add to the growing body of literature demonstrating that spatial context information (both allocentric and egocentric) is crucial and pervasive in EAM.

The current study demonstrates the importance of an individual differences approach to studying EAM. Individual differences in EAM were reflected by the volumes of specific regions in the brains of healthy young participants, suggesting that these behavioural tendencies likely go beyond our findings. They may represent stable recollection traits that ultimately influence the subjective experience of remembering. Such important differences may be lost in group analyses, leading to conclusions that do not generalize across all individuals.
Chapter 3
Temporal dynamics of retrieval: ERF correlates of episodic autobiographical memory

3.1 Introduction

Episodic autobiographical memories unfold over time, allowing individuals to re-experience events from their past in detail. While a rich body of literature has examined the neural correlates of EAM, few studies to date have studied the dynamics of its retrieval. Predictions about the temporal dynamics of EAM may be gleamed from different space-based theories and models of memory. As outlined in Chapter 1, the scene construction theory posits that the hippocampus retrieves and integrates multimodal information from neocortical areas, reconstructing them into a coherent spatial context (Hassabis and Maguire, 2007), which can later be manipulated and used for visual imagery by neocortical regions. Scene construction accounts view spatial context as integral to the process of remembering and imagining, and thus one implication is that spatial context is a scaffold for EAM (Hassabis and Maguire, 2007; Robin et al., 2015). In addition to the hippocampus, posterior parietal regions including retrosplenial cortex, posterior cingulate cortex, and precuneus are fundamental to scene construction (Hassabis, Kumaran, & Maguire, 2007; Irish et al., 2015; Mullally et al., 2014). According to another space-based model, the BBB model, the hippocampus is important for allocentric space-based representations during early memory retrieval (Becker & Burgess, 2001; Byrne, Becker, & Burgess, 2007). The retrosplenial cortex translates these allocentric representations into egocentric perspectives which the precuneus then uses for visual imagery. Together these models implicate the hippocampus, retrosplenial cortex, and precuneus in early space-based computations which are thought to be important for memory retrieval.

Limited research supports the dynamics proposed by scene construction and BBB models. In Chapter 2 we showed that individuals tend to recall location information early and spontaneously and that this tendency is associated with faster memory retrieval, but importantly identified high individual variability in this tendency (Hebscher, Levine, & Gilboa, 2017). This demonstrates an overall temporal precedence for spatial information in memory, but suggests that early spatial
representations are not ubiquitous at the behavioural level. At the neural level, a study using intracranial recordings demonstrated very early spatial context reinstatement in the hippocampus during a recognition memory task of objects encoded in a virtual navigation task (Miller et al., 2013). While this finding supports an early role for the hippocampus in spatial functions during memory retrieval, it is unclear how it may apply to EAM given the use of a virtual navigation encoding stage, and the fact that spatial navigation was the only information associated with recall. Several fMRI studies have found hippocampal activity during early memory construction, the stage at which individuals search for and reconstruct an event, and later precuneus/parietal activity during elaboration, which involves retrieving the details and recollecting the event (Addis et al., 2007; Daselaar et al., 2008; Weiler et al., 2010). While these fMRI studies provide some insight into the retrieval dynamics of EAM, they are limited in their temporal resolution, making it difficult to determine precise temporal dynamics. Additionally, while these studies demonstrate hippocampal and parietal activation, they are not able to determine the causal roles of these regions in dynamic memory processes, or whether these roles are related to processing spatial information.

Based on the literature suggesting that spatial information has primacy in memory, it is possible that cueing individuals with spatial information might allow for more efficient recall by speeding up the initial process of scene construction, similar to a pattern completion mechanism. Indeed, in Chapter 2 we showed that hippocampal CA2/CA3 grey matter volume is positively associated with less effortful recall of spatial cues, suggesting that individuals with larger hippocampi may benefit more from spatial cues. However, observing dynamic neural activity during retrieval is necessary to determine whether spatial cues show this proposed benefit at the neural level. A small number of studies have used electrophysiological recordings to study the dynamics of episodic and autobiographical memory. Early studies using EEG to measure slow cortical potentials during autobiographical memory retrieval identified early left frontal negativity and later temporal and occipital negativity (Conway, Pleydell-Pearce, & Whitecross, 2001; Conway, Pleydell-Pearce, Whitecross, & Sharpe, 2003), but future studies did not investigate these patterns of evoked activity further. More recently, Renoult et al (2016) showed that autobiographically significant names (famous names that easily bring to mind episodic memories) are associated with increased amplitude of a signature of episodic recollection, the late positive component (LPC), compared to names with low autobiographical significance. The
LPC is typically largest over posterior electrodes and is thought to reflect recollection-sensitive activity in the parietal lobe (Rugg & Curran, 2007). Several studies have also linked the LPC to the hippocampus and surrounding MTL regions, suggesting that these regions contribute to the generation of the LPC (Addante, Ranganath, Olichney, & Yonelinas, 2012; Düzel, Vargha-Khadem, Heinze, & Mishkin, 2001; Hoppstädt, Baeuchl, Diener, Flor, & Meyer, 2015). While the LPC has been studied extensively in episodic memory, much remains unknown about its function in EAM. In addition to EEG, some have used MEG to record dynamic activity during EAM, but these studies focus on the frequency domain by looking at measures of power and phase synchrony averaged across time periods, rather than capitalizing on the high temporal resolution of MEG (Fuentemilla et al., 2014, 2017). Others have used intracranial recordings to examine oscillatory activity during EAM, but recordings were limited to specific MTL structures (Foster, Kaveh, Dastjerdi, Miller, & Parvizi, 2013; Steinworth et al., 2010). Thus, the existing literature offers limited insight into the temporal dynamics of autobiographical memory.

While some theories implicate the hippocampus, retrosplenial cortex, and precuneus in early space-based computations during memory retrieval, little evidence exists supporting these predictions. Importantly, none of the studies described above examine how these memory network regions are crucially involved in the temporal dynamics of EAM. In the present study, we used inhibitory TMS to determine the causal role of the precuneus in dynamic memory processes. Previous studies have used TMS to understand the causal role of parietal regions in autobiographical (Bonnici, Cheke, Green, FitzGerald, & Simons, 2018; Thakral et al., 2017) and episodic memory (Bonni et al., 2015; Nilakantan et al., 2017; Wang et al., 2014; Wang & Voss, 2015; Yazar et al., 2014), some of which have shown associated and sustained alterations of neural activity (Nilakantan et al., 2017; Wang et al., 2014; Wang & Voss, 2015). We aimed to observe how altering activity in the precuneus affects the temporal order of EAM at the behavioural level by measuring reaction times and early spatial representations, and at the neural level using MEG. Given the proposed role of the precuneus in the temporal dynamics of EAM (Byrne, Becker, & Burgess, 2007), we hypothesized that inhibitory precuneus stimulation would disrupt the dynamics of memory retrieval as reflected by event related fields (ERFs) and behaviour. We also examined how spatial cues influence the neural dynamics of EAM in order to test the idea that spatial information plays an early role in memory retrieval. One prediction based on scene construction theory is that spatial cues will elicit earlier evoked activity,
reflecting more efficient recall. However, based on our previous findings of high individual variably in the tendency to recall location information early and the ability to benefit from spatial cues, it is possible that spatial cues will not lead to earlier neural activity at the group level. Finally, we sought to identify the LPC and examine its behavioural correlates to determine whether this component reflects recollection during EAM as it does in episodic memory.

3.2 Methods

3.2.1 Participants

23 healthy young participants (14 females, mean age = 26.3, range = 19-36) were tested on a within-subjects combined TMS-MEG paradigm. Participants were recruited from the Rotman Research Institute’s healthy volunteer pool. Participants had completed an average of 16.4 (range = 14-21) years of formal education, were all right-handed, native or fluent English speakers, had normal or corrected-to-normal vision, and were free from a history of neurological illness or injury, psychiatric condition, substance abuse, or serious medical conditions. Based on TMS safety guidelines, participants were excluded if they had a history of losing consciousness (fainting), had a prior experience of a seizure, or had a diagnosis or family history of epilepsy. All participants provided informed consent prior to participating in the experiment in accordance with the Rotman Research Institute/Baycrest Hospital ethical guidelines.

3.2.2 Procedure

Participants received cTBS to their left precuneus and to a control region (vertex) on separate days, at least 24 hours apart (mean = 5.4 days). Immediately following cTBS, participants completed the EAM task inside the MEG scanner which was located nearby. All participants completed the MEG scan within an average of 27.4 (SD = 3.8) minutes measured from the end of cTBS. Average time between the end of cTBS and the start of MEG was 6.04 (SD = 1.5) minutes. Anatomical MRIs for each participant were collected in a separate session.

3.2.3 Stimuli and task

The EAM task was a modified version of the one used in Chapter 2 (section 2.2.2.2). At least 48 h prior to the study, participants provided the names of familiar places, objects and people in an
online interview. Locations, people and objects were used as cues because they are elements that commonly make up an event (Addis, Pan, Vu, Laiser, & Schacter, 2009; Burgess, Maguire, et al., 2001). Participants were instructed to name the first twenty items that came to mind and to limit items to those encountered within the past year.

Based on the online interview, sixty cue words were created for each participant, 20 per category. These were randomly divided between the two stimulation sessions so that each session included 30 cues, and each session was broken down into 3 runs to be used in the MEG scanner. E-Prime 1.2 software was used to display the items and collect response data. Items were presented in a randomized order. Participants were instructed to use the words as cues in order to recall personal events that are specific in time that had occurred in approximately the last year, not including the past week. Specific events were defined as “past events from a specific time and place for which you were personally involved.” Cue words were displayed for a maximum of 10 s and participants were instructed to retrieve a specific past event related to the cue as quickly as possible. Participants were asked to press a button on the response box corresponding to their right index finger as soon as a memory came to mind. Trials in which no memory was retrieved were discarded. The retrieval phase was terminated when a memory was retrieved, after which participants saw a slide asking “What was the very first thing that came to mind”, and had to choose one of the following four options: person, object, place, other. An elaboration phase followed in which participants were prompted to imagine the event in as much detail as possible for 8 s. Next, participants rated the memory on four scales aimed at measuring different phenomenological characteristics of the memory. They were given a maximum of 5 s per rating scale. Participants were asked to rate the effort required to bring the event to mind (1= very easy, 6= very effortful), feelings of re-experiencing the event (1= not at all, 6= completely), recall of setting (1= not at all, 6= distinctly), and perspective (1= saw event through my own eyes, 6= saw myself from an external perspective) (Scales adapted from Arnold et al., 2011; Addis et al., 2007). Participants were instructed to rate the experience of remembering and not the event itself. Response options on the screen appeared in square boxes representing the response box used in the MEG scanner, with each box representing one of the 4 buttons for each hand (excluding the thumb of each finger). Participants completed practice trials outside of the MEG to familiarize themselves with the task before moving on to the test trials. See Figure 3.1 for a depiction of the episodic autobiographical memory task.
Figure 3.1. Episodic autobiographical memory paradigm. Participants were cued with familiar locations and non-locations (people, objects), and told to recall a past event in relation to this word. They pressed a button when they had this event in mind.

3.2.4 TMS procedure

Participants received cTBS to their left precuneus (MNI -14, -66, 56) and to a control region (vertex; MNI 0, -15, 74) on separate days. The order of these sessions was counterbalanced. Participants were blind to the type of stimulation they received (precuneus or vertex) and later interviews indicated they could not distinguish between the two. The precuneus was chosen as a target region based on our interest in this regions role in egocentric perspective during EAM (Freton et al., 2014; Hebscher, Levine, & Gilboa, 2017; Chapter 2). We chose the left precuneus based on evidence showing that episodic/autobiographical memory is predominately associated with left-lateralized parietal activity (Kim, 2011; Rugg & Vilberg, 2013; Shimamura, 2011). The left precuneus target region was selected based on a custom meta-analysis of 13 studies with the keyword ‘egocentric’ using NeuroSynth (neurosynth.org). Within this map, the target region was selected by choosing the coordinates with the highest z-score that would be the most accessible with TMS (the most superficial area). Prior to stimulation, both stimulation site coordinates were warped from MNI to individual space and the stimulation site was chosen based on individual anatomy from whole-brain anatomical MRIs as the most superficial region that was closest to these coordinates.

At the beginning of the first stimulation session, resting motor threshold (RMT) was measured for each participant as the lowest intensity that produced motor evoked potentials (MEPs) above 50 µV in 5 out of 10 trials, recorded from the right first dorsal interosseous muscle. The Brainsight frameless stereotaxic neuronavigation system (Rogue Research, Montreal, Quebec,
Canada) was used to target the selected stimulation sites. Three anatomical landmarks located on the face were used to co-register the anatomical MRI to the participant’s head. An infrared camera (Polaris Vicra, Northern Digital) recorded sensors attached to the participant and the TMS coil, allowing for real-time tracking of the TMS coil over the participant’s MRI. A biphasic Super-Rapid Stimulator 70 mm coil (Magstim Co., Whitland, Dyfed, UK) was used to deliver a modified continuous theta burst stimulation (cTBS; 200 pulses delivered at 30 Hz, repeated at 5 Hz) at 80% RMT, lasting for approximately 1 minute. The coil was positioned perpendicular to the stimulation site. Although standard cTBS protocols are delivered at 50 Hz, we decided to lower the burst frequency to 30 Hz due to limitations of the coil circuitry, leading to overheating at high intensities. Reducing the frequency of stimulation allowed us to stimulate at a higher intensity than would be possible at 50 Hz. Similar protocols have previously been shown to induce stronger MEP suppression compared to 50 Hz cTBS at a reduced intensity (Wu, Shahana, Huddleston, & Gilbert, 2012).

3.2.5 MEG acquisition

MEG was recorded in a magnetically shielded room at the Rotman Research Institute with a 151-channel whole-head system with first order axial gradiometers (CTF MEG, Coquitlam, BC, Canada) (VSM MedTech Inc.), at a sampling rate of 625 Hz. Participants sat in an upright position and the behavioural task was projected onto a screen in front of them. For the first 4 participants MEG data was recorded continuously during the 30 minute behavioural task. We subsequently divided the behavioural task into three equal blocks approximately 10 minutes in length in order to reduce overall measures of head movement. To further minimize head movement, a towel was used to provide a tighter fit within the helmet. Head position was tracked at the beginning and end of each recording block by coils placed at three fiducial points on the head. Average head position across runs was used for source localization and was co-registered with fiducial points marked on the anatomical MRI. After acquisition, continuous signals were divided into epochs corresponding to each trial.

3.2.6 Behavioural analyses

Repeated-measures ANOVAs were used to test for the effect of cue-type and stimulation-type on the behavioural dynamics of retrieval. Dependent variables were ease of recall ratings and
reaction times. A paired-samples t-test was used to compare place-other ratios (described below) for precuneus and vertex stimulation sessions to determine whether precuneus stimulation affects the temporal dynamics of EAM.

### 3.2.6.1 Place-other ratio calculation

To measure the tendency to recall a location before other information, we calculated a ‘place-other’ ratio, similar to that reported in Chapter 2 (section 2.1.5.2). We first excluded responses that matched the cue (e.g. location-cued memories where participants selected place as the first thing that came to mind). Each response type was then tallied across all other cue-types, allowing for calculation of likelihood ratios for each participant. To form a ratio of place responses versus other responses, we computed the proportion of place responses for person and object cues, the proportion of person responses for object and place cues, and the proportion of object responses for place and person cues. Because several participants had proportions of zero for either person or object responses (i.e. they never reported a person came to mind first when not cued with a person), we decided to sum these proportions to form an ‘other’, or non-location, responses condition. We then divided the proportion of place responses by the proportion of other responses to form a ‘place-other’ ratio. This ratio represented the likelihood of spontaneously reporting that a location first came to mind when not cued with one, relative to the likelihood of reporting that something else came to mind first. We were not able to compute place-other ratios for 1 participant for their precuneus stimulation session, and 1 participant for vertex stimulation session because these participants had proportions of zero for ‘other’ responses. Additionally, we were not able to record responses for the first thing that came to mind for one participant (vertex session) due to technical difficulties with the MEG response box. Thus, we had data for both sessions for a total of 20 participants.

### 3.2.7 MEG analyses

MEG data was preprocessed using Brain Electrical Source Analysis (BESA) Research 6.1. Noisy or bad channels were either interpolated or defined as bad. We marked the same one channel as bad for 11 participants. One participant was found to have noisier data compared to others so we marked 10 channels during their vertex stimulation session. For each participant, we first performed a manual check of the data to remove large artifacts such as muscle tension. For
periodic artifacts like eye-blinks, vertical and lateral eye movements and cardiac activity, we performed ICA removal, such that 1-3 components were defined for each participant based on their topography. After ICA correction, an automated artifact scan was run on all participant files to remove signal containing excessively high amplitudes that was not detected manually or through ICA correction. The data files were then averaged, yielding an average of 28.3 (SD = 3.0) (94.3%) accepted trials for construction and 27.6 (SD = 3.1) (92%) accepted trials for elaboration across participants. Next, the data was filtered using a low cutoff filter at 0.53Hz (forward, 6dB/oct) and a high cutoff filter at 30Hz (zero phase, 24dB/oct).

3.2.7.1 ERF analyses

3.2.7.1.1 Effects of place-cues on the dynamics of retrieval

To test the prediction that spatial information plays an early role in retrieval, we performed repeated measures ANOVAs on ERFs to compare cue-types, combined across both stimulation sessions for elaboration and construction. We used both stimulation sessions because limiting analyses to only vertex stimulation sessions resulted in an under-powered analysis (<10 trials for each condition), which is problematic for event-related analyses due to higher signal-to-noise ratio. Note that we analyzed the differences between cues rather than the report of the first thing that came to mind, which may also provide a measure of early spatial representation. We chose to look at cues due to unequal numbers of trials for this later measure. As an example, if a participant more often reported that a location came to mind first, they would necessarily have fewer responses of a person or object coming to mind first. This resulted in large numbers of trials for certain conditions and small numbers of trials for other conditions, which presents difficulties for ERF analysis. Thus, we used cue-types which were evenly distributed for all participants. All ERF analyses were performed for 0-1000 ms of elaboration and construction stages using BESA Statistics 2.0, which includes permutation-based correction for multiple comparisons. We used a cluster alpha of 0.05, 1000 permutations, with clusters defined using a channel distance of 4 cm resulting in an average distance of 7.45 neighbors per channel.
3.2.7.1.2 Effects of precuneus stimulation on the dynamics of retrieval

We performed paired-samples t-tests between ERFs for the two stimulation sessions (precuneus vs vertex), irrespective of cue-type, to determine whether the precuneus plays a causal role in the temporal dynamics of retrieval.

3.2.7.2 MEG source localization

We applied Classical Low Resolution Electromagnetic Tomography Analysis Recursively Applied (CLARA) to source localize significant results at the sensor level (BESA Research 6.1). CLARA iteratively localizes activity by reducing the source space during each estimation. Two iterations were computed with a voxel size of 7mm$^3$, and data were regularized using the default singular value decomposition cutoff of 1%. The solution was computed using an adult realistic head model and registered against the standardized BESA finite element model created from the average of 24 anatomical MRIs in Talairach-Tournoux coordinate space. We ran source localization on significant clusters as previously determined using paired t-tests and repeated measures ANOVAs in BESA Statistics. For each significant cluster, we computed source localization for a 30 ms time window around the peak time point.

3.2.7.3 Late positive component

In a final set of exploratory analyses, we sought to identify the LPC, a component commonly associated with recollection. We extracted amplitudes for the peak of this component (600-800 ms) over each right parietal sensor for memory elaboration. To determine if the LPC is associated with memory performance, we performed a series of correlations between peak LPC amplitude, averaged across all sensors, and subjective memory measures. Subjective memory measures included perspective rating, effort rating, place-other ratio, and memory vividness (average re-experiencing and setting ratings—see 4.4.1 for further information).
3.3 Results

3.3.1 Behavioural results

To determine factors affecting the dynamics of EAM retrieval, we compared reaction times and ease of recall ratings between cue-types and stimulation sessions. Repeated measures ANOVAs revealed a significant main effect of cue-type on ease of recall ratings (F(2,40) = 5.81, p = .010, \( \eta^2 = .225 \)), but no main effect of stimulation (F(1,20) = .50, p = .488, \( \eta^2 = .024 \)) and no stimulation X cue interaction (F(2,40) = .22, p = .806, \( \eta^2 = .011 \)). Post-hoc comparisons revealed that person-cued memories led to greater ease of recall compared to place (p = .007) and object cues (p = .018). There were no significant main effects or interactions for reaction time (all p’s > .379). These findings demonstrate that precuneus stimulation does not have a causal effect on ease of recall or reaction times. They also indicate that cue-type affects ease of recall ratings, with person-cues leading to the easiest recall of memories, but that reaction time is unaffected by cue-type. These findings are consistent with those from Chapter 2, and suggest that place-cues do not lead to faster or less effortful recall of memories, and actually lead to more effortful recall compared to person-cues. As shown in Chapter 2, this effect may be mediated by neuroanatomical individual differences, although we did not measure this in the present study.

Next, we compared place-other ratios between precuneus and vertex stimulation sessions to determine whether precuneus plays a causal role in the behavioural dynamics of EAM retrieval. Paired-samples t-tests revealed a non-significant but marginal effect of stimulation on place-other ratios (t(20) = 1.81, p = .085, CI [-.09, 1.34]), such that precuneus stimulation led to higher ratios compared to vertex stimulation. This non-significant effect suggests that precuneus stimulation leads to a marginal increase in the tendency to recall locations before other information. Note that this analysis may have been underpowered due to missing place-other ratios for some participants.

Average place-other ratios were 1.61 (SD = 1.71) for vertex stimulation sessions, and 2.18 (SD = 2.68) for precuneus stimulation sessions. These findings demonstrate that participants are on average more likely to report that a location came to mind first, but show high variability in this
tendency, consistent with the results from Chapter 2. See Appendix B for a visual depiction of place-other ratios for each stimulation session.

3.3.2 Evoked responses

Visual inspection of the evoked responses to cues during memory construction revealed typical, well-established components related to written word processing. Around 100 ms after cue onset there was a positive inflection in right occipital sensors resembling the P1 response, which reflects visual word processing (Kutas, Van Petten, & Besson, 1988). We also observed a well-formed M170 component over occipital and frontal sensors, peaking at around 100-200 ms post cue onset. The M170 corresponds with the N170 in EEG, which is a typical response to stimuli like faces and words, also thought to reflect visual processing (Bentin, Mouchetant-Rostaing, Giard, Echallier, & Pernier, 1999). We also saw a M400 (N400) over posterior electrodes at around 350-500 ms, which typically reflects higher-level semantic processing of words (Bentin et al., 1999). Thus, cues elicited evoked responses consistent with well-established word processing components.

3.3.3 Effects of place-cues on the neural dynamics of retrieval

To test the prediction that spatial cues will elicit differential early neural activity, we compared evoked responses for different cue-types. Permutation-based repeated measures ANOVAs revealed 4 significant clusters during memory construction. We found a very early significant effect of cue-type during construction over right occipital and parietal sensors (cluster 1; 0-72 ms; p = .041; Figure 3.2a, left), such that place-cues led to more positive evoked activity compared to person-cues (t = 4.74, p < .001), and object-cues (t = 3.66, p = .003). This effect seemed to be driven by an earlier rise in the P1 waveform for place-cues. However, as semantic processing of words is thought to occur at around 400 ms following stimulus onset (Bentin et al., 1999), this effect is too early to be considered genuinely related to cue identity and is likely a spurious finding which we did not pursue with source localization. Later in construction we found a significant effect of cue-type (cluster 2; 286-474 ms; p < .001; Figure 3.2a, right) over right and central posterior and occipital sensors, such that place-cues led to reduced amplitudes compared to person cues (t = -4.99, p < .001), but were not significantly different than object cues (t = 1.50, p = .147). Person-cues led to significantly higher amplitudes than object-cues (t=
Source localization for this cluster (427-457) was non-significant, although there was a trend (p = .059) towards less activation for place vs object-cues in left MTL, primary motor, and posterior cingulate (Figure 3.2c).

Another significant cluster around the same time occurred over left temporal and occipital sensors (cluster 3; 288-416 ms; p = .036; Figure 3.2b, left), such that both place- and person-cues led to increased negative amplitudes compared to object-cues (t = -3.91, p = .005; t = -4.55, p < .001), but place and person-cues were not significantly different (t = 1.18, p = .249). Source localization for this cluster was non-significant. Slightly later in construction, a left parietal/occipital cluster demonstrated a significant effect of cue-type (cluster 4; 499-629 ms; p = .002; Figure 3.2b, right). Post-hoc comparisons revealed that both place- and object-cues led to more negative amplitudes compared to person-cues (t = -4.64, p < .001; t = 4.87, p < .001), but place and object-cues were not significantly different from one another (t = 0.91, p = .373). Source localization for this cluster was non-significant. See Table 3.1a for cluster statistics.
Figure 3.2. Cue-based ERFs during memory construction. Significant effects of cue-type over (a) predominately right-sided and (b) left-sided sensors. Plots (top) show ERFs for a single sensor of the significant cluster, with coloured panels showing significant time points for that reported sensor. Scalp maps (below) show distribution of contributing sensors at the reported time point, also color-coded. (c) Non-significant (p = .059) source localization for the second cluster (purple box) at 442 ms, showing reduced activation for place-cued memories compared to object-cued memories.

At elaboration, we found a significant effect of cue-type over frontal and temporal sensors (cluster 5; 888-962 ms; p = .026; Figure 3.3, Table 3.1b), such that place- and object-cued memories had significantly lower amplitudes compared to person-cued memories (t = -3.56, p = .005; t = 3.04, p = .012), but place- and object-cued memories were not significantly different from one another (t = 0.26, p = 0.796). Source localization for this cluster was not significant. These results indicate that cue-type influences the dynamics of early memory construction when participants are searching for and bringing to mind a memory, as well as later memory elaboration when participants are recalling the details of that event and recollecting it. These
findings do not show that spatial cues elicit earlier neural activity and therefore do not support the prediction that spatial information plays an early role in memory retrieval at the neural level.

**Table 3.1.** Cluster statistics for cue-based analysis (rmANOVAs)

<table>
<thead>
<tr>
<th>Cluster number</th>
<th>Times (ms)</th>
<th>p</th>
<th>Place</th>
<th>Person</th>
<th>Object</th>
<th>Paired contrasts</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Construction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0-72</td>
<td>.041</td>
<td>13.01</td>
<td>-8.19</td>
<td>-8.67</td>
<td>**   ** n.s.</td>
</tr>
<tr>
<td>2</td>
<td>286-474</td>
<td>&lt; .001</td>
<td>7.03</td>
<td>22.19</td>
<td>2.81</td>
<td>** n.s. **</td>
</tr>
<tr>
<td>3</td>
<td>288-416</td>
<td>.036</td>
<td>-26.66</td>
<td>-32.86</td>
<td>-9.09</td>
<td>n.s. ** **</td>
</tr>
<tr>
<td>4</td>
<td>499-629</td>
<td>.002</td>
<td>-14.44</td>
<td>3.37</td>
<td>-17.20</td>
<td>** n.s. **</td>
</tr>
<tr>
<td>(b) Elaboration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>888-962</td>
<td>.026</td>
<td>5.78</td>
<td>22.55</td>
<td>4.75</td>
<td>** n.s. *</td>
</tr>
</tbody>
</table>

* *p < .05, ** p < .01

**Figure 3.3.** Cue-based ERFs for elaboration. Plot shows evoked activity for a left frontal sensor, with the grey panel showing significant time points for that sensor. Scalp map shows distribution of contributing sensors at 899 ms. Place-cued memories had significantly lower amplitudes compared to person-cued but not object-cued memories.
3.3.4 Effect of precuneus stimulation on the neural dynamics of retrieval

We next assessed the effect of precuneus stimulation on the dynamics of retrieval to determine the causal role of the precuneus in EAM retrieval. Paired-samples t-tests revealed that precuneus stimulation altered evoked activity at different stages of memory retrieval. During early construction, precuneus stimulation led to reduced negative amplitudes compared to vertex stimulation around midline frontal sensors, with precuneus stimulation appearing to delay the change in amplitude (cluster 1; 448-547 ms; p = .039; Figure 3.4a, left). Source localization for this effect (474-504 ms) failed to reach significance, but showed a trend towards reduced activity for precuneus stimulation in bilateral precuneus (p = .070). During later construction also around frontal sensors, we found that precuneus stimulation led to greater negative activity compared to vertex stimulation (cluster 2; 724-816 ms; p = .004; Figure 3.4a, right). Source localization for this effect (755-785 ms) identified a significant cluster in the right precuneus and premotor area with greater amplitudes for precuneus compared to vertex stimulation (p = 0.017) (Figure 3.4b). See Table 3.2a for cluster statistics. These findings suggest that precuneus stimulation alters evoked responses during EAM construction such that an initial reduction or shift in activity is followed by an increase in activity, with both effects likely occurring in the precuneus.

During later elaboration, amplitudes for memories following precuneus stimulation were again reduced compared to vertex stimulation in frontal-midline sensors (cluster 3; 856-1000 ms; p = .014). Source localization for this effect was non-significant. See Figure 3.5 and Table 3.2b.
Figure 3.4. Differences between precuneus and vertex stimulation sessions during construction. (a) ERFs for two significant clusters shown over a right frontal sensor with significant time points for that sensor highlighted in grey (top). Below, associated scalp maps show distribution of contributing sensors for both significant time intervals. (b) Source localization for the second significant cluster showing greater right precuneus activation for precuneus compared to vertex stimulation (745-793). Clusters in blue are non-significant (p > .109).

Figure 3.5. ERFs showing differences between precuneus and vertex stimulation sessions during elaboration. Plot shows ERF over a left frontal sensor with significant time points for that sensor highlighted in grey. Associated scalp map shows distribution of contributing sensors for the significant cluster at 984 ms.
Table 3.2. Cluster statistics for paired-samples t-tests

<table>
<thead>
<tr>
<th>Cluster number</th>
<th>Times (ms)</th>
<th>p</th>
<th>Vertex mean</th>
<th>Precuneus mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Construction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>448-547</td>
<td>.039</td>
<td>-17.34</td>
<td>-2.84</td>
</tr>
<tr>
<td>2</td>
<td>724-816</td>
<td>.004</td>
<td>5.71</td>
<td>-11.65</td>
</tr>
<tr>
<td>(b) Elaboration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>856-1000</td>
<td>.014</td>
<td>23.58</td>
<td>4.55</td>
</tr>
</tbody>
</table>

Together these results suggest that precuneus stimulation alters the temporal dynamics of retrieval at both construction and elaboration. During early memory construction, precuneus stimulation appears to shift activity forward in time, perhaps indicating a slower or delayed response, while later in construction stimulation leads to more prolonged negative activity in the right precuneus. Precuneus stimulation also leads to a large reduction in amplitude during elaboration across a widespread cluster of frontal/midline sensors. These findings support the hypothesis that the precuneus plays a causal role in the neural temporal dynamics of EAM.

3.3.5 Late positive component

In a final set of exploratory analyses, we sought to identify a late positive component commonly associated with recollection. The LPC is typically largest over posterior electrodes and is thought to emerge in parietal areas in EEG studies, with analogous positive modulations reported in MEG (Evans & Wilding, 2012; Tibon, Vakil, Levy, & Goldstein, 2014). Thus, we first examined posterior sensors for vertex stimulation sessions to determine whether EAM retrieval similarly demonstrates the LPC. We identified a positive inflection resembling the LPC at approximately 600-800 ms over right parietal sensors during elaboration, the stage during which we expect recollection to occur. We did not observe this component during construction, likely because this stage is associated with search processes that typically differentiate EAM from typical lab-based episodic memory tasks.
To determine if the LPC is associated with memory performance, we extracted amplitudes for the peak of this component (600-800 ms) for each participant for each right parietal sensor. We found a significant negative correlation between peak amplitude, averaged across all sensors, and perspective ratings such that greater amplitudes were associated with lower egocentric perspective ratings (r = -.54, CI [-.78, -.17], p = .008). See Figure 3.6a. Peak amplitude was not significantly correlated with memory vividness, effort, or place-other ratio (all p’s > .25). The same analysis for precuneus stimulation sessions revealed no significant correlation between LPC peak amplitude and perspective rating across all right parietal sensors (r = -.12, CI [-.51, .31], p = .583) (Figure 3.6b). Notably, the correlation between perspective rating and LPC peak amplitude was significantly greater for vertex stimulation than precuneus stimulation (z = -1.97, p = .025), indicating that this association is reduced or eliminated by precuneus stimulation. Paired-samples t-tests comparing peak amplitudes revealed a non-significant trend towards reduced LPC amplitudes for precuneus compared to vertex stimulation (t(22) = 1.96, CI [-.97, 24.7], p = .068).

Next, we examined the correlation between perspective ratings and peak LPC amplitude separately for each right parietal sensor. For vertex stimulation sessions, the majority of sensors (7/9 sensors) were significantly correlated with perspective rating, while no sensors for precuneus stimulation sessions were significantly correlated with behaviour (all p’s > .26). As seen in Figure 3.6c, two sensors for vertex stimulation sessions were not significantly correlated with behaviour, and these sensors also demonstrated relatively small LPCs (MRP21, MRP31), while sensors with larger LPCs were more likely to be significantly and strongly correlated with behaviour. These findings show that greater LPC over parietal sensors is associated with the tendency to recall events from less of a purely egocentric perspective. Furthermore, precuneus stimulation disrupts the relationship between LPC and perspective rating.
Figure 3.6. Late positive component. (a) Significant correlation between perspective rating and peak amplitude of the LPC across all right parietal sensors for vertex stimulation session, and (b) non-significant correlation for precuneus stimulation. Greater egocentric recall is reflected by higher values on the rating scale. (c) Plots for individual right parietal sensors with corresponding $r$ and $p$ values for correlation with perspective ratings, for vertex stimulation sessions.

3.4 Discussion

The primary aim of this study was to elucidate the temporal dynamics of EAM at the neural level. Motivated by space-based models of memory, we examined how spatial information affects the dynamics of retrieval and found that place-cues alter memory construction and elaboration, but did not find evidence to support an early neural advantage for spatial cues. Based on the proposed role of the precuneus in the dynamics of memory retrieval (Byrne et al., 2007), we also set out to test the causal role of this region. Precuneus stimulation altered activity during early memory retrieval, delaying the evoked response in time, suggesting that this region plays a causal role in the temporal dynamics of EAM. Finally, we demonstrated that the LPC, a well-established neural correlate of episodic recollection, was associated with spatial perspective...
during EAM retrieval. Precuneus stimulation disrupted this association, suggesting that this region is important for representing different spatial perspectives during EAM.

### 3.4.1 Effects of place-cues on the dynamics of retrieval

Motivated by space-based models of memory, we examined whether spatial cues would alter the dynamics of recall by comparing behavioural measures and event-related fields for memories cued by places to those for non-spatial cues. One prediction derived from these models was that spatial cues would lead to more direct access to memory by partially bypassing the initial process of scene construction. We found that place cues altered the neural dynamics of retrieval during early construction and elaboration. During early construction, place cues led to reduced positivity compared to non-spatial cues in right posterior sensors, in line with the idea that spatial cues require less processing. Source localization for this effect revealed a non-significant trend ($p = .059$), such that place cues led to reduced left MTL, primary motor, and posterior cingulate activation compared to object-cued memories. Although non-significant, this source localization finding is also consistent with the prediction that spatial cues require less processing, specifically in areas responsible for scene construction. We also found differences between cue-types over left posterior sensors around the same time during construction, but these differences did not reflect reduced amplitudes for spatial cues. Rather, we found that object cues led to reduced amplitude modulation compared to person and place cues, contrary to the prediction about spatial cues. Later in construction, person cues led to reduced amplitude modulations compared to place and object cues, also around left posterior sensors. Taken together, these findings demonstrate that different cues elicit distinct spatiotemporal activity, suggesting that memories may be processed differently depending on how they are accessed. Spatial cues appear to require less processing at specific time points in certain regions, perhaps including the MTL, but more processing in other regions, although we are unable to determine these regions with certainty due to the lack of significant source localization results. However, it is important to note that these analyses included both stimulation sessions due to low numbers of trials within a single stimulation session, and thus it is possible that precuneus stimulation differentially affected different cue-based memories, possibly obscuring differences between cues. Future studies should examine event-related neural responses to different cues using larger numbers of trials in the absence of stimulation to confirm these findings.
Importantly, spatial cues did not lead to earlier evoked neural activity, nor did they lead to faster or less effortful recall of memories. Contrary to predictions derived from scene construction theories, these findings do not support an early advantage of spatial cues. We previously found that spatial information has temporal precedence in EAM in a majority of participants, but importantly reported high variability in this tendency (Hebscher, Levine and Gilboa, 2017; Chapter 2). We also found variability in the ability to benefit from spatial cues in Chapter 2, with some participants able to recall spatial cues with greater ease than person cues, but others showing the reverse trend. This effect was mediated by individual differences in hippocampal volume. Thus, it is possible that variability in the tendency to rely on or benefit from early spatial information, perhaps related to individual neuroanatomical individual differences, may explain why we did not find earlier evoked neural activity for spatial cues at the group level.

Nonetheless, our findings do not support predictions based on scene construction theory that spatial information is represented early and ubiquitously, consistent with findings from Chapter 2.

The present study measured evoked neural responses to spatial cues in order to determine whether spatial information confers an early neural advantage. We did not measure evoked responses in relation to the tendency to recall locations before other information, which is another measure of reliance on early spatial representations. We were not able to analyze this measure due to unequal and low numbers of trials for some participants, making ERF analyses unreliable. See section 3.2.7.1.1 for a more in-depth explanation. It is also important to note that, based on this measure, our findings here and from Chapter 2 indicate that participants on average were more likely to spontaneously recall locations before other information. This means that, regardless of what they were cued with, the majority of participants often brought a location to mind early during memory retrieval. If participants were often thinking about a location, there may have been less distinction between cue-types, making comparisons between them more difficult. This limitation may have reduced our likelihood of finding significant differences between cue-types.
3.4.2 Causal role of the precuneus in the dynamics of EAM

We found that construction and elaboration stages of memory retrieval were differentially affected by precuneus stimulation. During early construction, precuneus stimulation led to reduced activity compared to vertex stimulation, reflected by a delayed rise of waveform amplitudes. This suggests that precuneus stimulation caused a delay or slowing of the evoked response during early construction, a stage during which participants are searching for and reconstructing a memory. Source localization for this effect revealed a non-significant trend towards reduced amplitudes in bilateral precuneus. Slightly later during construction, precuneus stimulation led to more negative amplitudes, which was source localized to the right precuneus. It is interesting that we stimulated the left precuneus and this later finding was localized to the right precuneus. One interpretation of these results is that precuneus stimulation initially delayed the evoked response to a cue by suppressing precuneus activity, but following this inhibition or delay the right precuneus compensated by increasing its activation, leading to a successfully retrieved memory. Although speculative, this interpretation fits with our finding that precuneus stimulation did not affect the behavioural dynamics of EAM, suggesting that the opposite hemisphere may be able to compensate for this inhibition. We also found that precuneus stimulation led to a large reduction in activity during later elaboration. Rather than reflecting a shift in activity, visual inspection of this finding suggested an overall inhibition of activity at this time point, which fits more with the inhibitory role of cTBS.

Scene construction and BBB models of memory implicate a network of regions including the hippocampus, retrosplenial cortex, and precuneus in early space-based functions believed to be central to memory retrieval (Hassabis, Kumaran, & Maguire, 2007; Irish et al., 2015; Mullally, Vargha-Khadem, & Maguire, 2014; Becker & Burgess, 2001; Byrne, Becker, & Burgess, 2007). Our findings thus support these models, showing that the precuneus is crucially involved in early memory processes, as early as 450 ms after cue presentation. It will be important for future studies to clarify the roles of the hippocampus and retrosplenial cortex in these early processes to properly determine the validity of these space-based models of memory.
3.4.3 Late positive component

As an exploratory analysis, we aimed to identify the late positive component in our data and determine its relation to subjective aspects of EAM. We identified a positive component resembling the LPC at approximately 600-800 ms during elaboration over right parietal sensors which was correlated with perspective ratings, but not with other measures of subjective EAM. Precuneus stimulation eliminated this relationship, demonstrating a causal role for this region in the association between LPC peak and perspective rating. Interestingly, the significant relationship between LPC and perspective was such that participants with greater LPC amplitudes tended to recall events from less of a predominately first-person perspective. Our perspective rating scale was a continuous scale which allowed participants to select the degree of first-person or third-person remembering, with mid-range ratings reflecting a combination of both perspectives. Notably, participants who scored the lowest on the perspective rating scale fell somewhere around the middle of the scale, suggesting that they were more likely to remember events from a combination of perspectives rather than from a predominately third-person perspective. Thus, mid-range ratings (associated with higher LPC amplitudes) may reflect more flexibility in the ability to translate perspectives, while higher ratings (associated with lower LPC amplitudes) may reflect less flexibility. Our results therefore suggest that participants more likely to flexibly shift perspectives during retrieval have greater peak LPC amplitudes. This finding fits with one previous study showing that parietal activity, in particular the central precuneus and right angular gyrus, is related to shifts in perspective during autobiographical memory retrieval (St. Jacques, Szpunar, & Schacter, 2016). It is also consistent with the BBB model’s prediction that translation between perspectives, or spatial updating, occurs repeatedly throughout memory retrieval (Byrne, Becker, & Burgess, 2007). Thus, these data are consistent with the idea that the LPC is important for the ability to translate spatial perspectives during EAM. Following precuneus stimulation, the LPC is no longer important for or sensitive to perspective, perhaps because an important node in this translation circuit has been altered.

The LPC is typically characterized by a positive modulation occurring around 500-800 ms predominately over posterior sites, often but not always exhibiting a left-sided maximum (Rugg & Curran, 2007). This component has mainly been studied in the context of episodic memory where it has been consistently linked to recollection (Rugg & Curran, 2007). While the majority
of these studies used EEG, analogous positive modulations have been reported in MEG (Evans & Wilding, 2012; Tibon et al., 2014). The LPC is sensitive to the amount of information recollected, suggesting that it reflects the representation or maintenance of recollected information (Vilberg, Moosavi, & Rugg, 2006; Wilding, 2000). Others have argued that this effect indexes attentional orienting to recollected information (Wagner, Shannon, Kahn, & Buckner, 2005). Our findings demonstrate that the LPC is also sensitive to perspective ratings, suggesting that spatial perspective affects some aspect of EAM recollection. One previous study has identified the LPC as being important for autobiographical memory, showing that autobiographically significant names (famous names that easily bring to mind episodic memories) are associated with increased LPC amplitude compared to names with low autobiographical significance (Renoult et al., 2016). Another study found reduced LPC amplitudes in individuals with severely deficient autobiographical memory (SDAM) during a recognition memory task, demonstrating an association between autobiographical memory ability and this component (Palombo et al., 2015). Our findings further support the importance of the LPC in autobiographical memory and importantly link this component to subjective aspects of EAM elaboration. Future studies are needed to further clarify the role of the LPC in autobiographical memory and its relationship to spatial perspective.

3.4.4 Conclusions

This study aimed to elucidate the temporal dynamics of EAM retrieval, which few studies to date have done. Contrary to predictions derived from scene construction theory, spatial cues did not confer an early neural advantage. However, we show that different cues elicit distinct spatiotemporal neural signatures, suggesting that multiple routes to memory retrieval exist. We also found that the precuneus plays a causal role in the neural, but not behavioural, dynamics of retrieval, in line with the proposed role of this region (Byrne et al., 2007). Finally, we show that an established neural component of recollection is related to the tendency to recollect EAMs from mixed spatial perspectives and that the precuneus is causally involved in this relationship. These findings provide novel insights into the role that spatial information plays in the temporal dynamics of EAM and help clarify the neural correlates of early memory retrieval.
Chapter 4
Identifying a causal role for the precuneus in network-wide theta and gamma oscillatory activity

4.1 Introduction

Episodic memory retrieval depends on the coordinated reinstatement of retrieved information from neocortical regions by the hippocampus and surrounding MTL regions (McClelland, McNaughton, & O’Reilly, 1995; Rolls, 2000). Interactions between MTL and parietal regions are thought to be particularly important for representing the spatial context of an event, a crucial foundation for the vivid recollection of episodic memories (Burgess, Becker, et al., 2001; Burgess, Maguire, Spiers, & O’Keefe, 2001b; Hassabis & Maguire, 2009; Robin et al., 2015).

Transformations between parietal-based egocentric and MTL-based allocentric representations are thought to be crucial for navigation and memory. As described earlier in this dissertation, the BBB model posits that the medial parietal cortex maintains and manipulates landmark locations from an egocentric perspective (Byrne, Becker, & Burgess, 2007). These egocentric representations are derived from long-term MTL-based allocentric spatial representations, with the retrosplenial cortex being responsible for translating between representations. While this model has not been directly applied to EAM, previous studies have shown that MTL and parietal structures are indeed associated with spatial aspects of EAM. It was recently demonstrated that the tendency to remember events from an egocentric perspective is associated with increased precuneus grey matter (Freton et al., 2014; Hebscher, Levine & Gilboa, 2017; Chapter 2), and that shifting perspectives during EAM retrieval is supported by the posterior parietal cortices, particularly the precuneus (St. Jacques et al., 2016). We also showed in Chapter 2 that hippocampal grey matter volume is associated with the ability to benefit from spatial cues (Hebscher, Levine & Gilboa, 2017; Chapter 2). However, these studies are unable to determine how such regions may communicate with one another to allow for information transfer.

Neural oscillations may be a mechanism by which widespread regions, such as the hippocampus and posterior parietal lobe, communicate during memory retrieval. Specifically, theta (3-7 Hz)
Oscillations are thought to mediate MTL-neocortical orchestration during memory retrieval and have been implicated in working (Payne and Kounios, 2009), episodic (Sederberg et al., 2003), spatial (Kaplan et al., 2014; 2017), and autobiographical memory (Fuentemilla et al., 2014; Steinvorth et al., 2010; Foster et al., 2013). Theta phase synchronization between distributed regions is thought to support neural communication and synaptic plasticity (Fell & Axmacher, 2011). Previous studies have found that MTL theta phase synchronizes with mPFC and precuneus (Fuentemilla et al., 2014), and with retrosplenial cortex theta during EAM (Foster et al., 2013). Interestingly, theta oscillations have also been proposed to facilitate communication between MTL and parietal regions for translation between allocentric and egocentric reference frames, although experimental evidence for this claim is lacking (Byrne et al., 2007).

Gamma oscillations (30-85 Hz) have also been implicated in memory processes, with increases in gamma power being associated with successful episodic memory encoding (Burke et al., 2013). Distinctions have been made between low (<60 Hz) and high gamma (>60 Hz) oscillations, which are thought to depend on different mechanisms and reflect distinct cognitive functions (Edwards, 2005). High gamma is thought to be an index of cortical processing, having been consistently reported across a variety of cognitive tasks and cortical regions (for review, see Crone, Korzeniewska, & Franaszczuk, 2011), including successful memory formation (Burke, Ramayya, & Kahana, 2015; Hanslmayr, Staresina, & Bowman, 2016). Spatially distributed local gamma may be coordinated by theta oscillations through phase-amplitude coupling (PAC), in which theta phase modulates gamma amplitude (Sirota et al., 2008). Theta phase modulation of gamma amplitude is thought to be a mechanism for communication between distributed regions during cognitive processes (Canolty, Edwards, Dalal, Soltani, & Nagarajan, 2007). Several studies have shown theta-gamma PAC in the rodent hippocampus during navigation (Bragin et al., 1995; Chrobak and Buzsaki, 1998; Colgin et al., 2009; Belluscio et al., 2012), and in the human MTL (Mormann et al., 2005; Axmacher et al., 2010; Staudigl and Hanslmayr, 2013) and neocortex during memory (Canolty et al., 2006; Sauseng et al., 2009; Maris et al., 2011; van der Meij et al., 2012; Kaplan et al., 2014). However, no studies to date have examined the interactions between theta and gamma oscillations in EAM.

Research examining oscillatory activity during EAM is lacking, with only a small number of studies finding theta phase synchronization (Foster et al., 2013; Fuentemilla et al., 2014), and
none finding theta-gamma PAC. More research is needed to (i) clarify the roles of theta/gamma oscillations within and across EAM network nodes including MTL, mPFC, retrosplenial cortex, and precuneus, (ii) understand the causal relationship between EAM network nodes and oscillatory communication and (iii) examine the unique contribution of spatial cognition in driving these oscillatory patterns. The present study aims to elucidate the communication between regions involved in EAM by measuring oscillatory activity in theta and gamma frequency bands during memory retrieval. We hypothesized that, relative to a rest period, EAM retrieval would be associated with increased theta and high gamma oscillatory activity in areas of the EAM network, as measured by power, theta phase coupling, and theta-gamma PAC. Phase coupling and PAC in particular may suggest a means of information transfer between these regions. Based on the established contribution of spatial context to EAM, we cued participants with location and non-location words and predicted that location cued memories would elicit differential oscillatory activity compared to non-location cued memories.

We further use TMS to examine whether the precuneus plays a causal role in the communication between regions during retrieval, mediated by theta and gamma oscillations. We predicted that precuneus stimulation would affect neural activity both within the precuneus and in regions functionally connected to the precuneus. We also measure changes in subjective EAM following TMS to better understand the causal role of the precuneus in EAM. Previous studies have used parietal TMS to alter autobiographical (Bonnici et al., 2018; Thakral et al., 2017) and episodic memory (Bonacci et al., 2015; Nilakantan, Bridge, Gagnon, Vanhaerents, & Voss, 2017; Wang et al., 2014; Wang & Voss, 2015; Yazar, Bergström, & Simons, 2014). One recent study demonstrated that rTMS to the lateral parietal lobe leads to long lasting changes in hippocampal-cortical functional connectivity which relate to improved episodic memory (Wang et al., 2014; Wang & Voss, 2015). In the present study, we used TMS to directly alter the activity of the precuneus in order to observe system-level changes in activity, specifically in the MTL and other structures that comprise the autobiographical memory network. Behaviourally, we predicted that stimulation would lead to differences in the tendency to recall events from an egocentric perspective and with measures of recall ease and vividness. However, due to previously reported variability and inconsistencies in studies using TMS to study memory (described in Chapter 1), these predicted behavioural differences may be subtle and variable across participants. We therefore hypothesized that such behavioural variability would be predicted by associated
changes in neural activity. Specifically, stimulation-induced changes in theta/gamma may predict associated changes in memory performance.

4.2 Methods

Participants, behavioral task, TMS procedure, and MEG acquisition methods are the same as reported in Chapter 3.

4.3 MEG Analyses

4.3.1 MEG source localization

MEG data were analyzed in source space using the adaptive beamforming technique Synthetic Aperture Magnetometry (SAM) implemented in CTF software (CTF Systems Inc., Port Coquitlam, BC, Canada). SAM is a beamformer technique used to compute the time course of virtual channels on a grid of locations (voxels) across the brain. SAM constructs a spatial filter from the data covariance matrix and a lead field map derived from the MRI head model. These spatial filters estimate the virtual signal of activity generated at the target location while minimizing signal power from all other locations. Weights were computed on a whole-brain grid and were multiplied by original sensor data to create a new, spatially filtered time series for each voxel with a final resolution of 5 mm$^3$. Analysis in source space is preferred over raw MEG sensor data because the beamforming procedure attenuates artifacts generated outside the brain, such as eye movements. The beamforming procedure also compensates for differences across participants in head shape and position (Olsen, Rondina, Riggs, Meltzer, & Ryan, 2013).

4.3.2 MEG power spectrum analysis

We first analyzed the MEG power spectrum which allowed us to examine power within theta and gamma frequency bands. As described above, previous studies have identified increases in theta and gamma power during memory retrieval relative to comparison conditions. We hypothesized that power within these frequency bands would be associated with EAM retrieval compared to rest.
Data for each successful trial was epoched into early memory construction and later memory elaboration. Memory construction was defined by the button press indicating that participants had an event in mind (-1020 to -100 ms before button press). 100 ms before button press was not analyzed in order to minimize evoked effects occurring due to the button press alone. We kept this time window as short as possible in order to capture the momentary retrieval of memory rather than a longer search through memory which may rely on different cognitive processes and neural mechanisms. This time window was also chosen to allow us to include trials with short response times which maximized the number of trials used in the analysis (mean = 28.0 trials per participant for vertex; 28.2 for precuneus stimulation sessions). A longer time window for construction would result in the inclusion of fewer trials because it would exclude trials with short reaction times. Elaboration was defined by the screen instructing participants to “imagine event in detail” (500 to 3000 ms). The first 500 ms of elaboration was not analyzed in order to minimize effects occurring due to the onset of a visual stimuli (“imagine the event in detail” screen), and eye movements due to reading this text. Power spectra were calculated within each time window for both stimulation and sham sessions. MEG source analysis was conducted using SAM (described above). Using this technique, we created single subject maps quantifying the change in theta (3-7 Hz) and high gamma (65-85 Hz) power between an active time window (construction or elaboration) and a baseline inter-trial rest time window of equal length. We chose to analyze high gamma based on its reported consistency across a variety of studies (Crone et al., 2011), and its relevance to memory (Burke et al., 2015). Consistent with a study demonstrating theta-gamma PAC during a spatial memory task using MEG, we defined our high gamma frequency band based as 65-85 Hz, although note that high gamma definitions differ across studies (Kaplan et al., 2014). These maps were warped into MNI space for subsequent analyses.

4.3.3 Phase coupling

We next computed theta phase coupling in order to measure functional connectivity between regions. Previous studies have demonstrated theta phase coupling between EAM network areas during memory retrieval (Foster et al., 2013; Fuentemilla et al., 2014). As before, epoched trial data were divided into early memory construction and later memory elaboration, using the same time windows as described above. The Weighted Phase Lag Index (wPLI) of the source-
localized time series was calculated using a left medial posterior parietal seed. The seed region for each participant was chosen as the voxel with the greatest theta power increase between memory and rest (as determined by SAM maps described above) within 12 mm of the group maximum coordinates. wPLI was calculated for memory construction, elaboration, and rest time windows. wPLI is a modified version of Phase Lag Index (PLI), which measures the strength of the coupling between two time series, where values close to one indicate a consistent nonzero phase relationship, and values close to zero indicate randomly distributed phase differences (Stam et al, 2007). wPLI has been shown to be more robust than PLI and does not overestimate effects caused by volume conduction or noise (Vinck, Oostenveld, Van Wingerden, Battaglia, & Pennartz, 2011). We calculated whole-brain wPLI maps, measuring phase coupling between the seed region and every other voxel in the brain using the FieldTrip toolbox in Matlab. Summary whole-brain wPLI images for each participant were then subjected to statistical analyses in AFNI.

4.3.4 Phase-amplitude coupling

We computed theta-gamma phase amplitude coupling to determine whether specific ROIs communicate across frequency bands during EAM retrieval. As described above, previous studies have found theta-gamma PAC during memory retrieval (Staudigl and Hanslmayr, 2013; van der Meij et al., 2012; Kaplan et al, 2014), but none have demonstrated PAC during EAM retrieval. PAC was calculated between the phase of an MTL theta seed and gamma amplitude of a left precuneus seed. Seed regions were chosen using a method similar to the one described above for phase coupling. We first identified coordinates within left precuneus and bilateral MTLs, separately, showing the greatest group-level theta power increases between memory (construction or elaboration) and rest. Group maximum was localized to right MTL for construction and left MTL for elaboration. We then identified a subject-specific seed by choosing the peak voxel within 12 mm of the group maximum coordinates for each region of interest and memory stage. As a control analysis, we also performed PAC between the same precuneus and MTL seeds, but using the theta phase of the precuneus seed and the gamma amplitude of the MTL seed (the reverse computation). We hypothesized that MTL theta phase would modulate precuneus gamma amplitude based on the established role for the MTL in
coordinating neocortical activity (McClelland, McNaughton, & O’Reilly, 1995; Rolls, 2000). We did not expect the reverse (precuneus theta phase modulates MTL gamma amplitude) to be true.

Time windows for elaboration were the same as used for power and phase coupling. For construction, we increased the time window to 1500 ms seconds because PAC measures are sensitive to the length of time window, with windows under 1 s producing inflated PAC measures (Seymour, Rippon, & Kessler, 2017). This cutoff resulted in an average of 25.7 trials per participant for vertex stimulation sessions and 25.3 trials for precuneus stimulation sessions. Measures of theta phase ($\phi_{f_p}$) and gamma amplitude ($f_a$) were calculated using a fourth order, two-pass Butterworth filter, and then applying the Hilbert transform. Bandwidth filters used were [3 7] for theta and [65 85] for high gamma. Coupling between theta phase values ($\phi_{f_p}$) and the phase of gamma amplitude envelope ($\phi_{f_a}$) were calculated at each time point ($n$) using a phase locking value modulation index (PLV-MI) (Cohen, 2008). Phase locking value (PLV) is similar to the wPLI calculated for theta phase coupling. PLV is computed as the vector length of phase differences over time from a signal (with length N), such that larger values reflect less phase difference variability between two signals. We calculated PAC for each trial and averaged these to obtain PLV values for each amplitude and phase pair. The same procedure was repeated using surrogate data created by shuffling trial and phase information (200 surrogates), which we used to normalize PLV values. This resulted in surrogate-normalized comodulograms for each condition displaying the degree of PAC between each phase and amplitude value, which we then subjected to statistical analysis. PAC was computed using the FieldTrip toolbox with code adapted from Seymour et al (2017).

\[
MI = \left| \frac{1}{N} \sum_{n=1}^{N} e^{i(\phi_{f_p}(n) - \phi_{f_a}(n))} \right|
\]

### 4.4 Statistical analyses

#### 4.4.1 Behavioural analyses

To test the hypothesis that precuneus stimulation would lead to differences in the quality of memory retrieval, we ran a series of paired-samples t-tests on rating scales from the EAM task,
comparing precuneus and vertex stimulation sessions. Given the lack of experimental evidence on the effects of TMS on EAM, we chose to investigate all rating scales. Rating scales for re-experiencing and setting were positively correlated for both sessions ($r > .50$), so the average of these scales was taken as a measure of vividness. We looked at the effect of precuneus stimulation on effort required to bring the event to mind (subsequently referred to as ease of recall), perspective (egocentric to allocentric), and vividness. All behavioural analyses were performed in RStudio.

4.4.2 MEG correlates of memory

To gain a better understanding of oscillatory underpinnings of EAM, we first examined MEG correlates of memory during vertex stimulation. As vertex stimulation is not expected to have an effect on memory, this session served as a control condition. Statistical analyses were performed on theta and gamma power, theta phase coupling, and theta-gamma phase-amplitude coupling.

4.4.2.1 Power spectrum

To test the hypothesis that EAM retrieval would be associated with increased theta and gamma activity, theta and gamma SAM maps for construction vs. rest and elaboration vs. rest within vertex stimulation sessions were analyzed using one-sample t-tests. We used one-sample t-tests because each SAM map was itself a comparison between memory and rest. All power spectrum statistics were performed in AFNI.

4.4.2.2 Phase coupling

To address the prediction that memory retrieval relative to rest would be associated with increased theta phase coupling, memory construction and elaboration stages were compared to rest using paired-samples t-tests. Next, we created separate wPLI maps for each cue type, within each session and time window. These maps were subjected to repeated-measures ANOVAs to test the hypothesis that location cued memories would elicit differential communication between regions (MTL-parietal) compared to non-location cued memories. Whereas in Chapter 3 we were unable to analyze cue-based differences within vertex sessions due to high signal-to-noise ratio from averaging, we did so here because phase coupling analyses are performed on a trial-by-trial basis and subsequently averaged. Indeed, others have performed theta phase coupling using a
similar number of trials (~10 trials per condition) (Fuentemilla et al., 2014; Kaplan et al., 2017). Separate ANOVAs were performed for memory construction and elaboration time windows. All theta phase coupling statistical analyses were performed in AFNI.

4.4.2.3 Phase-amplitude coupling

To test the prediction that MTL theta modulates neocortical gamma during EAM retrieval, comodulograms for memory construction and elaboration stages were compared to rest using non-parametric permutation-based statistics. First, a paired-samples t-test was performed between memory (construction or elaboration) and a rest period of equal length. Monte Carlo estimates of the significance probabilities were calculated by randomly permuting comparisons over 1000 iterations, using a cutoff threshold of $p < 0.05$. All values exceeding this threshold were grouped into clusters, and the maximum t-value within each cluster was compared against a null distribution obtained by shuffling the data 1000 times and calculating the largest cluster-level t-value for each permutation. A threshold of $p < 0.05$ was used for the permutation-based cluster-level comparison. We did not compare cue-types due to the possibility that PAC measures may be sensitive to using a small number of trials (<10 trials for each cue). Previous studies measuring PAC typically use a larger number of trials, so the efficacy of using PAC on small sets of trials cannot be determined.

4.4.3 Effects of precuneus stimulation on oscillatory measures

We next examined the effect of precuneus stimulation on oscillatory activity by comparing precuneus to vertex stimulation sessions for theta/gamma power, theta phase coupling, and PAC. All measures reflected relative differences between memory and rest for each participant.

4.4.3.1 Power spectrum

To test the prediction that precuneus stimulation would affect neural activity, SAM masks were subjected to paired t-tests comparing precuneus to vertex stimulation for both time windows and frequency bands. To examine the association between stimulation-induced neural and behavioural changes, we performed linear regressions on power differences between sessions with behavioural difference scores as predictors (change in ease of recall, perspective, vividness). Power differences were calculated as precuneus – vertex stimulation for theta ($\Delta$-
theta power) and gamma (Δ-gamma power). Behavioural difference scores were calculated such that larger numbers indicate precuneus stimulation led to behavioural improvements in memory (Δ-ease of recall, Δ-perspective, Δ-vividness). This analysis allowed us to determine the association between differences in theta/gamma power and differences in memory following stimulation.

4.4.3.2 Effects of precuneus stimulation on phase coupling

To test the prediction that precuneus stimulation will affect communication between regions, wPLI maps were subjected to paired t-tests comparing precuneus to vertex stimulation for both time windows. The association between stimulation-induced neural and behavioural changes were also examined using linear regressions (described above).

4.4.3.3 Effects of precuneus stimulation on phase-amplitude coupling

To test the prediction that precuneus stimulation will affect theta and gamma oscillatory activity, PLV-MI comodulograms for memory construction and elaboration (relative to rest) following precuneus stimulation were compared to those following vertex stimulation, using the non-parametric permutation-based statistics described above. Next, we examined whether differences in PAC following precuneus stimulation are associated with behavioural changes following stimulation. We calculated PAC differences (Δ-PAC) by subtracting comodulograms for vertex from precuneus stimulation during memory retrieval relative to rest. Correlations between behavioural difference scores (Δ-ease of recall, Δ-perspective, Δ-vividness) and Δ-PAC comodulograms were computed using the non-parametric permutation-based statistics described above.

4.4.4 Effects of precuneus stimulation on baseline neural activity

In a final set of analyses, we examined the effects of precuneus stimulation on neural activity in the absence of a memory task. Theta phase coupling maps and PAC commodulograms were subjected to paired-samples t-tests comparing precuneus to vertex stimulation during the inter-trial rest period (2500 ms).
4.4.5 Cluster corrections

SAM and wPLI maps were thresholded at p < 0.005 using a minimum cluster size to keep family-wise error rate at p < 0.05. Cluster sizes were determined based on the spatial smoothness of the data using Monte Carlo simulations from the 3dClustSim tool in AFNI using calculated FWHM values. As different maps have different smoothness values, we obtained cluster sizes separately for each map. Cluster thresholds were 78 voxels (FWHM 21.8) for SAM theta maps, 137 voxels (FWHM 28.9) for SAM gamma, and 24 voxels (FWHM 11.6) for wPLI maps.

4.5 Results

4.5.1 Behavioural results

We first investigated whether precuneus stimulation would lead to differences in the quality of memory retrieval by performing a series of paired-samples t-tests on rating scales from the EAM task, comparing precuneus and vertex stimulation sessions. These analyses revealed no significant differences between precuneus and vertex stimulation (all p’s > .46). Data for each participant plotted by stimulation session are shown in Appendix C.

Based on these results and on interviews conducted following each participant’s final session, we identified a potential order effect on subjective ratings of remembering. This order effect appeared to be influencing participants’ second stimulation session, such that they would complete subjective rating scales relative to their performance in their first session. In other words, subjective memory during the second session appeared to be dependent on subjective memory during the first session, which may have obscured potential differences between stimulation types due to counterbalancing. To confirm this order effect, we tested for an interaction between session order and session type using a repeated measures analysis of covariance (ANCOVA) with rating scales for precuneus and vertex sessions as within-subjects factors and session order (i.e. counterbalancing order: precuneus stimulation or vertex stimulation first) as the between-subjects factor. This analysis revealed a significant interaction between session order and session type on vividness ratings ($F(1,21) = 5.10, p = .035, \eta^2 = .195$) but not on effort rating ($F(1,21) = 0.84, p = .369, \eta^2 = .039$) or perspective ($F(1,21) = 0.10, p = .755, \eta^2 = .005$). We also found a main effect of stimulation type on vividness ratings
when order was held constant (F(1,21) = 4.83, p = .039, \eta^2 = .187), but no significant effect of stimulation on effort or perspective ratings (all p’s > 0.28), suggesting that the order of counterbalancing significantly interacted with the effects of stimulation on memory vividness.

Based on this significant interaction we performed a post-hoc exploratory analysis on vividness ratings using each participant’s first session only, such that we compared participants with precuneus stimulation first (n = 12) to those with vertex stimulation first (n = 11). This analysis had a between-subjects design, which several previous parietal-TMS studies have used (cf. Yazar et al, 2014; Bonni et al., 2015; Wang and Voss, 2015). Independent-samples t-tests revealed a significant difference in vividness ratings, such that precuneus stimulation led to less vivid memories compared to vertex stimulation (t(21) = -2.34 p = .030, CI [-.98 -.06]) (See Figure 4.1). Although there was no significant interaction between session order and session type on effort rating, we also found a significant difference between stimulation sessions on effort ratings, such that precuneus stimulation led to more effortful recall compared to vertex stimulation (t(21) = 2.62, p = .016, CI [.11 .98]).

![Figure 4.1](image.png)

**Figure 4.1.** Exploratory between-subjects analysis showing that precuneus stimulation leads to (a) reduced vividness ratings and (b) reduced ease of recall compared to vertex stimulation. Effort ratings are reversed and displayed as ease of recall ratings in (b).
4.5.2 MEG correlates of episodic autobiographical memory

In order to gain a better understanding of oscillatory underpinnings of EAM, we first examined MEG correlates of memory during vertex stimulation sessions only. The subsequent sections describe results for theta and gamma power, theta phase coupling, and theta-gamma phase-amplitude coupling.

4.5.2.1 Power spectrum during memory retrieval

We first examined SAM maps for construction and elaboration compared to rest for vertex stimulation sessions to characterize oscillatory correlates of EAM. One-sample t-tests revealed that compared to rest, memory construction was associated with theta power increases in a bilateral occipital lobe cluster extending slightly into the precuneus, and a right frontal cluster covering the orbitofrontal cortex, vmPFC, and inferior frontal gyrus (Figure 4.2a; Table 4.1a). Gamma power increases during memory construction were found within a large cluster covering bilateral precuneus, occipital lobes, and dorsal PFC (Figure 4.2c; Table 4.1c). Memory elaboration was associated with theta power increases bilaterally in the occipital lobe, precuneus, inferior and superior parietal lobe including the angular gyrus, retrosplenial cortex, MTL, mPFC, and cerebellum (Figure 4.2b; Table 4.1b). Gamma increases during elaboration relative to rest were found in bilateral frontal and prefrontal regions, precuneus, retrosplenial cortex, occipital lobes, and left cerebellum (Figure 4.2d; Table 4.1d). All results are thresholded at $p < .005$, cluster corrected. These results support the role of theta and gamma oscillations in EAM, which few studies to date have examined. Theta activity was present in a network of regions commonly activated in autobiographical memory studies (Svoboda, McKinnon, & Levine, 2006), while gamma activity was found in a network encompassing mostly representational cortices and dorsal PFC. Furthermore, these results show that different patterns of theta and gamma power underlie construction and elaboration, with elaboration eliciting a stronger and more widespread network of activity.
Figure 4.2. Power increases during EAM retrieval. Theta power increases during (a) construction and (b) elaboration relative to rest in the vertex stimulation session (p < .005, cluster corrected). Gamma power increases during (c) construction and elaboration (d) relative to rest (elaboration gamma map thresholded at p < 0.001 for visualization purposes).

Table 4.1. Memory vs rest: Power at vertex stimulation

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</tr>
<tr>
<td>R orbitofrontal cortex, vmPFC, inferior frontal gyrus</td>
<td>117</td>
<td>3.87</td>
<td>12</td>
<td>34</td>
<td>-10</td>
</tr>
<tr>
<td><strong>(b) Theta: Elaboration &gt; rest</strong></td>
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<tr>
<td>L and R cerebellum, occipital lobe, precuneus, inferior and superior parietal lobe, retrosplenial cortex, MTL, mPFC</td>
<td>4140</td>
<td>7.38</td>
<td>27</td>
<td>70</td>
<td>-29</td>
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</table>
4.5.2.2 Phase coupling during memory retrieval

To examine how theta phase coupling supports memory retrieval, we created whole-brain wPLI maps for memory construction, elaboration, and rest following vertex stimulation, using a subject-specific seed. The seed was located within 12mm of the medial parietal group average for theta power increases relative to rest, but encroached on retrosplenial or medial occipital structures for some participants. wPLI maps for memory construction and elaboration were then compared to rest. Paired-samples t-tests revealed increased theta coupling between the seed region and right MTL during memory construction compared to rest (Figure 4.3a; Table 4.2a). Elaboration was not associated with significant differences in theta coupling compared to rest (no clusters passed threshold). In line with our hypothesis, these findings show that MTL and parietal regions communicate via theta phase coupling during early EAM retrieval.

4.5.2.2.1 Cue-based analyses

We next performed repeated-measures ANOVAs on the same whole-brain wPLI maps to test the hypothesis that location cued memories would elicit differential activity compared to non-location cued memories. During memory construction, there was a main effect of cue in the left MTL. Post hoc comparisons revealed a large cluster in the left MTL showing reduced phase coupling with the seed region for place cued memories compared to both person and object cued memories (Figure 4.3b; Table 4.2b). The same effect was found in a cluster in the left cerebellum. No significant differences between cue types were found during elaboration. These results demonstrate that place cued memories elicited less parietal-MTL and parietal-cerebellum
theta coupling compared to object and person cued memories. We later discuss these findings in the context of a hypothesis that place-cues are granted more direct access to memories (see Discussion).

Figure 4.3. Whole-brain theta phase coupling results. (a) t-test showing increased theta coupling between a left parietal seed (blue box) and the right MTL during memory construction. (b) ANOVA showing reduced phase coupling between the seed region and MTL for place versus person and object cued memories during memory construction (contrast between place and person/object). Blue box shows an example seed region for one participant.

Table 4.2. wPLI at vertex stimulation

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<tr>
<td>(a) t-test: Construction &gt; rest</td>
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<tr>
<td>R MTL, cerebral peduncle</td>
<td>59</td>
<td>3.97</td>
<td>38</td>
<td>-16</td>
<td>-4</td>
</tr>
<tr>
<td>(b) ANOVA: Place &gt; person/object (construction)</td>
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<td></td>
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<tr>
<td>L MTL, thalamus</td>
<td>170</td>
<td>-4.71</td>
<td>-18</td>
<td>-16</td>
<td>-20</td>
</tr>
<tr>
<td>L cerebellum</td>
<td>51</td>
<td>-5.34</td>
<td>-12</td>
<td>-50</td>
<td>-24</td>
</tr>
</tbody>
</table>
4.5.2.3 PAC during memory retrieval

In order to determine whether the MTL and parietal lobe communicate via theta-gamma phase-amplitude coupling during EAM retrieval, we calculated a measure of modulation index (PLV-MI) between the theta phase of an MTL seed and the gamma amplitude of a left parietal seed. All individual maps were normalized by surrogate datasets and then subjected to paired t-tests. Simulation-based cluster corrected t-tests revealed increased PAC between the left parietal lobe and right MTL during memory construction (p < 0.05, corrected), but not between the left parietal lobe and left MTL during elaboration compared to rest. See Figure 4.4. PAC between the right MTL and left parietal lobe during elaboration relative to rest was also non-significant. As a control analysis, we tested for PAC between theta phase of the parietal seed and gamma amplitude of the MTL seed (the reverse direction as above). As predicted, this analysis revealed no significant differences in PAC during memory compared to rest (no clusters passed initial p < 0.05 threshold). Thus, MTL theta appears to modulate parietal gamma during construction, but parietal theta does not modulate MTL gamma. These results support previous claims that MTL theta plays a role in coordinating neocortical gamma, suggesting a means of information transfer between these widespread regions.

Figure 4.4. Comodulograms showing MTL-parietal PAC during (a) construction vs rest between right MTL and left parietal lobe and (b) elaboration vs rest between left MTL and left parietal lobe. Black dotted lines show areas of significantly different phase-amplitude coupling between memory and rest (p < 0.05, cluster corrected).
4.5.2.4 Exploratory analyses

To explore the relationship between EAM and theta and gamma oscillatory activity further, we performed a series of exploratory analyses examining the association between subjective EAM and oscillatory activity. Given the lack of experimental evidence examining oscillatory activity during EAM, we chose to investigate all rating scales measuring subjective EAM (ease of recall, perspective, vividness). We first performed a series of multiple linear regressions using rating scales as predictors of theta and gamma power, and theta phase coupling. Outcome variables were SAM power maps and wPLI maps. All outcome variables reflected relative differences between memory (construction and elaboration) and rest for each participant. Results were thresholded at p < 0.005 and cluster corrected using the same methods described above. All linear regressions were performed in AFNI.

During construction, greater theta power in a cluster encompassing the left somatosensory cortex, angular gyrus, and MTL was predicted by higher vividness ratings. Ease of recall positively predicted theta power in the left motor cortices during construction (see Table 4.3a). No other SAM maps were significantly predicted by rating scales. These findings suggest that greater theta power in a widespread network of regions during memory construction is related to easier and more vivid recall. Interestingly, theta power during elaboration and gamma power at both stages was not related to subjective EAM.

Linear regressions on wPLI maps revealed that theta phase coupling at construction and elaboration was significantly associated with vividness, ease of recall, and perspective ratings. At construction, higher vividness ratings predicted less phase coupling between the seed region and right insular cortex and occipital lobe, while ease of recall positively predicted seed-right cerebellum coupling and negatively predicted coupling with bilateral ventral PCC. At elaboration, vividness ratings positively predicted coupling between the seed region and left ventral PCC/precuneus. Higher egocentric perspective ratings predicted greater coupling between the seed and right fusiform and angular gyrus. See Figure 4.5 and Table 4.3b. These findings demonstrate that greater theta phase coupling between posterior regions during memory elaboration is related to vivid recall of memories from more of an egocentric perspective.
We next examined the association between theta-gamma PAC and subjective EAM using non-parametric permutation-based correlations implemented in FieldTrip. Correlations were performed between PAC comodulograms for memory relative to rest and all three rating scales. As separate correlations were run for each rating scale, final cluster-corrected p-values were additionally corrected for multiple comparisons (false discovery rate corrected, p < .05). PAC during construction relative to rest was not significantly correlated with rating scales (cluster p’s > .05, corrected). PAC during elaboration relative to rest was significantly positively correlated with memory vividness at 7 Hz theta (cluster p < .05, corrected), but not with any other rating scale. These findings suggest that greater MTL-parietal communication during elaboration via PAC is associated with higher vividness ratings. Taken together, these findings demonstrate that theta power, theta phase coupling, and theta-gamma PAC are functionally related to subjective EAM measures. Note however that vividness ratings were confounded by counterbalancing order, making it difficult to interpret associations between oscillatory measures and vividness ratings.

Table 4.3. Exploratory analysis: Regions showing significant prediction by behavioural change

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<tr>
<td><strong>(a) Power: theta</strong></td>
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<tr>
<td><strong>Construction: vividness</strong></td>
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<tr>
<td>L primary somatosensory, STG, fusiform, angular gyrus, MTL</td>
<td>229</td>
<td>5.38</td>
<td>-58</td>
<td>-30</td>
<td>46</td>
</tr>
<tr>
<td><strong>Construction: ease of recall</strong></td>
<td></td>
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<tr>
<td>L premotor cortex, primary motor cortex</td>
<td>103</td>
<td>4.80</td>
<td>-28</td>
<td>-26</td>
<td>56</td>
</tr>
<tr>
<td><strong>(b) wPLI</strong></td>
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<tr>
<td><strong>Construction: vividness</strong></td>
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<td></td>
</tr>
<tr>
<td>R insular cortex, occipital lobe</td>
<td>31</td>
<td>-4.25</td>
<td>22</td>
<td>-65</td>
<td>10</td>
</tr>
<tr>
<td><strong>Construction: ease of recall</strong></td>
<td></td>
<td></td>
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<tr>
<td>R cerebellum</td>
<td>137</td>
<td>5.41</td>
<td>52</td>
<td>-45</td>
<td>-49</td>
</tr>
<tr>
<td>L and R ventral PCC</td>
<td>50</td>
<td>-3.87</td>
<td>7</td>
<td>-10</td>
<td>35</td>
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</table>
**Elaboration: vividness**

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<tr>
<th>Region</th>
<th>t-value</th>
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<tbody>
<tr>
<td>L ventral PCC, ventral precuneus</td>
<td>27</td>
<td>3.48</td>
<td>-17</td>
<td>-45</td>
<td>30</td>
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**Elaboration: perspective**

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<tr>
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<tbody>
<tr>
<td>R fusiform gyrus, angular gyrus</td>
<td>90</td>
<td>4.07</td>
<td>42</td>
<td>-65</td>
<td>15</td>
</tr>
</tbody>
</table>

*STG = superior temporal gyrus*

**Figure 4.5.** Exploratory linear regressions for theta phase coupling maps. Behavioural predictors for phase coupling during memory construction vs. rest (top) and elaboration vs. rest (bottom) using a left parietal seed. Blue box (top right) shows example seed region for one participant. Scatter plot (bottom right) shows example visualization for the significant association between perspective rating and precuneus-angular gyrus theta phase coupling.

4.5.3 Effects of precuneus stimulation on oscillatory activity

4.5.3.1 Effects of precuneus stimulation on power spectrum

We next set out to test the prediction that precuneus stimulation will affect neural oscillations by subjecting SAM maps for memory (relative to rest) to paired t-tests comparing precuneus to vertex stimulation. Results revealed no overall group differences between precuneus and vertex
stimulation sessions during memory construction or elaboration for theta or gamma maps (all clusters > 78 for theta, 137 for gamma).

Next, behavioural difference scores between precuneus and vertex stimulation were added as predictors in a series of multiple linear regressions to assess the association between changes in theta/gamma power and behavioural changes. We performed regressions on Δ-theta power and Δ-gamma power separately (change in power: precuneus > vertex). As before, all analyses were performed on memory relative to rest. At construction, Δ-ease of recall negatively predicted Δ-theta power such that easier recall of memories following precuneus stimulation was associated with lower theta power in a cluster including bilateral anterior cingulate cortex and premotor cortex (Table 4.4a). In other words, participants who found it more difficult to retrieve memories following precuneus stimulation showed increased theta power in this cluster. No predictors were significant for Δ-gamma power during construction (cluster p’s > .05).

During memory elaboration, Δ-ease of recall positively predicted Δ-theta and Δ-gamma power. Greater Δ-theta power in the left MTL was predicted by easier recall of memories following precuneus stimulation (Figure 4.6a; Table 4.4a). Greater Δ-gamma power in a large cluster with its peak in the right occipital lobe and also encompassing the MTL, fusiform gyrus, and inferior temporal gyrus also predicted easier recall of memories post precuneus stimulation (See Figure 4.6a; Table 4.4a). Easier recall of memories also predicted increased gamma power in a cluster in the left putamen and MTL. In other words, participants who found it easier to recall memories following precuneus stimulation had associated increases in theta and gamma power in these clusters. Participants who found it more difficult to recall memories following precuneus stimulation had decreased power in these clusters. Neither Δ-perspective nor Δ-vividness were significant predictors of changes in power. These results suggest that individual differences in behavioural response to precuneus stimulation are accompanied by relative differences in theta and gamma power post-stimulation. Specifically, participants who show greater stimulation-induced theta and gamma power increases in their MTLs and surrounding regions tended to recall memories with greater ease post-stimulation.
Figure 4.6. Δ-theta power (a) and Δ-gamma power (b) post-precuneus stimulation predicted greater Δ-ease of recall of memories post-stimulation. Scatter plots (right) are visualizations of the significant effect of effort rating predicting MTL theta power post-stimulation.

Table 4.4. Regions showing significant prediction by change in behaviour

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<tr>
<th>Label</th>
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<tr>
<td><strong>(a) Power</strong></td>
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<tr>
<td><em>Construction: theta (Δ-ease of recall)</em></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>L and R ACC, premotor cortex</td>
<td>152</td>
<td>-4.38</td>
<td>7</td>
<td>9</td>
<td>60</td>
</tr>
<tr>
<td><em>Elaboration: gamma (Δ-ease of recall)</em></td>
<td></td>
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<tr>
<td>R occipital lobe, fusiform, inferior temporal gyrus, MTL</td>
<td>1089</td>
<td>4.53</td>
<td>50</td>
<td>-70</td>
<td>-14</td>
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L putamen, MTL

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<td></td>
<td>331</td>
<td>4.25</td>
<td>-22</td>
<td>-40</td>
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**Elaboration: theta (Δ-ease of recall)**

L MTL (hippocampus, parahippocampal, fusiform)

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<tr>
<td></td>
<td>96</td>
<td>4.55</td>
<td>-32</td>
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<td>-19</td>
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**(b) wPLI**

**Construction (Δ-vividness)**

L temporopolar area, inferior frontal gyrus, OFC, vmPFC

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<td></td>
<td>213</td>
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**Elaboration (Δ-vividness)**

R primary somatosensory, primary motor, premotor

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<td></td>
<td>139</td>
<td>4.59</td>
<td>32</td>
<td>-30</td>
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L and R vmPFC

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<td></td>
<td>33</td>
<td>4.29</td>
<td>2</td>
<td>34</td>
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R cerebellum

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<tr>
<td></td>
<td>31</td>
<td>5.10</td>
<td>7</td>
<td>-75</td>
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**Elaboration (Δ-ease of recall)**

R cerebellum

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<td></td>
<td>83</td>
<td>-3.48</td>
<td>17</td>
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<td>-54</td>
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4.5.3.2 Effects of precuneus stimulation on phase coupling

To test the prediction that precuneus stimulation will affect communication between regions, wPLI maps for memory construction and elaboration (relative to rest) were subjected to paired t-tests comparing precuneus to vertex stimulation. No significant differences were found between vertex and precuneus stimulation sessions (all clusters > 0.05), however one cluster fell just below the threshold of 24 voxels. This cluster, which included a portion of the right MTL (23 voxels, t = 4.19; x = 37, y = -30, z = 0), demonstrated greater phase coupling with the left parietal seed region for precuneus compared to vertex stimulation during memory elaboration. Although this cluster was just below the significance threshold, this result provides preliminary evidence that precuneus stimulation increases phase coupling between the left parietal lobe and right MTL during elaboration.
Next, difference scores for ease of recall, perspective, and vividness ratings were added as predictors to a linear regression to determine whether individual differences in stimulation-induced phase coupling could be explained by variance in behavioural changes, similar to the analysis on theta and gamma power reported above. As before, all analyses were performed on memory relative to rest. During construction, Δ-vividness positively correlated with Δ-theta phase coupling between the seed region and a large cluster encompassing the left temporopolar area, inferior frontal gyrus, OFC, and vmPFC (Table 4.4b). At elaboration, Δ-vividness positively predicted Δ-theta phase coupling with the right primary motor, primary somatosensory, and premotor cortices, as well as bilateral vmPFC, and right cerebellum post stimulation. In other words, participants who recalled memories more vividly after precuneus stimulation demonstrated the greatest increases in stimulation-induced phase coupling between the parietal seed and these clusters. Also during elaboration, Δ-ease of recall negatively predicted phase coupling with the right cerebellum. See Table 4.4b. These results mirror the theta and gamma power results described above and together demonstrate that individual differences in the oscillatory after-effects of precuneus stimulation are related to variability in the behavioural response to stimulation. Specifically, greater theta phase coupling between posterior parietal and temporofrontal regions following precuneus stimulation is related to improvement in memory vividness following stimulation. Note again that these findings should be interpreted cautiously due to vividness ratings being confounded by counterbalancing order. Stimulation-induced increases in theta and gamma power in the MTL and surrounding regions are associated with easier recall of memories post-stimulation. Interestingly, changes in power were correlated with ease of recall but not vividness ratings, while changes in phase coupling were predominately associated with vividness ratings, suggesting that communication between widespread regions may be more important for memory vividness than power within regions.

4.5.3.3 Effects of precuneus stimulation on PAC

To further test the prediction that precuneus stimulation will affect network-wide oscillatory activity, PAC comodulograms for memory versus rest following precuneus stimulation were compared to those following vertex stimulation sessions. Simulation-based cluster corrected t-tests revealed a significant effect of precuneus stimulation at construction such that stimulation
led to decreased right MTL-precuneus PAC compared to vertex stimulation (Figure 4.7a). There was no significant effect of precuneus stimulation on PAC at elaboration (no clusters passed initial p < 0.05 threshold). See Figure 4.7b. Control analyses measuring PAC between MTL gamma amplitude and parietal theta phase revealed no significant differences between precuneus and vertex stimulation. This demonstrates that the above effect is specific to MTL theta phase and precuneus gamma amplitude, and not the reverse. These findings show that precuneus plays a causal role in MTL-parietal phase-amplitude coupling. Cluster-corrected correlations between Δ-PAC and Δ-behaviour were non-significant (all p’s > 0.05).

![Figure 4.7](image)

Figure 4.7. Comodulogram showing change in MTL-parietal PAC for precuneus compared to vertex stimulation during (a) memory construction vs. rest between right MTL and left parietal lobe and (b) elaboration vs. rest between left MTL and left parietal lobe. Black dotted lines show areas of significantly different phase-amplitude coupling between precuneus and vertex stimulation (p < 0.05, cluster corrected)

4.5.4 Effects of precuneus stimulation on baseline neural activity

Finally, to determine the effects of precuneus stimulation on neural activity in the absence of a memory task, theta phase coupling maps and PAC comodulograms for rest were compared between precuneus and vertex stimulation. Paired-samples t-tests revealed that precuneus stimulation decreased phase coupling between the left parietal lobe and a right MTL cluster at rest (Figure 4.8). There was no significant effect of precuneus stimulation on PAC at rest (all cluster p’s > .05). These results suggest that precuneus stimulation disrupts MTL-parietal communication as measured by theta phase coupling, and that these effects can be observed in
the absence of a memory task. Note that stimulation did not reduce theta phase coupling during memory retrieval vs. rest, suggesting that, despite a reduction in baseline activity, phase coupling is adequately recruited for task purposes.

![Figure 4.8](image)

**Figure 4.8.** Effects of precuneus stimulation on baseline neural activity. Precuneus stimulation led to decreased theta phase coupling between left parietal seed and right MTL at rest (2.5 s of rest) (66 voxels, t = -3.68; x = 32, y = -36, z = -4).

### 4.6 Discussion

A primary aim of this study was to elucidate the communication between regions involved in EAM by measuring oscillatory activity in theta and gamma frequency bands during memory retrieval. We took three measures of oscillatory activity: theta/gamma power, theta phase coupling, and theta-gamma phase-amplitude coupling. We found that EAM retrieval is associated with increases in all three measures relative to an inter-trial rest period, suggesting that widespread regions interact via theta and gamma oscillations during EAM. Importantly, we identify theta-gamma phase-amplitude coupling during EAM for the first time, demonstrating a mechanism for information transfer between the MTL and parietal lobe.

A second aim of this study was to determine whether the precuneus plays a causal role in the communication between regions during retrieval and in subjective measures of EAM, using continuous theta burst stimulation. We found that precuneus stimulation altered communication between parietal lobe and MTL by modulating theta phase coupling and theta-gamma PAC,
confirming a causal role for the precuneus in theta and gamma oscillatory activity. We also found tentative evidence to suggest that precuneus stimulation altered subjective memory, and that TMS-induced behavioural and neural changes are related. These findings suggest that stimulation alters subjective EAM and neural oscillations, but that it affects individuals in different ways. Participants who showed greater stimulation-induced theta and gamma oscillatory activity also showed the greatest behavioural protection against the inhibitory effects of cTBS, consistent with a compensatory explanation.

4.6.1 MEG correlates of EAM

4.6.1.1 Theta power and phase synchronization

EAM retrieval was associated with increases in theta oscillatory activity relative to rest. During early memory construction, we found theta power increases in occipital lobes and medial prefrontal regions, while later elaboration was associated with theta power increases across a wider network of regions including occipital lobe, precuneus, inferior and superior parietal lobe, retrosplenial cortex, MTL, mPFC, and cerebellum. Theta oscillations are thought to mediate MTL-neocortical communication and have been implicated in various memory processes (Foster et al., 2013; Fuentemilla et al., 2014; Kaplan et al., 2014; Sederberg et al., 2003; Steinvorth et al., 2010). While previous EAM studies have mainly focused on MTL theta, here we demonstrate that theta oscillations across a widespread network of regions are important for different stages of memory retrieval. These findings converge with fMRI studies identifying a similar network of brain regions during autobiographical memory (for review, see Svoboda, McKinnon, & Levine, 2006). They also suggest that theta oscillations may be a means of communication between regions in this widespread network, although note that increased power does not imply coupling.

While concurrent power increases do not imply communication between regions, theta phase coupling does. Using a subject-specific seed in the left medial posterior parietal lobe, we identified a cluster in the right MTL that was phase synchronized with the seed during EAM construction. Thus, theta phase coupling is a mechanism by which remote regions such as the MTL and parietal lobe communicate during early memory retrieval. Fuentemilla et al (2014) similarly found theta phase coupling during autobiographical memory recollection, using an MTL seed and identifying clusters in the precuneus and mPFC. It is worth noting that
participants in their study listened to recordings of their memories, so the search or construction process was minimized, whereas our task required participants to search for a memory in response to a more general cue. Interestingly, we found MTL-parietal theta phase coupling during early memory construction but not during elaboration, the stage which most closely resembles Fuentemilla et al.’s task. One possible explanation for this difference in results is that Fuentemilla et al used general semantic knowledge retrieval as a comparison for EAM, while we used inter-trial rest. As our rest period was non-directed it is possible that in some cases participants were still recollecting memories from the previous trial or constructing scenarios that recruit similar processes. This may have resulted in less distinction between elaboration and rest as there may be substantial overlap between cognitive processes during these phases.

Our finding of MTL-parietal theta phase synchronization during early memory construction is consistent with predictions from the BBB model that theta oscillations coordinate MTL-parietal translations between spatial reference frames (Byrne et al., 2007). We demonstrate that MTL-parietal interactions are present when participants are bringing to mind an event during this early construction phase. During later elaboration, MTL-parietal communication may not be recruited to the same extent because a memory has already been brought to mind, and translation between spatial reference frames may have already occurred. At this stage the parietal window, a population of neurons likely within the precuneus, may be carrying out its function of representing and manipulating egocentric information for mental exploration (Byrne et al., 2007). We also found that place cues elicited less MTL-parietal theta phase synchronization during construction compared to other cues (people and objects). These findings show that MTL-parietal theta phase coupling is sensitive to spatial cues, supporting a spatial role for communication between these regions in EAM. Less coupling may be needed when spatial information is provided as a direct cue, but when a non-spatial cue is provided spatial context needs to be retrieved and thus greater coupling is needed. Non-spatial cues may also require more MTL-parietal communication to translate the retrieved spatial context into an egocentric representation to be used for imagery. Note that this interpretation is speculative as we have no direct measure of translation between spatial reference frames.
4.6.1.2 Gamma power and theta-gamma phase-amplitude coupling

In addition to theta, we also examined gamma power and theta-gamma phase-amplitude coupling. During memory construction, high gamma power increased relative to rest in occipital/posterior parietal and dorsal prefrontal regions, and during elaboration we found widespread gamma increases in occipital and parietal lobes, retrosplenial cortex, PFC, and cerebellum. Gamma oscillations are typically associated with visual perception (Hall et al., 2005; Hoogenboom, Schoffelen, Oostenveld, Parkes, & Fries, 2006), but more recently have been implicated in memory processes (Burke et al., 2013; Solomon et al., 2017; Steinvorth et al., 2010). Here we find strong increases in high gamma power during EAM across a widespread network including representational cortices and dorsal PFC. Notably, gamma power was strongest at elaboration, suggesting that retrieving the details of a memory and recollecting it depend more on gamma activity than searching for and constructing a memory.

Interestingly, some have demonstrated using intracranial recordings that increases in gamma power correlate with gamma desynchronization and that gamma desynchronization is associated with successful memory formation (Burke et al., 2013; Solomon et al., 2017). Solomon et al (2017) argue that this is because high gamma may largely reflect stochastic, non-oscillatory, spiking neural activity, but report that in rare occasions (1% of electrodes in their intracranial EEG study), gamma activity is organized into synchronized oscillations that coordinate activity between widespread regions. In contrast, one recent study found that EAM but not general semantic memory retrieval was associated with increased gamma synchrony (Fuentemilla et al., 2017). Notably, this study defined the gamma frequency band as 27-45 Hz, which is low compared to gamma as defined by previously described studies (typically at least 30–80 Hz but sometimes higher). Higher gamma may be reflective of stochastic spiking neural activity more likely to desynchronize, whereas slower gamma could reflect oscillatory activity more likely to synchronize across regions. Indeed, one review concluded that memory-related high gamma activity reflects an asynchronous signal that is a biomarker of neural activation (Burke et al., 2015). While we did not examine gamma synchrony in the present study, our finding of widespread high-gamma power increases during memory retrieval are consistent with high gamma power, and possibly desynchronization, being important for memory-related processes.
Having demonstrated widespread increases in gamma power and MTL-parietal theta phase coupling, we next investigated whether local gamma amplitude is modulated by the phase of MTL theta oscillations. We found PAC between MTL theta phase and parietal gamma amplitude during early memory construction compared to rest. Interestingly, MTL theta modulated precuneus gamma but the reverse was not true, supporting the MTLs role in coordinating neocortical activity. A number of studies have identified theta-gamma coupling in humans (Axmacher et al., 2010; Staudigl & Hanslmayr, 2013; Canolty et al., 2009; Kaplan et al., 2014), but ours is the first to demonstrate this phenomenon in EAM. These novel findings fit with the notion that theta and gamma oscillations play an important role in MTL-neocortical coordination, perhaps serving to mediate these interactions.

It is interesting that we found increases in theta phase coupling and PAC measures during early memory construction relative to rest, but not during elaboration relative to rest. As discussed above, it is possible that MTL-parietal communication is more crucial for bringing an event to mind than elaborating on it. MTL-parietal communication may also be recruited during elaboration, but to a lesser extent. Interestingly, we found that MTL-parietal PAC during elaboration was associated with more vivid recall of memories, and theta phase coupling between posterior regions during elaboration was related to memory vividness and other subjective EAM measures. These findings suggest that communication between distributed regions during elaboration may be more important for subjective aspects of recollection, whereas communication during construction may be more vital for bringing an initial event to mind. Thus, despite not demonstrating group-level increases relative to rest, theta phase coupling and PAC during elaboration appear to have functional relevance, perhaps being important for the vividness and ease of recollection. It is also possible that the use of inter-trial rest phase as comparison for elaboration reduced our likelihood of identifying differences due to the similarity between these phases. Nonetheless, together these results suggest that the MTL and parietal lobe interact via theta phase coupling and theta-gamma PAC during early EAM retrieval.
4.6.2 Effects of precuneus stimulation

4.6.2.1 Behavioural effects of precuneus stimulation

We found tentative evidence to suggest that precuneus stimulation alters subjective memory vividness and ease of recall. Although we found no significant differences in behaviour when measured within-subjects, post-hoc analyses confirmed that the order of counterbalancing significantly interacted with the effects of stimulation on memory vividness. This order effect prompted us to perform an exploratory between-subjects analysis comparing each participant’s first session only, which revealed that inhibitory precuneus stimulation led to decreased memory vividness and more effortful recall compared to vertex stimulation. Very few studies have used TMS to examine the causal role of the precuneus in memory. One study found that repetitive TMS to the precuneus modestly enhanced episodic memory in patients with Alzheimer’s disease (Koch et al., 2017), while an earlier study from the same group found that precuneus cTBS enhanced source memory retrieval (Bonni et al., 2015). The only two TMS-EAM studies to date both targeted the angular gyrus and reported reduced internal episodic details compared to vertex stimulation. Thakral et al (2017) additionally found increased external semantic details, while Bonnici et al (2018) found a reduction in the number of events recalled from a first-person perspective (Thakral et al., 2017). Our findings add to this limited literature by demonstrating a causal role for the precuneus in EAM.

Contrary to our hypothesis, precuneus stimulation did not affect the tendency to recall events from a first-person perspective. While we previously found that precuneus volume is positively associated with recalling autobiographical memories from a first-person perspective (Hebscher, Levine & Gilboa, 2017; Chapter 2), the present study does not support a causal role for the precuneus in this function. It is possible that we were not successful in targeting the exact region of the precuneus responsible for egocentric processing in every participant because we did not use a functional participant-specific target. Indeed, the degree of change in perspective rating between stimulation sessions was highly variable across participants (see Appendix C), suggesting that stimulation had a greater effect on some participants than others. Future studies could use a functionally-defined target for each participant, although it is possible that this region would not be superficial enough to target in every participant. An alternative interpretation of
these results is that the precuneus is involved in egocentric processing during EAM, but not causally so, perhaps due to its interactions with other posterior parietal regions like the angular gyrus (Bonnici et al., 2018). This interpretation will be discussed in more detail in the General Discussion (Chapter 5). Future TMS studies are needed to clarify the nature of the precuneus’ role in egocentric processing.

4.6.2.2 Oscillatory effects of precuneus stimulation

Having demonstrated that theta and gamma oscillations mediate the communication between widespread regions during EAM, we next examined whether the precuneus plays a causal role in this communication. We show that the precuneus plays a causal role in theta and gamma oscillatory activity underlying MTL-parietal communication. Precuneus stimulation altered communication between parietal lobe and MTL as demonstrated by reduced PAC during memory construction compared to rest. Although we did not find a significant effect of precuneus stimulation on phase coupling during construction, we did find a subthreshold decrease in MTL-parietal phase coupling, suggesting the same pattern of effects for phase coupling and PAC. This difference in significant findings may be explained by the stricter threshold used for phase coupling results to account for the whole-brain nature of this analysis, compared to a region of interest approach for PAC.

At rest, precuneus stimulation reduced MTL-parietal theta phase coupling, demonstrating that stimulation alters baseline phase coupling. Interestingly, precuneus stimulation led to an increase in MTL-parietal phase coupling during elaboration relative to rest that was one voxel short of passing our clustering threshold, suggesting that stimulation affected memory elaboration in the opposite direction than during rest. These findings suggest a compensatory response to stimulation such that the increase in phase coupling for elaboration relative to rest is greater following precuneus stimulation. In other words, precuneus stimulation disrupts baseline MTL-parietal communication, but when individuals must recollect a memory they compensate for stimulation by increasing phase coupling more than they normally would. Thus, we may be better able to see the inhibitory effects of TMS at rest when no specific demands are placed on the network. Note that this compensatory response was not seen during construction, suggesting that stimulation differentially affects construction and elaboration stages. Interestingly, as we
discuss below, some participants also showed a compensatory increase in power following precuneus stimulation, but only during elaboration. Together these findings suggest that compensatory responses to stimulation may be more likely to occur during elaboration than construction.

We also found that stimulation-induced changes in MTL power during memory retrieval were associated with changes in memory following stimulation. Specifically, ease of recall (effort rating) significantly predicted changes in MTL theta and gamma power during elaboration. Together with our previous findings that individual differences in effort ratings are associated with hippocampal volume (Chapter 2; Hebscher et al, 2017), these findings indicate that this measure of subjective EAM is sensitive to MTL structure and function. We also found that stimulation-induced changes in vividness were associated with greater parietal-frontotemporal theta phase coupling following stimulation. Previous studies have demonstrated communication between these regions via theta oscillations, finding that mPFC theta couples with posterior MTL/retrospenial cortex theta (Kaplan et al, 2017) and parietal gamma during spatial memory and imagery (Kaplan et al, 2014). In line with these studies, our findings suggest that parietal-prefrontal theta phase coupling is important for memory vividness. Although the direction of these effects cannot be determined, one interpretation is that precuneus stimulation modifies behaviour through alteration of power and phase coupling. Participants for whom stimulation more strongly inhibits this oscillatory activity also show the greatest behavioural deficit in response to TMS. On the other hand, some participants demonstrate an excitatory response to stimulation as evidenced by increases in theta/gamma power and phase coupling, and therefore show memory benefits following precuneus stimulation. Individual differences in the response to stimulation may depend on a number of factors including brain state at the time of encoding and pre-stimulation connectivity (Keller et al., 2018; Solomon et al., 2017), although we were unable to demonstrate this in the present study. An alternative interpretation of these results is that changes in theta/gamma power and theta phase coupling are correlates of behavioural change in response to TMS. However, we and others (Watrous, Fell, Ekstrom, & Axmacher, 2015) do not consider neural oscillations to be simple epiphenomena of behaviour. Evidence against the epiphenomena argument comes in part from studies using transcranial alternating current stimulation to entrain neural oscillations, finding that entrained rhythms alter behaviour (Helfrich et al., 2014; Javadi & Spiers, 2015; Polania, Nitsche, Korman, Batsikadze, & Paulus, 2012).
Thus, we believe that oscillations reflect mechanisms of action rather than epiphenomena of behaviour, but note that this later interpretation cannot be ruled out in the present study.

4.6.3 Conclusions

We show that MTL and parietal lobe interact via theta and gamma oscillatory activity during EAM. Our results support the notion that theta phase coupling and theta-gamma phase-amplitude coupling mediate MTL-neocortical coordination during memory processes. We further show that precuneus stimulation leads to an overall pattern of inhibition of theta and gamma oscillatory activity and subjective EAM, demonstrating a causal role for this region. Variability in the oscillatory after-effects of stimulation are related to behavioural after-effects, suggesting that some individuals are able to compensate for the inhibitory effects of stimulation, while others are not. Our results indicate that continuous theta burst stimulation can be used to causally alter oscillatory activity, and that these affects are long-lasting. These findings demonstrate the feasibility of using TMS and MEG to study autobiographical memory.
Chapter 5
General Discussion

5.1 Summary

This dissertation aimed to explore the temporal dynamics of EAM and the role spatial information plays in its retrieval, using a combination of behavioural, neuroimaging, and neurostimulation approaches. The results from the studies in this dissertation shed light on the importance of early spatial representations to EAM, as well as the behavioural and neural dynamics of EAM retrieval.

Chapter 2 showed that spatial information contributes to the efficiency and phenomenology of EAM, demonstrating a temporal precedence for recall of spatial information at the behavioural level. Importantly, there was a large amount of individual variability in EAM performance, with some individuals better able to capitalize on early spatial information than others. We further found that individual differences in spatial aspects of EAM were reflected in hippocampus and precuneus grey matter volumes. The tendency to recollect memories from an egocentric, or first-person, perspective was associated with larger precuneus volume, while the ability to benefit from spatial cues was associated with hippocampal CA2/CA3 volumes. These findings provide insight into the behavioural dynamics of EAM and the neural correlates of spatial aspects of EAM.

Building on the findings from Chapter 2, Chapter 3 examined the temporal dynamics of EAM at the neural level using MEG, which very few studies to date have done. We showed that while spatial cues alter the dynamics of EAM, they do not confer an early neural advantage. Rather, different cues elicited distinct spatiotemporal patterns of activity, suggesting that multiple routes to memory retrieval exist. Using TMS we found that the precuneus is causally involved in the neural dynamics of EAM recollection, with stimulation shifting the dynamics of retrieval in time. We also showed that evoked activity during memory elaboration resembles a well-known ERP correlate of episodic memory, the late positive component, providing an important link between the neural correlates of episodic and autobiographical memory. Interestingly, these results
showed that the LPC was associated with spatial perspective ratings and that precuneus stimulation eliminated this association. The results from Chapter 3 help clarify the temporal dynamics of EAM at the neural level, providing insight into the role that spatial information plays in its retrieval.

While Chapter 2 examined the neural correlates of spatial aspects of EAM, the use of structural MRI did not allow for investigation of dynamic activity or network interactions. Chapter 4 therefore assessed how regions representing spatial information interact dynamically by measuring oscillatory activity during EAM retrieval. We found that theta and gamma oscillations underlie MTL-medial parietal communication during retrieval. Specifically, we demonstrated theta-gamma phase-amplitude coupling during EAM, identifying a mechanism by which these regions may transfer information. We also showed that the precuneus plays a causal role in network-wide theta and gamma oscillatory activity, and provided preliminary evidence for a causal role for this region in subjective aspects of EAM. Finally, we found that variability in the behavioural after-effects of precuneus stimulation is related to changes in MTL theta and gamma power, and parietal-frontal theta phase coupling. These findings shed light on the high variability commonly found in TMS studies, suggesting that such variability may be related to neural activity beyond the site of stimulation.

5.2 Theoretical implications

The primary theoretical motivation for this dissertation was derived from space-based theories of memory. Scene construction is considered fundamental to the vivid recollection of memories (Hassabis and Maguire, 2007; Robin et al., 2015; Burgess et al., 2001), and is thought to occur early and ubiquitously by the hippocampus (Hassabis & Maguire, 2007). The BBB model posits that spatial information initially represented by the hippocampus and surrounding MTL regions is translated into parietal-based egocentric spatial representations. The posterior parietal cortex, specifically the precuneus, maintains and manipulates spatial information from an egocentric perspective to be used for mental imagery in memory (Byrne et al., 2007). Theta oscillations are thought to underlie this translation process, with the hippocampus transmitting information to parietal structures during peaks in theta, and receiving during troughs. Below I will discuss the
extent to which findings from the studies in this dissertation support predictions derived from these theories.

5.2.1 Early spatial information and the hippocampus

In Chapter 2 we demonstrated that spatial information plays an early and important role in EAM retrieval, but not a ubiquitous one. The majority of participants tended to spontaneously recall location before other information, a putative measure of ‘scene construction’, and this tendency was associated with faster reaction times. In line with the proposed early role of spatial context during memory retrieval, these findings suggest that some individuals can capitalize on early spatial information, allowing them to recall memories more quickly. However, the variability in this tendency argues against the notion that early scene construction always acts as a critical scaffold for memory retrieval, a central prediction made by scene construction theories. We also did not find an association between hippocampal volume and our putative measure of scene construction, contrary to the prediction that the hippocampus plays a fundamental role in scene construction. Rather, we found tentative evidence linking hippocampal CA2/CA3 volumes to the ability to benefit from spatial cues, suggesting that the hippocampus plays a role in representing spatial context for some individuals more than others. These findings are also in line with the established role of CA3 in pattern completion, the ability to retrieve a complete memory via a partial cue (cf. Neunuebel & Knierim, 2014; Schapiro, Kustner, & Turk-Browne, 2012). As we used an automated segmentation tool to obtain hippocampal subfield volumes, it will be important for future studies to verify this association using manual segmentation and high resolution scans.

While Chapter 2 demonstrated an early advantage for spontaneously recalled spatial information, in Chapter 3 we found that cueing individuals with spatial information did not allow for more efficient or quicker recall. Although different cues led to distinct spatiotemporal patterns of activity, spatial cues did not elicit earlier neural activity, nor did they lead to faster or less effortful recall. These findings highlight the distinction between spontaneous and cued recall of spatial information. As described in Chapter 3, it is possible that the tendency to recall spatial information when not cued with a location may have obscured potential differences between cue-types. Although we were not able to do so here, future studies could assess the evoked response
to spontaneous, rather than cued, recall of spatial information in order to gain a better understanding of neural representations of early spatial information.

Another possible explanation for this finding is that, similar to our findings in Chapter 2, there is high individual variability in the tendency to benefit from spatial cues, variability that may be related to hippocampal volume. Although we observed such variability in Chapter 2, Chapter 3 did not have a sufficient number of participants to formally analyze individual differences on this trait. Nonetheless, these studies together suggest high individual variability in representations of spatial information during EAM. While we identified an overall tendency for participants to spontaneously report spatial information early, we did not find a group-level advantage for spatial cues. Thus, although these findings are in partial agreement with scene construction theory, they do not support several central predictions of this theory.

5.2.2 Precuneus and subjective EAM

The precuneus has been implicated in mental imagery during memory retrieval, specifically from a first-person or egocentric perspective. In Chapter 2 we showed that precuneus grey matter volume is positivity associated with the tendency to recall EAMs from an egocentric perspective, in line with one other previous study (Freton et al., 2014). However, we failed to find a causal role for the precuneus in egocentric processing during EAM in Chapter 4, contrary to our hypothesis. One possible explanation for this finding is that our measure of perspective was not sensitive enough to show potentially subtle changes caused by stimulation. Another possibility is that the precuneus is involved in egocentric processing during EAM along with a network of other posterior parietal and MTL regions, but its role in this function is not causal. One recent study found that TMS to the angular gyrus reduced the number of autobiographical memories experienced from a first-person perspective, while also reducing the number of internal details recalled (Bonnici et al., 2018). The authors interpret this result as implicating the angular gyrus in integrating memory features within an egocentric framework to enable the subjective experience of remembering. Interestingly, in Chapter 4 we found that precuneus-angular gyrus theta phase coupling is modulated by perspective ratings, with more coupling predicting higher egocentric ratings. Other studies have implicated both the angular gyrus and precuneus in shifting visual perspectives during autobiographical memory (Iriye & Jacques, 2018; Jacques,
Szpunar, & Schacter, 2016). Thus, it may be the case that interactions between these regions are important for representing events from an egocentric perspective, with the angular gyrus playing more of a critical role than the precuneus.

In Chapter 3 we showed that spatial perspective ratings were associated with the late positive component, a well-established neural correlate of episodic recollection. Greater LPC amplitudes over right parietal sensors were associated with mid-range perspective ratings, likely reflecting the tendency to flexibly recall memories from multiple perspectives. Precuneus stimulation eliminated this association, suggesting that this region is crucially involved in neural processing of spatial perspective during EAM retrieval. Although precuneus stimulation did not significantly alter LPC at the group level, we did find a trend towards precuneus stimulation reducing LPC amplitudes. The LPC is thought to reflect recollection-sensitive activity in the parietal lobe (Rugg & Curran, 2007), and has also been found to be associated with the retrosplenial cortex and MTL (Addante et al., 2012; Düzel et al., 2001; Hoppstädter et al., 2015), although different memory tasks may determine the exact source of the LPC. Our results additionally implicate the precuneus in the LPC during EAM. Although we did not source localize this effect, it is likely that a network of regions is involved including previously identified posterior parietal regions, MTL, and retrosplenial cortex. Our finding of the LPC being related to perspective ratings also fits with the BBB model’s prediction that the same network of regions (MTL, retrosplenial cortex, medial parietal) is involved in translating spatial information between different perspectives (Byrne et al., 2007). The findings from Chapters 3 and 4 together suggest that the precuneus’ involvement in spatial perspective may not be purely egocentric and likely depends on interactions with other regions.

We also show that the precuneus plays a causal role in non-spatial behavioural and neural aspects of EAM. In an exploratory between-subjects analysis of EAM rating scales, we found tentative evidence to suggest that precuneus plays a causal role in memory vividness and ease of recall, with inhibitory TMS leading to lower ratings compared to vertex TMS. These findings suggest that precuneus stimulation makes it more difficult for participants to retrieve a memory, and once they do retrieve one they recollect it less vividly. These findings fit with previous studies that have found a relationship between precuneus activity and memory vividness (cf. Gilboa et al., 2004; Richter et al., 2016; Sheldon & Levine, 2013). Our findings add to the results
from these studies by showing that precuneus’ role in memory vividness is causal. The precuneus’ role in memory vividness may be related to its role in visual imagery, for which it has been termed ‘the mind’s eye’ (Fletcher et al., 1995). Indeed, neuropsychological studies have shown that visual imagery is central to autobiographical memory, with visual memory impairments leading to profound amnesia (Greenberg & Rubin, 2003). Thus, these studies point to a visual, but not spatial, causal role for the precuneus in EAM, although these roles may not be mutually exclusive.

We also found a causal role for the precuneus in the temporal dynamics of EAM at the neural level, with precuneus stimulation delaying the evoked response during early construction. Precuneus stimulation also altered oscillatory activity underlying MTL-parietal communication. Together these findings suggest that the precuneus is a central node in the EAM network, crucially contributing to memory vividness and dynamic neural activity. Importantly however, they fail to support a space-specific causal role for the precuneus in EAM.

5.2.3 MTL-parietal interactions

In Chapter 2 we showed that the precuneus and hippocampus are associated with spatial aspects of EAM. Building off these results, in Chapter 4 we measured oscillatory activity during early memory construction to determine how regions representing spatial information interact to produce a coherent memory. We found that the MTL and medial parietal lobe demonstrate theta phase coupling and theta-gamma phase-amplitude coupling during early memory construction. In the context of the BBB model, one interpretation of this finding is that MTL-based allocentric spatial representations are translated into parietal-based egocentric representations via theta oscillations in the milliseconds before participants report that they have retrieved a memory. We further found that spatial cues elicited less left MTL-parietal theta phase synchronization during construction compared to non-spatial cues, suggesting that communication between these regions is sensitive to spatial information. In line with this finding, in Chapter 3 we found that spatial cues led to reduced amplitudes during early construction, with a non-significant trend of this effect being source localized to the left MTL. Based on the scene construction theory assumption that all memories are played out within a spatial context (Hassabis & Maguire, 2009), one interpretation of these results is that place cues require less processing because they partially
bypass the construction stage of memory retrieval. Person and object cues may require more MTL-parietal communication (via theta oscillations) in order to retrieve and construct a spatial context and translate it into a representation that can be used for imagery. Importantly however, in Chapter 3 we found no evidence that place cues elicit earlier neural activity, suggesting that an early advantage for spatial information may be better characterized by a reduction, rather than a shift, in activity. Although these findings are consistent with the predictions derived from space-based theories, they are speculative because we have no direct behavioural measure of spatial reference frame translation or scene construction during this period.

Taken together, the findings from the studies in this dissertation support an early and important role for spatial information in EAM retrieval, but not a ubiquitous or automatic one. Consistent with space-based theories of memory, we found that precuneus and hippocampus represent spatial information during EAM, and these regions interact via theta and gamma oscillations, with spatial cues modifying the degree of interaction. Finally, we find that the precuneus plays a crucial role in subjective EAM, dynamic neural activity, and neural processing of spatial perspective during EAM. However, we do not find evidence supporting a space-specific causal role for the precuneus in EAM. The BBB model predicts that the parietal window, a population of neurons likely located within the precuneus, maintains and manipulates egocentric information for mental exploration. Our results suggest that the parietal window may not be located exclusively in the precuneus, but might include nearby posterior parietal regions such as the angular gyrus. It is thus possible that interactions between a wider network of regions including the precuneus are crucial for this function. Moreover, these findings demonstrate that the precuneus is important for memory vividness, as suggested by models of autobiographical memory that do not emphasize spatial processing. Future studies are needed to more carefully probe the role of the precuneus in representing spatial information during memory retrieval.

5.3 Neural oscillations

Long-term memory retrieval depends on communication between medial temporal lobe and neocortical regions, thought to be supported by neural oscillations (Fell & Axmacher, 2011). However, research examining the oscillatory correlates of autobiographical memory is lacking, with only a small number of studies identifying theta and gamma oscillations during EAM
Of these studies, two identified theta phase coupling (Foster et al., 2013; Fuentemilla et al., 2014), and two examined low gamma, finding phase synchrony and power increases, respectively (Fuentemilla et al., 2017; Steinvorth et al., 2010). In Chapter 4 we identified theta phase coupling between the MTL and parietal lobe during EAM retrieval, similar to findings from Fuentemilla et al (2014), and more generally in line with a growing body of literature implicating theta oscillations in information exchange between distributed regions.

We also demonstrated for the first time that theta-high gamma phase amplitude coupling underlies MTL-parietal communication during EAM. PAC is thought to play a functional role in cognition by allowing activity to be integrated across multiple spatial and temporal scales. Some have proposed that theta-high gamma PAC in particular is important for learning and memory because it regulates long term synaptic potentiation (LTP) (Canolty & Knight, 2010). This proposal has been supported by studies showing that LTP is effectively induced when stimulation is administered to rats at a pattern corresponding to theta-gamma PAC (high gamma bursts recurring at theta rates) (Hölscher, Anwyl, & Rowan, 1997; Huerta & Lisman, 1995; Larson, Wong, & Lynch, 1986). Others have proposed that theta phase modulation of gamma reflects the temporal sequencing of items necessary for both spatial navigation and long-term memory retrieval (Lisman & Buzsáki, 2008). In the context of this proposal, one function of theta-gamma PAC may be to support the sequential organization of items in an event, allowing recall of a temporally coherent autobiographical memory. While our data do not permit investigation of these proposals, our findings more generally support the notion that theta phase modulation of gamma amplitude is important for memory of complex, multi-modal, extended events (For reviews, see Fell & Axmacher, 2011; Lisman & Buzsáki, 2008). It will be important for future studies to investigate whether other autobiographical memory network nodes communicate similarly to better understand how theta-gamma PAC supports autobiographical memory.

5.4 TMS

Previous TMS studies have often found complex and inconsistent effects on neurocognitive functions (Héroux, Taylor, & Gandevia, 2015). Similar to previous studies examining the effects
of parietal stimulation on episodic memory (Thakral et al., 2017; Yazar et al., 2014), our results showed high variability in individual response to TMS. Our results also demonstrate that such variability is reflected in oscillatory activity beyond the site of stimulation, highlighting the importance of considering individual differences in TMS studies. In Chapter 4 we argued that some participants showed a compensatory response to inhibitory stimulation such that they had increased theta and gamma oscillatory activity following stimulation which correlated with improved memory. Others showed the opposite pattern, although it is unclear why these participants responded so differently to TMS. Further research is needed to determine the complex factors underlying the neural and behavioural variability in response to TMS.

One source of variability may be related to the method of localizing stimulation site. The simplest method of determining stimulation site is using standard 10-20 EEG positions, which does not account for structural or functional brain differences. Using an individual subject’s structural MRI to target specific coordinates can account for individual anatomical differences, but not for differences in structure-function relationships (Sack et al., 2009). This approach is most successful when coordinates are chosen based on functional neuroimaging data. A final approach that accounts for both structural and functional individual differences is the use of participant-specific fMRI data to determine stimulation site. Sack et al (2009) directly compared these methods and found that while all were accurate and valid, the simplest approach (10-20 EEG) required over nine times more participants than the most complex method (individual fMRI coordinates) to achieve sufficient power for a significant effect. In Chapters 3 and 4 we used individual structural MRIs to target specific coordinates determined by previous functional neuroimaging data. Sack et al (2009) concluded that this technique required 9 participants to observe a significant effect of right parietal TMS on a number comparison task. However, it is important to note that this task is likely less variable than our EAM task with less possibility for the use of compensatory cognitive strategies. While we were not able to control for individual differences in functional localization in the present studies, future studies could use a functionally-defined target for each participant to better account for this variability.

One unexpected finding from Chapter 4 was that the order of counterbalancing stimulation sessions interacted with the effect of stimulation on EAM. When we examined rating scales for participants’ first stimulation session we saw that precuneus stimulation inhibited subjective
EAM, but did not find the same effect when we compared their second session. The subjective nature of our task may have contributed to this effect, such that participants compared their second session to their first. In other words, it is possible that the first stimulation session served as an individual ‘baseline’ with which participants compared subsequent performance on the EAM task. Thus, looking at the first stimulation session allowed us to observe more objective responses. Importantly, we found this effect even though we spaced stimulation sessions by at least 24 hours (mean = 5.4 days), which should have minimized interference between sessions. These findings have implications for within-subjects TMS studies measuring subjective behaviour and demonstrate that certain precautions should be taken to minimize interference or dependence between sessions. Future studies should include a baseline task prior to each stimulation session, enabling calculation of the change from baseline for each session which could then be compared between sessions. Future studies should also space sessions by a longer period of time to reduce the likelihood of interference between sessions.

5.5 Conclusions

The studies in this dissertation help elucidate the neural and behavioural dynamics of EAM retrieval and offer insights into the contributions of spatial information to EAM. These findings demonstrate that spatial information plays an early and important role in EAM retrieval, but not a ubiquitous one. At the neural level, the precuneus and hippocampus, and dynamic interactions between these regions, are implicated in spatial aspects of EAM. These findings help clarify interpretations of space-based theories of memory and how they may apply to EAM. By moving beyond traditional approaches to studying EAM, the studies in this dissertation provide novel insights into the dynamic and causal involvement of autobiographical memory network nodes. In particular, these studies demonstrate the feasibility of using TMS to determine the causal roles of specific regions in EAM, which very few studies to date have done. They also show that examining specific patterns of oscillatory activity may uncover important information about episodic and autobiographical memory. Future research is needed to further clarify the key contributions of specific regions and the dynamic activity underlying widespread neural communication during EAM.
References


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hippocampal theta rhythm induces long-term potentiation that can be depotentiated by stimulation on the negative phase in area CA1 in vivo. *Journal of Neuroscience, 17*(16), 6470–6477.


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Appendices

Appendix A. Exploratory regression analyses from Chapter 2

Table A.1. Exploratory regression analyses on behavioural measures used in a priori analyses

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Effort Difference</th>
<th>Re-experiencing Difference</th>
<th>Visual Difference</th>
<th>Setting Difference***</th>
<th>Place-person ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Step 1</td>
<td>Step 2</td>
<td>Step 1</td>
<td>Step 2</td>
<td>Step 1</td>
</tr>
<tr>
<td>Age</td>
<td>0.07</td>
<td>-0.09</td>
<td>-0.34*</td>
<td>-0.42*</td>
<td>0.11</td>
</tr>
<tr>
<td>Gender</td>
<td>-0.40*</td>
<td>-0.54*</td>
<td>-0.32</td>
<td>-0.45</td>
<td>0.05</td>
</tr>
<tr>
<td>TIV</td>
<td>-0.20</td>
<td>-0.33</td>
<td>-0.09</td>
<td>-0.20</td>
<td>0.13</td>
</tr>
<tr>
<td>Precuneus</td>
<td>-0.10</td>
<td>-0.04</td>
<td>-0.11</td>
<td></td>
<td>-0.21</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>0.41</td>
<td>0.23</td>
<td>0.14</td>
<td></td>
<td>-0.11</td>
</tr>
<tr>
<td>PHC</td>
<td>0.11</td>
<td>-0.06</td>
<td>0.07</td>
<td></td>
<td>0.08</td>
</tr>
<tr>
<td>RSC</td>
<td>0.03</td>
<td>-0.26</td>
<td>-0.13</td>
<td></td>
<td>-0.07</td>
</tr>
<tr>
<td>mOFC</td>
<td>-0.13</td>
<td>0.17</td>
<td>-0.22</td>
<td></td>
<td>-0.37</td>
</tr>
<tr>
<td>Superior parietal</td>
<td>-0.06</td>
<td>0.05</td>
<td>0.55*</td>
<td></td>
<td>0.36</td>
</tr>
<tr>
<td>$R^2$</td>
<td>0.12</td>
<td>0.25</td>
<td>0.16</td>
<td>0.22</td>
<td>0.02</td>
</tr>
<tr>
<td>$F$</td>
<td>1.74</td>
<td>1.17</td>
<td>2.43</td>
<td>1.02</td>
<td>0.32</td>
</tr>
</tbody>
</table>

Note: $\beta$ values reported

*TIV* = total intracranial volume, *PHC* = parahippocampal cortex, *RSC* = retrosplenial cortex, *mOFC* = medial orbitofrontal cortex

* $p < .05$
Table A.2. Exploratory regression analyses on behavioural measures not used in a priori analyses (averaged) from Chapter 3.

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Effort Rating</th>
<th>Re-experiencing Rating</th>
<th>Recall of Setting</th>
<th>Visual Details</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Step 1</td>
<td>Step 2</td>
<td>Step 1</td>
<td>Step 2</td>
</tr>
<tr>
<td>Age</td>
<td>0.29</td>
<td>0.33</td>
<td>-0.21</td>
<td>-0.29</td>
</tr>
<tr>
<td>Gender</td>
<td>0.09</td>
<td>0.07</td>
<td>-0.04</td>
<td>0.07</td>
</tr>
<tr>
<td>TIV</td>
<td>-0.24</td>
<td>-0.12</td>
<td>0.09</td>
<td>0.62</td>
</tr>
<tr>
<td>Precuneus</td>
<td>0.06</td>
<td>-0.05</td>
<td>0.47</td>
<td>0.17</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>-0.12</td>
<td>-0.01</td>
<td>0.13</td>
<td>0.13</td>
</tr>
<tr>
<td>PHC</td>
<td>-0.14</td>
<td>0.07</td>
<td>0.24</td>
<td>0.39*</td>
</tr>
<tr>
<td>RSC</td>
<td>-0.24</td>
<td>-0.07</td>
<td>0.01</td>
<td>0.06</td>
</tr>
<tr>
<td>mOFC</td>
<td>0.30</td>
<td>-0.51</td>
<td>-0.26</td>
<td>-0.31</td>
</tr>
<tr>
<td>Superior parietal</td>
<td>-0.19</td>
<td>-0.05</td>
<td>-0.13</td>
<td>-0.09</td>
</tr>
<tr>
<td>R^2</td>
<td>.15</td>
<td>.27</td>
<td>.05</td>
<td>.12</td>
</tr>
<tr>
<td>F</td>
<td>2.25</td>
<td>1.33</td>
<td>0.68</td>
<td>0.68</td>
</tr>
</tbody>
</table>

Note: β values

* p < .05

TIV = total intracranial volume, PHC = parahippocampal cortex, RSC = retrosplenial cortex, mOFC = medial orbitofrontal cortex
Appendix B: Place-other ratios from Chapter 3.

**Figure B.1.** Frequency distribution for place-person ratio, by participant, for both stimulation sessions. Ratios greater than 1 reflect the tendency to report place over other information as the first thing that came to mind when recalling a memory, when not cued with a location. The dotted line represents the point at which place and other responses were equal.
Appendix C: Exploratory within-subjects analysis on the behavioural effects of TMS from Chapter 4

**Figure C.1** Within-subjects analysis of EAM rating scales showing change for each participant between precuneus and vertex stimulation sessions.