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Neural Networks Involved in Spatial and Temporal Pattern Separation

Doctor of Philosophy, Fall 2012

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Psychology, Ryerson University

Critical to episodic memory is pattern separation (PS), the storage of similar inputs as distinct and nonoverlapping. Spatial and temporal PS have been shown to be related to disparate subfields of the hippocampus (HC) in rodents. Extra-HC structures involved have not yet been elucidated. The current work provides an exploratory investigation into the neural correlates of spatial and temporal PS, employing functional magnetic resonance imaging and univariate and multivariate analysis techniques. In Experiment 1, behavioural spatial and temporal memory tasks were developed that assess varying PS demands. Objectives for the experiment were met, in that accuracy was lower and reaction time higher for conditions requiring more engagement of PS. In Experiment 2, whole-brain regions as well as the neural networks involved in spatial and temporal PS were examined, and functional connectivity of the HC was observed. Univariate data revealed unique areas of activation based on information type being encoded (i.e., spatial vs. temporal). The cuneus and HC were uniquely involved in the spatial task, while a wider area of regions including middle occipital and medial frontal areas were activated in the temporal task. Multivariate analyses were convergent with the spatial and temporal context memory literature. The HC, parahippocampal gyri, prefrontal cortices, and precuneus were part of a correlated network in the spatial task. Bilateral prefrontal cortices, including the orbitofrontal cortex were involved in the temporal task. Further, the multivariate analysis revealed qualitatively distinct networks based on memory processing stage (i.e., encoding vs. retrieval). Interestingly, the network included anterior HC in spatial encoding, and posterior HC in spatial and temporal

retrieval, consistent with an influential theory positing a rostrocaudal gradient along the HC for encoding and retrieval. Functional connectivity analyses revealed connectivity of the posterior HC seed with temporal and superior parietal areas in the spatial task, and with frontal areas in the temporal task, suggesting the right posterior HC interacts with regions differently based on information type. Results confirm and extend findings from previous literature demonstrating HC involvement in PS, and also suggest HC and extra-HC involvement varies based on processing stage and information type.

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It takes a village to earn a doctorate and this work is as much a product of the efforts and support of my supervisor, colleagues, friends, and family as my own. First and foremost, thank you to the many participants that devoted their time and efforts to this project. Thank you to my advisor, Dr. Todd Girard for your guidance, thoughtfulness, and knowledge. Dr. Julia Spaniol, thank you for your insight and perspective into my work. Tara Stallberg, our Program Administrator, thank you for your attention to detail, organization, and for putting up with my endless stream of emails! Gabe Nespoli, for your help in all things technology-related. Katie Herdman, I am truly grateful for your limitless efforts and assistance. Oren Weiner, our dedicated volunteer lab research assistant, for assisting me with pilot data collection.

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With one singular exception, time's arrow is straight. Unidirectionality of time is one of nature's most fundamental laws. It has relentlessly governed all happenings in the universe—cosmic, geological, physical, biological, psychological—as long as the universe has existed. Galaxies and stars are born and they die, living creatures are young before they grow old, causes always precede effects, there is no return to yesterday, and so on and on. Time's flow is irreversible. The singular exception is provided by the human ability to remember past happenings. When one thinks today about what one did yesterday, time's arrow is bent into a loop. The rememberer has mentally traveled back into her past and thus violated the law of the irreversibility of the flow of time. She has not accomplished the feat in physical reality, of course, but rather in the reality of the mind, which, as everyone knows, is at least as important for human beings as is the physical reality. When Mother Nature watches her favorite creatures turning one of her immutable laws on its head, she must be pleased with her own creativity.

(Tulving, 2002, pp. 1-2)

Chapter 1: Memory and Pattern Separation

Main objective: The main objective of this body of work is to examine spatial and temporal pattern separation in humans, processes that are critical to episodic memory. In particular, I aim to 1) develop spatial and temporal pattern separation tasks that show behavioural sensitivities to separation manipulations and 2) elucidate the whole-brain patterns of activity as well as neural networks involved in pattern separation using functional magnetic resonance imaging. First, I investigate whether the areas of activation and neural networks involved in pattern separation are influenced by information type (i.e., spatial versus temporal). Second, I examine whether conditions requiring more pattern separation show a different pattern of neural activity than conditions requiring less. Third, I investigate the neural networks involved in pattern separation at both the encoding and retrieval processing stages.

The human hippocampus has been central to the study of memory since Scoville and Milner (1957) investigated memory deficits in H.M., a patient with bilateral medial temporal lobe (MTL) lesions. In particular, the hippocampus has been known to play a particularly important role in episodic memory, a process that involves the encoding and retrieval of the perceptual information from events in one's past (Tulving, 1972). In recent years, with the advent of high-resolution blood oxygen level dependent functional magnetic resonance imaging (BOLD fMRI) techniques, the differential roles of hippocampal subfields in cognition have come to the fore in the human episodic memory literature (Carr, Rissman, & Wagner, 2010). These studies have identified the respective roles played by subfields of the hippocampus in pattern separation, a computational neural process inherently required for adequate episodic memory

(Norman & O'Reilly, 2003). Pattern separation is responsible for the storage of similar, overlapping inputs as orthogonalized (i.e., less similar) representations (Yassa & Stark, 2011).

The burgeoning investigation of the subregional correlates of pattern separation is shedding light on low-level computational processes performed by the hippocampus, but several questions remain unanswered. The extra-hippocampal regions involved in pattern separation have yet to be elucidated. In addition, distinct patterns of activity might be expected based on the type of information undergoing pattern separation processes (Yassa & Stark, 2011). For instance, Gilbert, Kesner, and Lee (2001) identified a double dissociation in the CA1 and CA3 subregions of the rodent hippocampus for spatial and spatial-temporal pattern separation. Contrary to the rodent literature, the neural correlates of pattern separation have only been studied in humans with object recognition tasks (e.g. Bakker, Kirwan, Miller, & Stark, 2008; Kirwan & Stark, 2007; Lacy, Yassa, Stark, Muftuler, & Stark, 2010), and comparisons have not been made between spatial and temporal pattern separation (Yassa & Stark, 2011). Further, although numerous studies have documented the neural substrates of spatial and temporal context memory encoding and retrieval more generally (Burgess, Maguire, & O'Keefe, 2002; Crane & Milner, 2005; Ekstrom & Bookheimer, 2007; Hayes, Ryan, Schnyer, & Nadel, 2004; Smith & Milner, 1989; Sommer, Rose, Glascher, Wolbers, & Buchel, 2005; Sommer, Rose, Weiller, & Buchel, 2005 Suthana, Ekstrom, Moshirvaziri, Knowlton, & Bookheimer, 2010; Tubridy & Davachi, 2010, among others), none have examined encoding- and retrieval-specific processes in a task that systematically examines pattern separation.

The focus of the current body of work is to examine the whole-brain neural networks in spatial and temporal pattern separation, both of which are thought to critically involve the hippocampus (Kesner & Hopkins, 2006). Spatial pattern separation and temporal pattern

separation, essential subcomponents of episodic memory, have been found to be reliant on hippocampal cell fields in rodents (Gilbert et al., 2001). The present studies aim to extend these findings by elucidating the whole-brain neural networks involved at encoding and retrieval in spatial and temporal pattern separation. In addition, another aim is to examine the regions functionally connected to the hippocampus when spatial or temporal pattern separation is engaged.

The following sections will provide a review of the background for my dissertation. An overview of hippocampal anatomy and information processing pathways will be followed by a general overview of episodic memory. I will then discuss the role of the hippocampus in spatial and temporal memory. Then an influential model of the role of the MTL in encoding and retrieval will be discussed in relation to other competing theories. A summary of the neural regions supporting the encoding and retrieval of spatial and temporal context memory will follow. The component processes of pattern separation and pattern completion will be defined and differentiated from other similar constructs in the literature, and the neurobiological mechanisms involved in pattern separation and completion will be discussed. Then I will summarize the current body of human neuroimaging studies examining pattern separation. The main objectives and hypotheses of my thesis will then be outlined, with a detailed summary of Partial-Least Squares, a statistical analysis method applied to examine neural networks in neuroimaging data (McIntosh, Bookstein, Haxby, & Grady, 1996).

Chapter 2: Literature Review

Hippocampal Anatomy and Projection Pathways

Although the general role of the hippocampus in episodic memory has been well-established, rodent and human studies have identified functional dissociations among hippocampal subregions. In addition, various episodic memory processes involving the hippocampus have been said to involve a common whole-brain functional network (Buckner & Carroll, 2007). To fully appreciate these, an understanding of hippocampal anatomy is useful, and a simplified overview of the anatomy and projection pathways of the hippocampus is provided here.

The MTL includes the region of forebrain along the ventromedial surface of the temporal lobe. In addition to the hippocampus, it includes the amygdala and parahippocampal gyrus, which contains the parahippocampal, perirhinal, and entorhinal cortices (Sweatt, 2004). Due to its curved shape in the coronal view, the name hippocampus was given to this structure, derived from the Greek word meaning seahorse (Duvernoy, 2005).

The subfields of the hippocampus are divided based on differences in cellular morphology, connectivity and development. Hippocampal subregions are labeled by CA fields, where CA refers to cornu ammonis in Latin, meaning ram's horn, and this name reflects the curved shape of these subfields. The dentate gyrus (DG), CA1, CA2, CA3, and CA4 make up the subfields of the hippocampus. Of the CA fields, CA1 and CA3 are the largest and most easily identified (Duvernoy, 2005; Figure 1).

Despite some structural similarities with other regions, the hippocampus boasts a unique neuroanatomy and functional connectivity. First, passage of information through the hippocampus is largely unidirectional. In addition, highly intrinsic associative interconnections

are a unique feature of the hippocampus. Further the hippocampus is one of a handful of structures into which processed multimodal sensory information is inputted (Amaral & Lavenex, 2007), and in fact the hippocampus receives input from all sensory modalities (Kesner & Hopkins, 2006).

Figure 1

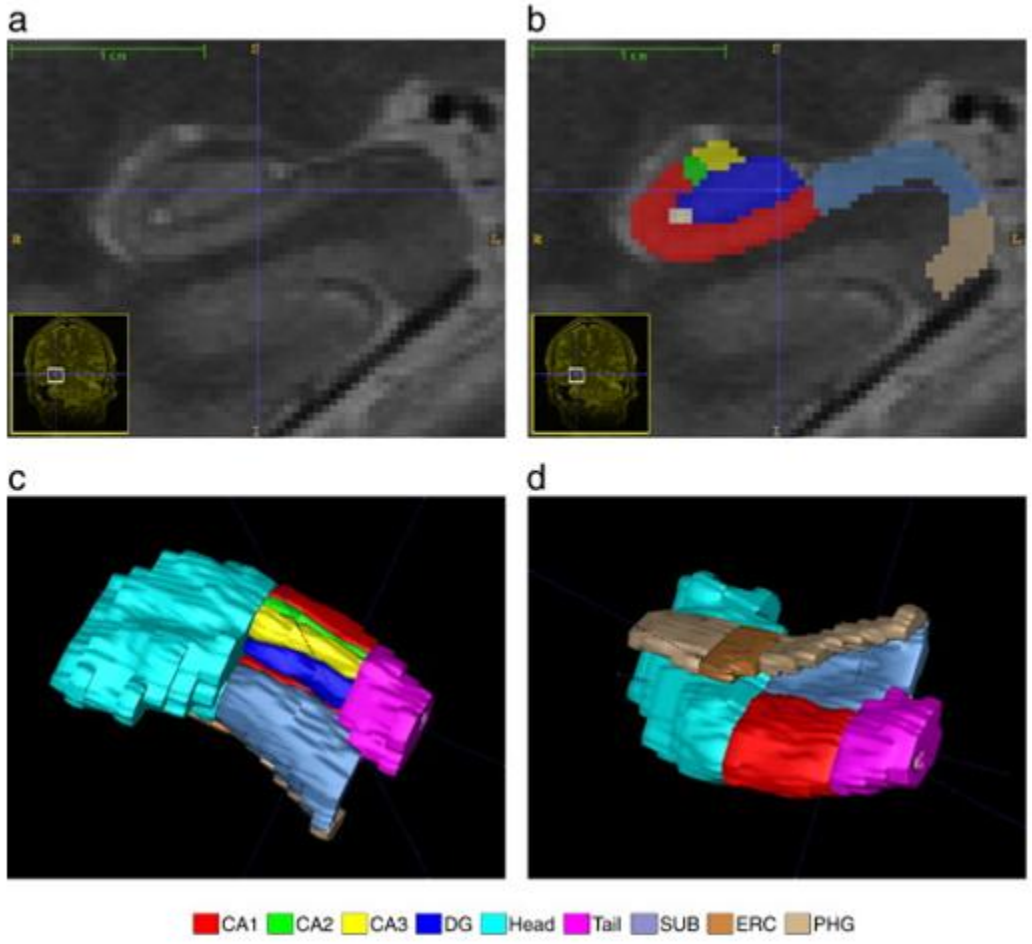


Figure 1. Human hippocampal subfields as displayed by MRI and manually traced. (a) T2-weighted image in coronal view. (b) Manually segmented hippocampus which was then overlaid on 3-D reconstructions of tracings in different rotated views of hippocampus body (head and tail regions omitted) c and d. SUB, subiculum. ERC, entorhinal cortex, PHG, parahippocampal

gyrus. From "Nearly Automatic Segmentation of Hippocampal Subfields *in vivo* Focal T2-weighted MRI," by P.A. Yushkevich, H. Wange, J. Pluta, S.R. Das, C. Craige, B.B. Avants, M.W. Weiner, S. Mueller, 2010, *NeuroImage, 53,* p. 1210. Copyright 2010 by Elsevier Inc. Reprinted with permission.

Connectivity within the hippocampus. An interesting feature of the hippocampus that distinguishes it from other regions in the brain is the extent of connectivity within itself. In fact, the majority of the inputs into regions of the hippocampus are from other regions of the hippocampus (Amaral & Lavenex, 2007). Intrahipppocampal circuitry involves two pathways: the *polysynaptic pathway* and the *direct pathway.* The polysynaptic pathway links all subregions of the hippocampus, whereas the direct pathway transfers information directly to CA1 neurons. In the polysynaptic pathway, information is transferred from the entorhinal cortex, the main cortical input into the hippocampus, to the DG, then CA3 via mossy fibre pathways, and then CA1 subfields via Schaffer collaterals (Duvernoy, 2005). The direct pathway, on the other hand, transfers information directly to the CA1 from the entorhinal cortex. After being processed by the hippocampus, these impulses are then outputted into the cortex and other regions via the subiculum. Notably, the vast majority of input (approximately 90%) travels through the polysnaptic path (Duvernoy, 2005). Nonetheless, the direct path remains an important one. I will now discuss some relevant details with regards to the hippocampus' dense interconnectivity, focusing on the stages of the polysynaptic pathway since this pathway characterizes the majority of inputs within the hippocampus.

DG to CA3 projections via mossy fibres. All projections from the DG are sent to the CA3 subfield through mossy fibre axons (Amaral & Lavenex, 2007), axons that are characterized by

their fine fibres lacking myelination (Duvernoy, 1995). The DG projection to CA3 reaches the border of the CA3 and CA2 subfields. Unlike CA3, the CA2 subfield does not have granule cell inputs with which to collect information from the incoming projections from the DG, and the presence of granule cell inputs in the CA3 subfield is one of the main features distinguishing the CA3 from the CA2 subfield. Each DG granule cell communicates with 15 CA3 cells, and these 15 pyramidal CA3 cells are distributed across the length of the CA3. Each CA3 pyramidal cell receives input from about 72 DG granule cells. Hence there are notions, albeit controversial, that input from the DG is very efficient at depolarization of the CA3 pyramidal cells (Amaral & Lavenex, 2007).

CA3 to CA3 and CA3 to CA1 connections. Connections within the CA3 subregion are generally termed associative connections, whereas Schaffer collaterals refer to projections from the CA3 to CA1. Despite differences in terminology it is important to note that both projections are collateral and they may potentially be communicating the same information (Amaral & Lavenex, 2007). The recurrent, collateral connectivity within the CA3 may play a role in the formation of associations in memory (Marr, 1971; Rolls, 1996). Projections from the CA3 pyramidal cells are the main input into CA1 cells, and all parts of the CA3 project to CA1. It is still unclear however, how many synapses one CA3 pyramidal cell makes onto a CA1 cell (Amaral & Lavenex, 2007). In contrast to cells in the CA3, pyramidal cells in the CA1 lack a massive associational network, suggesting these two subregions may have different roles in information processing.

Connectivity outside the hippocampus. As mentioned, the hippocampus is unique as a recipient of very processed multimodal sensory input from a wide variety of associational and sensory cortices across the brain, including key subcortical forebrain, diencephalic, and

brainstem nuclei (Amaral & Lavenex, 2007; Duvernoy 1995). A distinctive function of the hippocampus may be the integration of sensory information conferred by its situation in a central location in the brain as well as the unique nature of its cellular organization (Amaral & Lavenex, 2007).

Input from the cortex that enters the polysynaptic pathway arrives through various association cortices such as the posterior parietal association cortex (BA 7) as well as temporal and occipital cortices (BA 40/39/22). The polysynaptic and direct pathways send outputs to different cortical areas. The main output of the polysynaptic pathway is to the anterior thalamic nucleus and other thalamic nuclei including the intralaminar nuclei and the hypothalamus. This information is then projected to the posterior cingulate cortex (BA 23), the retrosplenial cortex (BA 29/30), and the anterior cingulate cortex (BA 24). The main input into the direct pathway of the hippocampus is through the inferior temporal association cortex (BA 20/37). This input reaches the entorhinal cortex through the perirhinal cortex (BA 35/36; Duvernoy, 2005; Figure 2). On the other hand, the direct pathway output projects to the inferior temporal association cortex, the temporal pole, and prefrontal cortex. As noted, the hippocampus appears to have a role in the spatial and temporal aspects of episodic memory. The CA3/DG and CA1 hippocampal subregions have been found to be preferentially important for spatial pattern separation and temporal pattern separation, respectively (Gilbert et al., 2001). These findings are discussed in more detail in a later section.

Figure 2

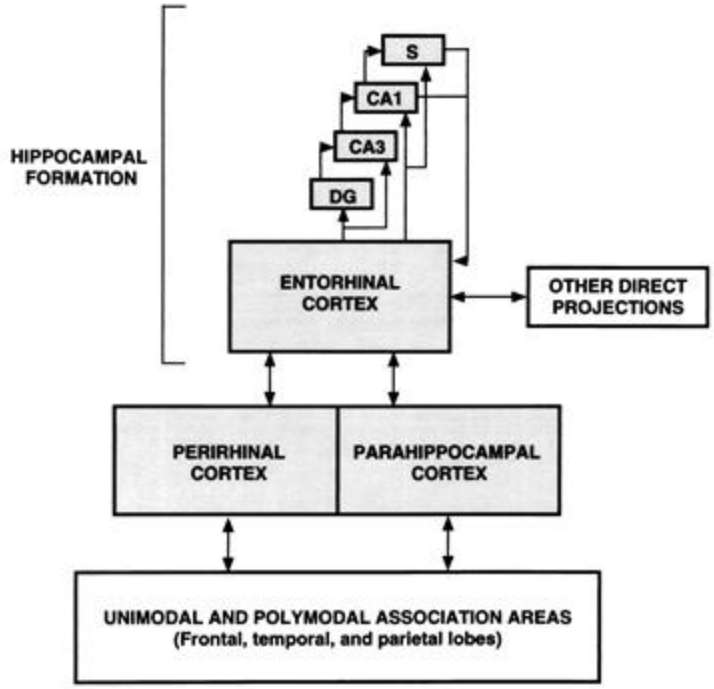


Figure 2. Overview of intra- and inter-hippocampal projections. Connections in and out of the hippocampal formation are reciprocal and come from and project to numerous association cortices throughout the brain. The entorhinal cortex receives direct projections from orbital frontal cortex, insular cortex, and superior temporal gyrus. S, subiculum. From "Structure and function of declarative and nondeclarative memory systems" by L.R. Squire & S.M. Zola 1996, *PNAS, 93,* p. 13518.Copyright 1996 by the National Academy of Sciences of the United States of America. Reprinted with permission.

Episodic Memory

One of the most fascinating marvels in nature is the ability of the human mind to travel back in time (Tulving, 2002; Wheeler, Stuss, & Tulving, 1997). This unique ability, episodic memory, is defined by Tulving (1993) as a neurocognitive mechanism allowing for the conscious

awareness of a past personal experience in subjective space and time. This system allows mental travel through subjective time, allowing the re-experiencing of the past. This is a memory system functionally different from semantic memory, or memory for facts (Tulving, 1983). Wheeler et al. (1997) suggest this distinct neurocognitive system has evolved in humans for the purpose of re-experiencing previous events (although the systems view is somewhat controversial- see Ashby & Ell, 2002).

Tulving (2002) summarizes the fundamental components of episodic memory. First, episodic memory is a hypothetical construct that is not synonymous with a particular memory test. There is no "pure" test of a single memory system, and all tasks involve multiple cognitive processes. Indeed, episodic memory requires drawing on semantic knowledge to fully recollect an experience from the past. Second, episodic memory is the sole memory system allowing the conscious recollection of previous experiences. Third, this ability to recollect previous experiences is unique to humans, with other animals possessing semantic and declarative memory in general, and other abilities to flexibly express information. That is not to say nonhuman animals are incapable of learning from experience; they are simply not aware of the experience in the same way that humans are.

The unique ability of humans to "mentally time travel" to the past involves autonoetic awareness, which is defined as the awareness of subjective time where certain events were experienced (Tulving, 2002). Autonoetic awareness is in contrast to noetic awareness, which allows the retrieval of information from semantic memory, and anoetic awareness, which allows the retrieval of procedural information (Tulving, 1993). In tasks requiring "remember" or "know" judgments, participants are asked to indicate at retrieval whether a given item is "remembered," that is, whether there is recollection of the item from encoding, or whether they

"know" the item was presented but cannot remember its particular occurrence. According to Tulving (1993) this "remember" and "know" distinction reflects autonoetic and noetic awareness, respectively. Therefore, episodic memory requires consciously "remembering" an event, rather than just "knowing" that it had occurred.

Episodic memory is about the "what," "where," and "when" of experiences, or memory about occurrences in certain places at certain times. While traditional experiments were concerned with only the "what" aspects of episodic memory, examination of the "where" and "when" aspects of episodic memory have now become an important topic of study (Johnson, Hashtroudi, & Lindsay, 1993; Tulving, 2002), and numerous studies indicate the important role of the hippocampus in both the "where" and "when" aspects of episodic memory.

The Hippocampus and Spatial and Temporal Memory

The hippocampus and spatial memory. To the extent that episodic memory is defined as memory for a personal event in a particular spatial-temporal context, spatial memory is integral to forming a coherent episode. Remembering the spatial context of events and being able to navigate and form a "cognitive map," or an allocentric, viewer-independent mental representation, allows one to remember and navigate a spatial environment (O'Keefe & Nadel, 1978). The role of the hippocampus in spatial memory has been well-established by a very large body of rodent (Becker, Olton, Anderson, & Breitinger, 1981; Kesner & Hopkins, 2006; Morris, Garrud, Rawlins, & O'Keefe, 1982; O'Keefe & Nadel, 1978) and human studies (Abrahams, Pickering, Polkey & Morris, 1997; Bohbot, Kalina, Stepankova, Prackova, Petrides, & Nadel, 1998; Crane & Milner, 2005; Maguire et al., 2003; Maguire, Nannery, & Spiers, 2006; Smith & Milner, 1981; 1989).

One meta-analysis aimed to assess whether the hippocampus has a general role in spatial memory or if only certain aspects of spatial memory are reliant on the hippocampus (Kessels, de Haan, Kappelle, & Postma, 2001). In particular the performance of hippocampally damaged patients was examined in maze learning, spatial working memory, object-location memory, and positional memory. Maze learning tasks employ both spatio-temporal and sequence learning given that participants need to remember the sequence of landmarks or events as they find their way through a maze. Spatial working memory tasks involve the active maintenance of spatial layout information for a short time period. Positional memory employs the mapping of metric spatial information, and involves the allocentric processing of precise Euclidean information in the environment. Object-location memory requires the associative binding of an item and its location. Hippocampally damaged patients were impaired on all spatial tasks examined, including maze learning, working memory, object-location memory, and positional memory. The largest impairment was found for positional memory, and the deficit in maze learning was relatively miniscule. The authors suggested the mild impairment in maze learning was due to frontal involvement that is important for sequence learning in addition to the hippocampus (see next section). Overall, performance was worse in the right hippocampal lesioned patients, consistent with well-established findings implicating the right hippocampus as being preferentially important for spatial memory compared to the left hippocampus. Notably, this lateralization effect was significant only in maze learning, positional memory, and object-location memory, but not in working memory, suggesting that working memory may not be preferentially reliant on one hemisphere (Kessels et al., 2001).

Crane and Milner (2005) examined spatial learning performance in patients with selective right amygdalo-hippocampalectomy and anterior temporal lobectomy (either with or without

sparing of the hippocampal area), as well as healthy controls. Participants were tested for their memory for the locations of an array of objects. Right hippocampal volume was a better predictor of performance compared to entorhinal and parahippocampal volume on a spatial array learning task, suggesting the right hippocampus plays a critical role in object-location memory.

An influential study examined hippocampal volume differences as a function of frequency of use of spatial information. Maguire et al. (2003) found that the gray matter volume of the right hippocampus correlated positively with years of experience as a taxi driver. Further, the relation of hippocampal volume had to do with the duration and frequency of use of spatial information, rather than a pre-existing navigational expertise. The hippocampus also appears to be important for facilitating flexible use of spatial information learned long ago. A former taxi driver with Alzheimer's disease and bilateral hippocampal damage was unable to navigate the previously familiar streets of London using a virtual reality driving simulator. Specifically, when commonly used roads could be used he was able to navigate normally, but this ability was impaired when he was required to use an alternate, uncommon route (Maguire, Nannery, & Spiers, 2006).

One perspective is that the hippocampus functions to support a "cognitive map" (O'Keefe & Nadel, 1978). The spatial arrangement of the environment is represented in the hippocampus similarly to a map. Both the formation as well as the storage of these maps requires the hippocampus. This view initially came about with the discovery of certain "place cells" in the hippocampus of freely moving rats. These cells fired maximally when rats were in particular locations in space. Place cell neurons are involved in the encoding of specific locations in space (O'Keefe & Dostrovsky, 1971).

Another view is that spatial memory is a special case of more general contextual memory, or the ability to form associations between various aspects of the environment, for instance memory for object-location or location-location. Specifically, the hippocampus is involved in spatial memory only because it is involved in forming relationships between objects and locations in the environment (Cohen et al., 1999; Eichenbaum, 2000).

In addition, the ability of humans to form associations between elements in space may not be contingent on navigation to the location of those items as it is for non-primate species. Rolls (1996) suggested that the CA3 subregion of the hippocampus in primates, including humans, contains "spatial view" cells. This appears to be related to the more sophisticated visual system of primates. Thus, one major function of the primate hippocampus is to associate spatial locations with objects in the environment even when the location is only viewed and not actually visited. Simply by viewing an object at some location can allow for the formation of object-place memories that can lead to a later recall of the location of the object seen.

The hippocampus and temporal memory. Episodic memory requires not just knowing where something occurred, but also when or in what order events occurred (Tulving, 2002). Temporal information processing involves the time-dependent learning and perceiving the order of environmental stimuli, a process that has been critically linked to the hippocampus (Sweatt, 2004).

Rodent studies have provided evidence for the role of the hippocampus in temporal information processing. In studies examining eye-blink conditioning, an animal blinks (conditioned response) in response to an auditory cue (conditioned stimulus) that signals an air puff (unconditioned stimulus). In delay conditioning, there is a delayed onset but the air puff occurs while the auditory cue is still present. In trace conditioning, there is a time delay between

the offset of the auditory cue and the air puff (Clark, Manns, & Squire, 2001). The time lag in trace conditioning has been found to selectively recruit the hippocampus in both animals and humans, possibly because it involves forming an association between two stimuli separated by a time interval (McEchron & Disterhoft, 1997). The amount of lag may preferentially require different subregions of the hippocampus in rats, with CA1 being more important for remembering two stimuli presented at a closer interval, while CA3 is more important for stimuli separated by longer intervals (Farovik, Dupont, & Eichenbaum, 2010). Further evidence for the role of the hippocampus in temporal information processing comes from the finding that hippocampally lesioned rats have trouble recalling sequences of odours over time (Fortin, Agster, & Eichenbaum, 2002). Thus, it appears that the hippocampus is involved in learning and remembering sequences (i.e., temporal ordering) of events, especially when there is a time delay or interference between events (Rawlins, 1985; Sweatt, 2004).

Integration of "where" and "when" in the hippocampus. The role of the hippocampus in spatial and temporal aspects of episodic memory has been established in the literature, but an outstanding question concerns how this information is integrated to form a coherent episode. Manns and Eichenbaum (2006) propose a model of hippocampal function in humans based on comparative data regarding MTL anatomy, in order to explain how spatial and non-spatial information is assimilated in the human hippocampus in service of declarative memory function. According to Manns and Eichenbaum (2006) the conserved hippocampus is cloaked by a divergent neocortex across species, and therefore translation of incoming information is species-specific. This model may provide insight into how the uniquely human ability of episodic memory evolved.

The structure and connectivity of the hippocampus is largely preserved across species, but there are substantial differences in neocortical regions between humans and other species (Manns & Eichenbaum, 2006). The unidirectional polysynaptic path from the DG to CA3 to CA1 to the subiculum mentioned above is consistent across species. However, there exist significant disparities between cortical size, laminar stratification, and number of polymodal association areas between human and non-human animals. Further, the amount of tissue devoted to a particular sensory function varies between species. These differences in neocortical organization are important because the hippocampus receives input from a number of different cortical areas (Amaral & Lavenex, 2007; Duvernoy 1995; Manns & Eichenbaum, 2006).

As noted above, the majority of inputs into the hippocampus arrive from the entorhinal cortex, and regions in the parahippocampal gyrus, such as the perirhinal, postrhinal, and parahippocampal cortices. The dorsal visual stream tends to project to the parahippocampal and postrhinal cortices, and this pathway is preferentially important for spatial information. The ventral stream projects to the perirhinal cortex and this is more important for nonspatial information (Duvernoy, 2005; Manns & Eichenbaum, 2006).

Manns and Eichenbaum (2006) propose that spatial and nonspatial information follow slightly different pathways through neocortical regions and the hippocampus. According to this model, spatial information reaches the postrhinal cortex, the medial entorhinal area, and then the CA3 and DG subregions. Nonspatial information, such as information for temporal sequences, passes through perirhinal and lateral entorhinal areas to reach the hippocampus. Here, the CA1 and subiculum may maintain veridical representations that allow for the temporal separation of events (Manns & Eichenbaum, 2006). Therefore, through these two distinct pathways from cortical to hippocampal regions, spatial and temporal components of information are integrated

in the hippocampus. Overall, they suggest the uniquely human ability to recollect and re-experience a past personal event in a particular spatial-temporal context may be accounted for by neocortical structure not apparent in other species (Manns & Eichenbaum, 2006). The hippocampus, in addition to supporting the integration of spatial and temporal information into episodic memory, appears to have a more general role in the encoding and retrieval of memories.

Encoding and Retrieval in the MTL: The HIPER Model

Over a decade ago, Lepage, Habib, and Tulving (1998) conducted a meta-analysis examining MTL activations at encoding and retrieval in 52 published positron emission tomography (PET) studies. An unprecedented finding was the rostrocaudal gradient of MTL activation related to stage of memory processing. In particular, 83% of rostral activations of the MTL related to encoding conditions, whereas 94% of activation at caudal sites was related to retrieval. On the basis of these findings, they proposed the HIPER (Hippocampal Encoding/Retrieval) model. This model suggests encoding-related processes are related to rostral portions of the MTL, while retrieval-related processes are related to caudal portions (Figure 3).

Figure 3

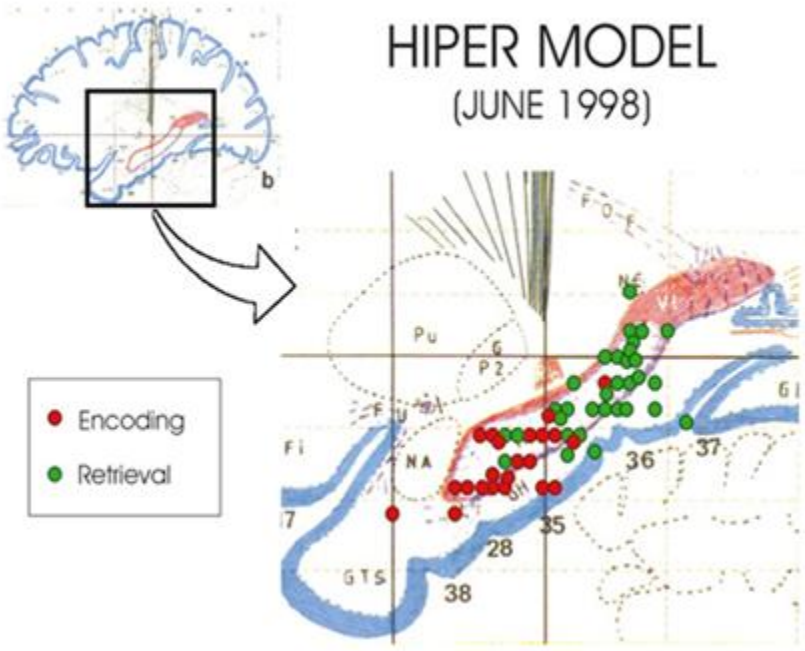


Figure 3. Findings from Lepage and colleagues' meta-analysis. The majority of encoding activations are concentrated in the rostral portions of the hippocampus, while the majority of retrieval activations are located in the caudal portions of the hippocampus. From "Hippocampal PET Activations of Memory Encoding and Retrieval: The HIPER Model" by M. Lepage et al., 1998, *Hippocampus, 8,* p. 317.Copyright 1998 by John Wiley and Sons. Reprinted with permission.

While the findings from this model were interesting, a neurobiological basis for why this distinction may occur was unclear. Lepage et al. (1998) considered the differential hippocampal activation a descriptive empirical regularity that warranted further study, and not a neurocognitive theory offering any explanations. Further, they acknowledged several contradictory or limiting findings from the literature as well. For instance, contradictory findings

existed with respect to fMRI studies, which found encoding-related activation in the caudal portions of the hippocampus (Lepage et al., 1998; Schacter & Wagner, 1999). Further, Lepage et al. (1998) suggested that the HIPER pattern may not hold for certain types of stimuli such as spatial information. Indeed, the model has been met with mixed findings over the years, with some supporting (Dolan & Fletcher, 1999; Prince, Daselaar, & Cabeza, 2005; Spaniol et al., 2009) and refuting (Giovanello, Schnyer, & Verfaellie, 2004; Grecius et al., 2003; Henson, 2005; Ludowig et al., 2008; Schacter & Wagner, 1999) evidence.

Schacter and Wagner (1999) raised questions regarding the HIPER model when they reviewed evidence presented by Lepage et al. (1998), and compared PET findings with fMRI studies. In addition to the findings of caudal portions of the hippocampus associated with encoding, the PET studies examined by Lepage et al. (1998) actually appeared to show *both* anterior and posterior MTL activations when reviewed by Schacter and Wagner (1999). However, the PET evidence did show a tendency for retrieval activations to appear in the posterior MTL regions (although not to the extent specified by Lepage et al.,1998), and this tendency was not as apparent in fMRI studies, which generally showed posterior MTL activation at encoding. Schacter and Wagner (1999) concluded these differences between PET and fMRI could have to do with task differences between the studies. For instance, tasks that require relational processing such as word pair tasks commonly used in PET, might account for the anterior hippocampal activation noted in PET. They propose anterior hippocampal regions instead involve relational memory, whereas posterior regions involve nonrelational memory. In addition, Schacter and Wagner (1999) state that another problematic aspect of the studies examined in Lepage et al. (1998) is that activation either at encoding or retrieval was examined, rather than including within-subjects designs. Based on these arguments, Schacter and Wagner

(1999) suggest that memory encoding involves both anterior and posterior MTL regions, and that the anterior/posterior disassociation in hippocampal function has more to do with the degree to which relational or associative processes are occurring.

One possible reason for the lack of anterior hippocampal activation in fMRI compared to PET could have to do with susceptibility artifact in the MTL (Veltman, Friston, Sanders, & Price, 2000). Schacter and Wagner (1999) indicated lessened activation of the hippocampus was unlikely to be due to susceptibility artifact, since signal loss tends to be most pronounced in inferior frontal and inferolateral temporal regions. However, this signal loss that occurs tends to be more relative than absolute, so other temporal lobe areas may still be susceptible to signal loss, but to a lesser extent (Ojemann et al., 1997).

Grecius and colleagues (2003) examined hippocampal involvement in the encoding and retrieval of presented words, and the extent to which susceptibility artifact could account for less pronounced activation in fMRI. This study found activation throughout the rostrocaudal extent of the hippocampus for encoding as well as retrieval, the data not supporting the HIPER model. Further, when the researchers set imaging parameters to minimize susceptibility artifact, namely the use of a shim technique and a gradient echo spiral pulse sequence rather than a traditional echo planar sequence, decreased anterior activation was less pronounced in a hippocampal ROI (Region of Interest) analysis. This suggests that susceptibility artifact may be accounting for the lack of anterior activation in fMRI studies compared to PET. The authors conclude the hippocampus does not show anterior-posterior differences in activation for encoding and retrieval.

Another study directly tested the HIPER model against Schacter and Wagner's (1999) hypothesis that anterior hippocampus supports relational processing rather than encoding per se.

Prince and others (2005) examined brain regions involved in encoding and retrieval of relational memory. Participants were scanned using fMRI while encoding and retrieving either associations between different words (semantic) or between words and their fonts (perceptual). During retrieval, participants were presented with either identical or recombined pairs. In the semantic condition, recombined pairs were those that presented words that were encoded in different pairs than presented initially. In the perceptual condition, the recombined pairs were those that had the same word pairs as during study, but this time the font was that as seen in another pair presented during study. Participants had to state whether the presented word pair at retrieval was the same as one they had seen previously. During retrieval, distinguishing between identical or recombined pairs required retrieving semantic associations in the semantic condition. In the perceptual condition distinguishing between identical and recombined pairs involved retrieving perceptual associations. They found encoding activity in the anterior hippocampus for subsequently correct items, and posterior hippocampus and parahippocampal cortex for successfully retrieved items. Importantly, in this study there were high relational memory demands in both encoding and retrieval phases, and therefore this dissociation is unlikely to be due to differential relational memory demands. However, the hippocampus still plays a general role in relational memory. The hippocampus was the only region active for both semantic and perceptual encoding and retrieval, suggesting a role for the hippocampus in relational memory (Prince et al., 2005). Another study contrasting the two theories of anterior hippocampal function found contrary results, suggesting the anterior hippocampus is important for relational memory rather than memory encoding in general (Giovanello et al., 2004).

Recently, a meta-analysis examining episodic encoding and retrieval found results that partially support the HIPER model. MTL regions more active during encoding than retrieval

included the left anterior hippocampus and the right amygdala. In contrast, the left parahippocampal gyrus was associated with retrieval. Although posterior hippocampal activation was not observed for retrieval, activation of the left parahippocampal gyrus was for retrieval, and thus the findings are in line with a general anterior to posterior differentiation in the MTL for encoding and retrieval (Spaniol et al., 2009).

Although findings in relation to the HIPER model are mixed, there has been support for a rostrocaudal gradient in the MTL with respect to encoding and retrieval processes. In the next section, neural regions involving encoding and retrieval for both spatial and temporal information will be discussed.

Spatial and Temporal Memory Encoding in Humans

The encoding of declarative memories has been attributed in large part to the MTL, and especially the hippocampus (Squire, Stark, & Clark, 2004). Spatial and temporal memory encoding have each been linked to both hippocampal (Burgess et al., 2002; Crane & Milner, 2005; Tubridy & Davachi, 2010) and extra-hippocampal structures (Duarte, Henson, Knight, Emery, & Graham, 2010; Jenkins & Ranganath, 2010; Sommer et al., 2005a;b).

In terms of spatial encoding, the right hippocampus appears to play a particularly important role (Bohbot et al., 1998; Burgess et al., 2002; Crane & Milner, 2005). In recent years, the advent of high-resolution imaging methods have allowed for the examination of functional dissociations between the subregions of the hippocampus. These studies have indicated different subregions of the hippocampus perform different functions in spatial memory encoding. For instance Suthana et al. (2010) found increased right CA2/3/DG activity for encoding compared to retrieval of egocentric information, and right subicular activity preferentially involved in retrieval of egocentric spatial information. Interestingly, another study by the same group has

pointed to the involvement of the right CA1 subregion in the encoding of allocentric spatial information when this was contrasted with encoding of egocentric spatial information (Suthana et al., 2009), suggesting there are subregional dissociations not just between encoding and retrieval but also between the encoding of egocentric and allocentric information. Other studies have implicated the parahippocampal cortex and inferior prefrontal cortex during encoding as important in subsequent memory for objects and their associated locations (Sommer et al., 2005a,b). Therefore prefrontal cortex, parahippocampal regions, as well as the hippocampus appear to play an important role in the encoding of spatial information.

Only a handful of human studies have investigated the neural correlates of temporal context memory encoding. These studies generally implicate the prefrontal cortex as well as the MTL. The orbitofrontal cortex, for instance, was found in one study to be important for temporal context memory encoding and retrieval, but not spatial context memory encoding and retrieval (Duarte et al., 2010). Another fMRI study assessed the association between encoding activity and activity at subsequent memory for temporal context (Jenkins & Ranganath, 2010). These findings are of particular interest to the present work, as they involve an examination of neural regions involved for fine and coarse temporal memory representations. This distinction between fine and coarse representations is important to the current work in pattern separation, a process that critically involves the creation of a fine-grained memory representation (Aimone, Deng, & Gage, 2010, and see below). Jenkins and Ranganath (2010) presented participants with four objects one at a time in each of several trials. Then outside of the scanner, participants were either (a) shown one object from a previously presented sequence and asked to mark a point on a line corresponding to the approximate time when that item was presented (coarse temporal memory test) or (b) shown three objects from the encoding phase and asked to indicate the order

they were presented in (fine temporal memory test). The posterior parahippocampal cortex predicted memory for fine temporal sequences, whereas prefrontal regions (rostrolateral PFC, dorsolateral PFC, and ventrolateral PFC) predicted coarse temporal memory (Jenkins & Ranganath, 2010). In another study, Tubridy and Davachi (2010) scanned participants during the encoding of word triplets that they had to recall the order of at the end of each run. Activations in the bilateral hippocampi and parahippocampi predicted successful recall of order. Collectively, these findings suggest the prefrontal cortex and MTL regions play an important role in temporal context memory encoding. Overall, these studies have suggested the hippocampus, parahippocampal gyrus, and prefrontal cortex are particularly important for the encoding of spatial and temporal information.

Spatial and Temporal Memory Retrieval in Humans

Recent neuroimaging studies in humans have examined neural correlates in the retrieval of spatial and temporal memories. The retrieval of context memory in general (including both spatial and temporal) may be associated with the right dorsolateral prefrontal cortex, the bilateral posterior parietal regions with visual scene processing, and the hippocampal complex in spatial-location memory retrieval (Hayes et al., 2004). In general, prefrontal areas and the MTL have been implicated in spatial and temporal memory context retrieval in human neuroimaging studies.

Smith and Milner (1989) found that patients with large right hippocampal lesions did not have a deficit in encoding, as evidenced by their ability to recall spatial information immediately after the presentation of the spatial location. However, these patients displayed rapid forgetting that led to an inability to retrieve information after a delay, suggesting the right hippocampus is

necessary for the retrieval and/or maintenance of spatial information but less important for the initial encoding of it.

More recently, a large body of literature has further pointed to the importance of MTL structures and prefrontal cortex in spatial context memory retrieval, as well as in temporal context memory retrieval, but these findings are mixed. Ekstrom et al (2011) utilized a virtual reality navigational task to assess the neural correlates of spatial and temporal source memory retrieval. In a virtual city, participants would act as taxi drivers that pick up a passenger from a central location and deliver them to a certain store in the city. In an fMRI scanner, participants were asked to recall either which of two objects was spatially closer to an object presented at study (spatial block) or which of two objects appeared temporally closer to an object presented at study (temporal block). Hippocampal involvement was identified in both spatial memory and memory for temporal order. The hippocampus was involved in both processes but parahippocampal activation was specific to spatial memory retrieval while prefrontal cortex was selectively involved in temporal order memory retrieval. Ekstrom et al (2011) suggest the hippocampus may have a role in general source memory, while the parahippocampus and prefrontal cortex may be uniquely involved in spatial and temporal source memory, respectively (Ekstrom et al., 2011). In a previous fMRI experiment with a similar experimental paradigm, Ekstrom and Bookheimer (2007) assessed memory for spatial context, temporal context, and landmark recognition. They found a double dissociation between the parahippocampal cortex and hippocampus activation in spatial and temporal episodic memory retrieval that were slightly inconsistent with the aforementioned results. Specifically, the parahippocampal cortex was more activated than the hippocampus in spatial memory retrieval. Conversely, the hippocampus was more activated than the parahippocampal cortex in temporal memory retrieval. Significant

activations were observed in the hippocampus, parahippocampal gyrus, and prefrontal cortex for both tasks. This finding is somewhat contrary to the finding by Ekstrom et al. (2011) but one reason for this inconsistency may be the differential contrasts employed in each study. In Ekstrom et al. (2011) direct contrasts were performed between spatial and temporal retrieval. In Ekstrom and Bookheimer (2007) however, spatial retrieval was contrasted with temporal and landmark retrieval, and temporal retrieval was contrasted with spatial and landmark retrieval. Therefore, the inclusion of the landmark condition may have played a role in this discrepancy.

Spatial and temporal context retrieval have also been identified by other studies as involving the hippocampus, parahippocampus, and prefrontal cortex. The right (Hayes et al., 2004) and bilateral parahippocampal gyri (Burgess, Maguire, Spiers, & O'Keefe, 2001) have been implicated in spatial context memory retrieval. An assessment of the association between hippocampal volume with spatial and temporal memory found that anterior hippocampal volume predicted performance on both spatial and temporal context memory retrieval tasks (Rajah, Kromas, Han, & Pruessner, 2010), suggesting the hippocampus may be important for both or for source memory retrieval more generally (Ekstrom et al., 2011; Rajah et al., 2010). Others have found that spatial memory retrieval also involves the prefrontal cortex (McCarthy et al., 1994; Rajah et al., 2010).

Another potential role of the hippocampus might be to bind mnemonic representations across spatial and temporal gaps in an event. Staresina and Davachi (2009) examined activation in the human hippocampus as a function of spatial and spatiotemporal discontinuity. In a given trial, participants were presented with a target object and a colour in one of three conditions. In the combined condition, an object was shown in a certain colour. On spatial discontiguous trials, the colour was spatially separated from the object. In spatiotemporally discontiguous

presentations, the object and its colour were separated temporally. They found that when a target object and its associated colour are presented across longer gaps in space and/or time, hippocampal engagement for binding of these elements increases (Staresina & Davachi, 2009). This finding is consistent with the extensive literature implicating the hippocampus in associative pattern completion processes (see below).

The prefrontal cortex may have a role in temporal memory retrieval. The role of the prefrontal cortex in temporal order or recency judgments has been identified in human neuroimaging (Cabeza, Anderson, Houle, Mangels, & Nyberg, 2000; Eyler Zorrilla, Aguirre, Zarahn, Cannon, & D'Esposito, 1996; Konishi, Uchida, Okuaki, Machida, Shirouzu, & Miyashita, 2002) as well as lesion studies (McAndrews & Milner, 1991; Milner, Corsi, & Leonard, 1991). Consistent with the aforementioned human study by Ekstrom and colleagues (2011), DeVito and Eichenbaum (2011) found that either hippocampal or medial prefrontal damage in rats impaired memory for the order of sequences, in line with Duarte et al.'s (2010) findings of orbitofrontal involvement in temporal memory in humans. These findings demonstrate the importance of the hippocampus and prefrontal cortex in order memory.

However, differing involvement of the prefrontal cortex between spatial and temporal context memory retrieval may not exist if differences in task structure are reduced. Rajah, Crane, Maillet and Floden (2011) equated task demands and performance in a spatial and temporal context memory tasks. Generally, the left prefrontal cortex is associated with spatial context retrieval, whereas the right prefrontal cortex is associated with temporal context retrieval (Rajah et al., 2010), but the authors questioned whether these task differences would exist if task structure and difficulty were equated. Participants encoded three faces for each of three separate time blocks. After a delay, they were shown three faces previously presented and asked to

indicate either the face that was initially presented in a certain location (spatial easy condition), or to order the three shapes either "from left to right" or "from right to left (spatial difficult condition)." In the temporal conditions, participants were asked to either select the face presented during a certain block (temporal easy condition), or to order the faces "from most to least recent" or from "least to most recent (temporal difficult condition)." In this way, a similar categorical-based task structure was used for both tasks. Participants reported using the same strategies for both tasks, and performance was equal between spatial easy and temporal easy, as well as spatial difficult and temporal difficult conditions. Contrary to previous findings, prefrontal cortex activity was similar for spatial and temporal context memory when structure and performance were equated (Rajah et al., 2011).

These studies examining spatial and temporal encoding and retrieval suggest subtle differences in regions involved between encoding and retrieval of spatial versus temporal information. For instance, the hippocampus appears to be involved in spatial and temporal encoding, the parahippocampal cortex appears to be important for the encoding of spatial information, and the prefrontal cortex is important for the encoding of temporal information. The hippocampus, parahippocampus, and left prefrontal cortex appear to be involved in spatial memory retrieval, and the hippocampus and right prefrontal cortex are involved in temporal memory retrieval.

Importantly, findings regarding activations at encoding and retrieval should be interpreted with caution, as they are difficult to parse out in a cognitive task (Suthana et al., 2010). Participants are engaging encoding processes during retrieval in order to gauge if the information is old or new. Likewise, participants are employing retrieval processes during

encoding to differentiate them from previously seen objects, especially for items that are presented later (Suthana et al., 2010).

Overall however, research demonstrates that different regions are involved in episodic encoding and retrieval depending on information type (i.e., spatial versus temporal). In this vein, we may expect information type may also influence the neural networks involved in pattern separation.

Pattern Separation and Pattern Completion

Over four decades ago, Marr (1971) put forth a prescient theory regarding the role of the hippocampus in memory coding. He described the hippocampus as a temporary memory store whereby sparse activations, associative retrieval mediated by recurrent connections within the hippocampus, and a consolidation process would then lead to information in the temporary store becoming permanent (Becker, 2005; Marr, 1971; Willshaw & Buckingham, 1990). In particular, the concepts of sparse activations and associative retrieval associated with recurrent connectivity characterize the processes of pattern separation and pattern completion respectively, processes that have been identified in the literature as reliant on the hippocampus (Kesner & Hopkins, 2006).

Pattern separation is the process of forming or transforming similar memories into different non-overlapping representations (Bakker et al., 2008). Pattern separation involves the encoding and retrieval of a fine-grained, distinct representation of a certain feature of the environment. Spatial pattern separation and temporal pattern separation are important components of episodic memory that involve separating objects and events spatially and temporally, respectively. The hippocampus and its subregions are involved in separating or

orthogonalizing events in space and time so that one event can be remembered as distinct from another event (Kesner & Hopkins, 2006).

A trade-off exists between the component processes of pattern separation and completion, such that pattern separation involves the formation of a new and distinct memory trace. This process is complementary to pattern completion, which involves the retrieval of a memory based on overlapping input (O'Reilly & McClelland, 1994). In order to effectively encode and retrieve a memory, optimal relative use of pattern separation and completion is necessary. A bias in one or the other, as seen in aging humans for instance, may manifest into global memory deficits (Paleja, Spaniol, & Girard, 2012).

In recent years, animal studies have identified preferential hippocampal involvement in pattern separation and pattern completion. For instance, in one study, rodents preoperatively performed a delay match-to-sample task where during the sample phase they would have to displace an object from a food well to obtain a food reward (Gilbert, Kesner, & DeCoteau, 1998). During test, rats were presented with two identical objects covering food wells, which were a short, medium, or far distance apart. The rats were to displace the object at the location observed at study to obtain the food. After rodents reached a 75% correct criterion, rats were given either hippocampal or control cortical lesions. Subsequent to surgery, they were re-tested. Rats with hippocampal lesions performed worse at the closest separations compared to control-lesioned rats, who performed equivalently to their pre-surgery performance. Importantly, performance at the largest spatial distance was equivalent for controls and hippocampally lesioned rats, suggesting these results are not due to the inability to recall the rules of the task (Gilbert et al., 1998). These results indicate the hippocampus is involved in being able to separate the locations of two nearby stimuli from one another, implicating the hippocampus in

pattern separation. However, to truly gain an understanding of these processes, they must be delineated from other similar constructs in the literature.

Pattern separation and pattern completion: new wine in old bottles? In considering the particular component processes of pattern separation and completion, it is critical to distinguish these from other similar processes. For instance, pattern separation and completion share common attributes to the processes of discrimination and generalization from the classical conditioning and operant conditioning literature, but there are important differences between these processes (Paleja, Girard, & Christensen, 2011). Pattern separation and completion are also not synonymous with the concepts of place cell remapping and stability. Further, it is important to demarcate recollection from pattern separation (Yassa & Stark, 2011).

In classical conditioning, the concepts of discrimination and generalization are measured by whether an organism's response to a similar stimulus is different (discrimination) or the same (generalization) to that of the trained stimulus. In operant conditioning, discrimination and generalization refer to the frequency of response emitted based on whether the animal has discriminated from or generalized to the trained stimulus. Specifically, the effectiveness of a stimulus to elicit such a response declines in proportion to the perceptual distance from the conditioned stimulus. This effect is known as a stimulus-generalization gradient (Mackintosh, 1974).

Generalization and discrimination traditionally refer to trained responses to conditioned stimuli. In contrast, pattern separation tasks rely on one-trial learning in a delayed matching-to-place paradigm. Pattern separation trials in humans do not involve numerous training trials to condition a response to one particular stimulus before an introduction to another similar stimulus, (e.g. spatial location). Therefore, there may be some shared elements between the concepts of

pattern separation and pattern completion with those of discrimination and generalization. However, pattern separation and pattern completion tasks differ from those used to study discrimination and generalization in the traditional classical and operant conditioning literature.

At a conceptual level, spatial pattern separation and completion also differ from behavioural conditioning and stimulus-response constructs in that spatial pattern separation and completion are thought to represent subprocesses of associative spatial memory. In line with this view, spatial pattern separation and completion are both highly dependent on hippocampal functioning. Spatial pattern separation involves the ability to discriminate between two spatial locations based on their allocentric relations to environmental cues, with less of an ability to do so when the *perceptually identical* target and foil are closer together than when they are further apart. Thus, despite surface similarities, it would also be misleading to characterize pattern separation as discrimination in the traditional sense.

Yassa and Stark (2011) highlight another important difference between the concepts of pattern separation and completion and place cell remapping and stability, respectively. Place cell remapping refers to the process whereby place cells display unique firing patterns in different environments (new pattern of activity is orthogonal to old pattern of activity), whereas stability involves place cells exhibiting identical firing patterns in the same environment (Yassa & Stark, 2011). Remapping can relate to pattern separation to the extent that input patterns are separated into non-overlapping outputs, and pattern completion to the extent that overlapping input is transformed to become even more overlapping. However, the crucial distinction involves the types of inputs involved. If similar but not identical patterns of input exist then pattern separation and pattern completion may be taking place. If the two environments are quite different these processes are unlikely to reflect pattern separation and completion. Pattern separation and pattern

completion relate specifically to a deviation from the linear relationship between input and output, where changes in input are equivalent to changes in output (Figure 4; Yassa & Stark, 2011).

Another important distinction is between pattern separation and recollection. According to dual-processing models, recognition memory can depend on one of the two processes of recollection or familiarity. Recollection refers to the retrieval of an item along with its original context, while familiarity refers to relatively automatic recognition in the absence of contextual information (Yonelinas, 2002). Studies indicate the hippocampus supports recollection-based processes rather than familiarity, while the parahippocampal gyrus appears to be important for familiarity-based processing (Daselaar, Fleck, & Cabeza, 2006).

Pattern separation, while important for engaging recollection, is not synonymous with it. Wilson, Gallagher, Eichenbaum and Tanila (2006) argue that the ability to recollect contextual features requires pattern separation abilities. According to this notion, the tendency of place cells in aged rodents to retain spatial firing patterns from familiar environments when moved to a novel environment reflects an inability to distinguish between contextual cues in the old and new environment, and thus an inherent failure in pattern separation. Indeed, both pattern separation and recollection are thought to be reliant on the hippocampus, and both require context retrieval. However, although recollection may require pattern separation in some instances, as both processes are heavily reliant on contextual cues, these processes are not the same (Yassa & Stark, 2011). When two memories are very disparate, (e.g. buying your first car versus your dog running away from home) pattern separation is not as crucial. However, pattern separation would be in demand in instances when memories are partially overlapping such as where your car is parked today versus yesterday. While recollection is a higher-order cognitive process, pattern

separation is a lower-level, more basic computational mechanism that provides orthogonalized outputs to overlapping inputs (Yassa & Stark, 2011).

Taken together, the above aspects highlight that although these may be similar concepts and may involve some overlapping cognitive processes, there are important distinctions that warrant the maintenance of the pattern separation and pattern completion terms in line with the computational and animal literatures regarding the role of the hippocampus that is of interest here. With that in mind, it is also important to re-iterate that pattern separation and pattern completion help us to understand network output as a function of input. This can aid in the understanding of other cognitive processes including object recognition and discrimination, visual perception, general contextual memory, novelty detection, and familiarity versus recollection (Yassa & Stark, 2011). The focus of the current body of work is pattern separation, and in particular I aimed to examine whether the regions involved in pattern separation are influenced by information type. Current literature pertaining to pattern separation will now be reviewed.

Figure 4

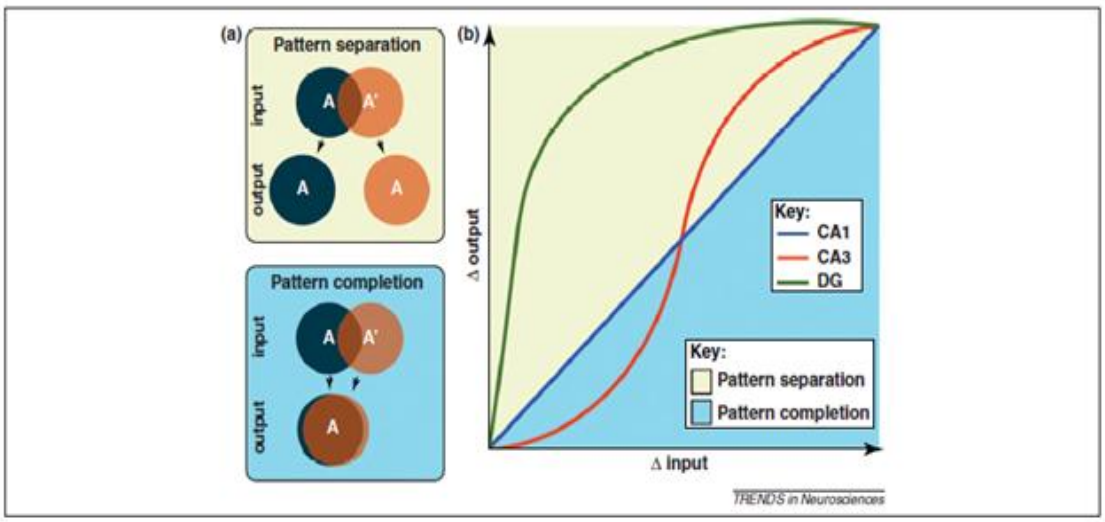


Figure 4. Diagram illustrating hippocampal subfield involvement in pattern separation and pattern completion as a function of input and output. (a) Pattern separation orthogonalizes the overlapping inputs of A and A' while pattern completion makes these representations overlap more. (b) A conceptual diagram showing a linear transformation in CA1 that is not apparent in CA3 and DG. Along the diagonal line (CA1) change in input is proportional to change in output. The yellow part of the diagram shows similar inputs being separated further at output (i.e., pattern separation). The blue portion shows the input being made increasingly overlapping because the change in output is less than the change in input (i.e., pattern completion). From "Pattern Separation in the Hippocampus," by M.A. Yassa and C.E.L. Stark, 2011, *Trends in Neurosciences, 34,* p. 516. Copyright 2011 by Elsevier. Reprinted with permission.

Spatial and Temporal Pattern Separation

Spatial pattern separation is important for remembering where something happened. In order to support contextual processing and thus episodic memory, it is necessary to be able to

optimally separate stimuli in the environment in space, allowing us to form unique representations of the places where events occur. Temporal pattern separation is similar, but it involves the orthogonalization of stimuli in time rather than space. Thus, this process allows us to temporally separate sequential stimuli or events in the environment.

Gilbert et al. (2001) showed that spatial and temporal pattern separation may be dependent on different hippocampal subfields (see Kesner & Hopkins, 2006 for a review). For spatial pattern separation, a delayed-match-to-sample for spatial location task was used. Rats were trained to displace an object covering a food-well that was baited. At test, they were to choose between two identical objects, one of which covered the same well as the sample object (correct) or a second that covered a different unbaited well (incorrect). Difficulty was manipulated by increasing or decreasing the distance between the two objects. The further apart the two objects were, the easier it was to discriminate between them. For the spatial temporal order pattern separation task, a radial arm maze was used. A sequence of eight arms was presented to the animal by sequentially opening each door one at a time to allow access to the food reward at the end of the arm. On the choice phase, doors for two of the arms were presented and the rat had to enter the arm that had occurred earlier in the sequence to get a reward. Similar to the spatial task, as the temporal distance in the sequence between the two choice arms decreased, the difficulty increased. The results showed that DG lesions in rats resulted in a deficit on the spatial task but not the spatial temporal task, whereas CA1 lesions resulted in a deficit on the spatial temporal task but not spatial task. These findings indicate that DG may be more important for spatial pattern separation, while the CA1 may be more important for temporal pattern separation. Notably, the effects of information type (i.e., spatial versus

temporal) in pattern separation processes have not yet been studied using neuroimaging in humans.

Neurobiological Mechanisms of Pattern Separation in the Hippocampus

The hippocampus has been identified as important for both forming associations between stimuli, filling in gaps in memory using a subset of available cues in the environment, as well as preventing interference from redundant stimuli. Computational models have further hypothesized how the different subfields of the hippocampus might be differentially involved in these processes.

A well-established role of the hippocampus is in supporting the formation of arbitrary associations. This includes paired-associate learning, which involves the binding of associations between objects with other objects, objects/events with places, as well as among places. The learning and subsequent retrieval of object-location (place) associations is largely reliant on the hippocampus (Kesner & Hopkins, 2006). In fact, both the discrete representations that make up episodic memory as well as the continuous representations that are characteristic of physical space (i.e., spatial memory) may be stored in the hippocampus in a single network (Rolls, Stringer, & Trappenberg, 2002).

A CA3 auto-associative network appears to be responsible for the formation and storage of arbitrary associations. Recurrent, collateral CA3 connectivity allows various elements of an episode to be automatically integrated into a unified representation. The CA3 functions as its own network due to its recurrent connectivity within itself, making associations between various stimuli in the environment (Marr, 1971; Rolls, 1996).

Given the ability of the hippocampus to form arbitrary associations, a related function of the auto-associative network is the completion of a memory given partial/incomplete or degraded

cues (i.e., pattern completion). The extensive intrinsic connectivity of the CA3 subregion allows for the retrieval of the entirety of the memory, based on the activation of a portion of the representation (i.e., a cue or subset of cues; Rolls, 1996, 1997). This function is in line with rodent studies that implicate the CA3 in pattern completion (Gold & Kesner, 2005; Nakazawa et al., 2002).

The DG appears to be particularly important for pattern separation in the hippocampus (Treves & Rolls, 1994). Pattern separation in the DG is thought to be achieved through the provision of distinct codes to the CA3 via the sparse yet powerful mossy fibre pathway. Specifically, the DG acts to orthogonalize input by removing redundant information before it reaches the CA3 cells (Becker, 2005; Rolls, 1996). However, the specific role of the DG has been debated, in that it may be more important for the formation of a fine-grained representation (i.e., high "memory resolution"), rather than orthogonalization of inputs per se (Aimone et al., 2010). Nevertheless, these processes are certainly not mutually exclusive. The role of the DG may be to reduce interference and thereby allow for the formation of a fine-grained memory. The DG would still be considered as having an important role in pattern separation because pattern separation acts to orthogonalize similar inputs in order to form a distinct, fine-grained memory. Indeed, the role of the DG in spatial pattern separation has been supported by evidence that spatial pattern separation is impaired with dorsal DG lesions and spared with dorsal CA1 lesions (Goodrich-Hunsaker, Hunsaker, & Kesner, 2008).

The DG and the CA3 both appear to be necessary for pattern separation to take place, however the role of the CA3 is not as well-defined. Studies suggest pattern separation in the CA3 may depend on the degree of difference between two inputs. Leutgeb, Leutgeb, Moser and Moser (2007) suggest that a dual set of mechanisms are involved in pattern separation. With only

a slight change in the environment at a fixed location, pattern separation occurs in the DG as well as CA3. Specifically, cortical inputs change their pattern of correlated activity in the DG and its cells therefore fire at different rates. This disambiguation of firing patterns is transferred to the CA fields via sparse connections between granule cells in the DG and pyramidal cells in the CA fields. Connections between granule cells in the DG and CA3 pyramidal cells (i.e, via the mossy fibre pathway) may allow for these uncorrelated firing patterns to transfer to the CA3 cells. These disambiguated firing patterns lead to the orthogonalization of memories in the hippocampus. With larger environmental change, pattern separation involves only an independent cell population in CA3, with little or no involvement of the DG (Figure 4). Others have also suggested the process CA3 engages in might differ as a function of environmental change (e.g. Lee, Yoganariasimha, Rao, & Knlerim, 2004; Leutgeb et al., 2007; Vazdarjanova & Guzowski, 2004; Yassa & Stark, 2011). Further study will clarify the role of CA3 in pattern separation. Nonetheless, slightly different aspects of spatial pattern separation appear to rely upon the DG and CA3 cell fields. Neurogenesis is one mechanism by which the DG may perform pattern separation.

Neurogenesis as a mechanism for pattern separation. Recent studies have implicated neurogenesis in the DG as central to pattern separation (Becker, 2005; Clelland et al., 2009; Sahay et al., 2011). In particular, the DG may play a role in preventing interference between two highly similar memories (Becker, 2005).

Neurogenesis appears to be important in the encoding and retrieval of fine-grained spatial information, as is required for pattern separation. Mice who exhibited exercise-related neurogenesis showed a heightened ability to discriminate between the adjacent spatial locations of two identical objects. These effects were not evident in older mice runners who exhibited low

basal cell genesis. These mice did not show an exercise-related increase in pattern separation abilities (Creer, Romberg, Sakksida, van Praag, & Bussey, 2010). Older adult humans who participated in an aerobic exercise training program showed increased hippocampal volume as well as increased levels of a hormone called Brain-derived Neurotropic Factor (BDNF), which mediates neurogenesis in the DG. Furthermore, this exercise training led to improvements on a delayed match-to-sample spatial memory task, suggesting neurogenesis may mediate spatial memory in adult humans (Erikson et al., 2011).

Becker (2005) proposed a computational model whereby neurogenesis in the DG may facilitate pattern separation. Specifically, newly sprouted neurons in the DG may aid in the creation of novel codes and hence distinct representations for similar events, especially for temporally spaced information. This is achieved by the neuronal replacement in the DG leading to diversity of neural codes between different learning trials. Because new neurons are formed only on the DG, it must be the DG that is involved in the formation of unique codes for novel events, rather than the retrieval of older memories using associative processes.

Another complementary viewpoint also posits that temporal judgments of memory onset are associated with the differential maturity of granule cells in the DG (Aimone, Wiles, & Gage, 2006). Contrary to previous beliefs that adult neurogenesis is nonexistent, the growth of new granule cells in the DG has now been well-established in adult animals as well as humans. Given that neurogenesis in the hippocampus is a continuous process whereby neurons mature, die, or are born, input to the CA3 from the DG in response to an identical input will change over time because of these changes in cell populations within the DG. This will result in a slightly different coding for memories based on the relative time of the event. For example, the reactivation of a past memory, for example hearing an old song, can result in memory recollection for events that

occurred at a similar point in time, for example, meeting Julie for the first time. The same set of neurons would have initially encoded both these memories. Memories that occurred at a different point in time from that of the old song, would have been adequately separated by different temporal tagging of information during encoding and therefore would not be invoked by hearing the new song. Therefore, one possible mechanism allowing us to make temporal recency judgments might be the ongoing birth, maturation, and death of neurons in the DG (Aimone et al., 2006). Friedman (2007), however, has pointed out that humans are quite poor at making judgments about the relative timings of events from their past that occurred at different points in time, casting doubt on the notion that humans make temporal judgments based on associations with events that occurred at a similar point in time. Instead, he contends that humans engage in "distance based processes" involving an awareness of the time that has passed in order to infer the timing of an event relative to the present.

Neuroimaging Studies Examining Pattern Separation in Humans

A handful of human neuroimaging studies have been conducted in recent years to investigate neural correlates of pattern separation. All of these studies have focused on regions within the MTL. Bakker et al. (2008) used high-resolution fMRI to measure hippocampal activity during a continuous recognition paradigm with images of common objects. A presented object might therefore be new, a repetition of a previously viewed object, or a slightly different version of a previously viewed object, a lure. If pattern separation was taking place in a certain subregion, the lure would be treated more like a new stimulus than a repetition by that subregion. Specifically, if the subregion is engaging in pattern separation, the subregion should show comparable activity to the presentation of the lure as it did to the initial presentation of the similar stimulus. In other words, the lure is being treated like a new stimulus by that subregion,

suggesting the lure event was successfully orthogonalized in that subregion. If a brain region was involved in pattern completion, it should respond as though the similar lure is a repeated stimulus. This approach is based on the assumption that if a similar object is processed as a repetition, then the responsive brain region is preserving the overlap/similarities between the two. It is involved in completing a representation of the same or similar object based on partial visual information to what was previously seen. The CA3/DG region demonstrated a strong bias toward pattern separation in this study (even with this high-resolution method, it was still not possible to confidently isolate CA3 from the DG and it was treated as a single region). A bias towards pattern completion was observed in various MTL regions, including the CA1, but not the CA3. Therefore, this task produced findings of subregional involvement that partially paralleled findings in the rodent and computational literature, that is, the role of CA3 and DG in pattern separation.

Lacy et al. (2010) used a similar paradigm to Bakker et al. (2008), except that lures were classified as either high- or low-similarity. They found that the CA3/DG and the CA1 have different pattern separation related transfer functions. While the CA1 is relatively resistant to small changes with activity varied in a graded fashion to changes in input, the CA3/DG showed a stepwise transfer function that was very sensitive to small input changes. In other words, the CA1 is resistant to small changes and therefore responds linearly to input. The CA3/DG on the other hand, is highly sensitive to small input changes, and can shift its representation flexibly to these changes. This study provides further converging evidence for the role of the CA3/DG in pattern separation.

Moreover, in terms of MTL structures more generally, the hippocampus appears to be more important than other MTL regions for pattern separation. Kirwan & Stark (2007) utilized

high-resolution functional magnetic resonance imaging (fMRI) to assess regions in the MTL involved in pattern separation. On each trial of a continuous recognition paradigm, a presented object might be new, a repetition of an object viewed previously, or a slightly different version of a previously viewed object (i.e., a lure) as in Bakker et al. (2008) explained above. Participants were asked to state whether the object was new, old, or similar to an object they had seen previously. Pattern separation was inferred by participants successfully discriminating a lure from an old object. In other words, they had to identify it as a "similar" object. This "similar" option was important because calling a lure "new" could just mean the participant never encoded the original variation of this cue. Identifying a lure as "similar" meant they had encoded the previous similar stimulus, but had successfully "separated" the two as distinctive stimuli. Hippocampal activity, and not parahippocampal, differentiated between correctly identified true stimulus repetitions, correctly rejected presentations of lure stimuli, and false alarms to similar lures.

Although the bulk of pattern separation human neuroimaging studies have explored the distinct roles for structures within the MTL, in particular the subfields within the hippocampus, the extra-hippocampal structures involved in pattern separation remain largely unexplored. In fact, studies indicate hippocampal subregional specificity may not be evident when overt recognition is required in a task. In these cases, the hippocampus as a whole may support pattern separation (Kirwan & Stark, 2007; Yassa & Stark, 2011). Importantly, the hippocampus does not function in isolation. Consideration of the workings of the hippocampus as a whole and with regions outside of the hippocampus, and how these regions are functionally connected to the hippocampus are worthy of further study, and would shed light on how the whole brain functions

to support pattern separation. The current body of work aims to elucidate whole-brain patterns supporting pattern separation.

Pattern Separation: Encoding or Retrieval?

Although the term pattern separation has been in increasing usage over the past two decades, there are still elements that remain unclear or unstudied (Aimone et al., 2011). Computational models (Becker, 2005; O'Reilly & McClelland, 1994), rodent studies (Jerman, Kesner, & Hunsaker, 2006) and human neuroimaging studies (e.g. Bakker et al., 2008; Kirwan & Stark, 2007) have often conceptualized pattern separation in the DG as a process that occurs during encoding. However it is unclear what the neural substrates are during the retrieval of pattern separated information.

In a comprehensive review, Kesner and Hopkins (2006) identify pattern separation in the hippocampus as occurring during both encoding and retrieval. According to these authors, pattern separation is involved in the orthogonalization of input (i.e., leading to the creation of a fine-grained memory trace), in the ability to distinguish between two representations, and also during the use of associative representations. For instance, when rats are placed in different starting positions in a water maze task, it is likely that there will be interference amongst spatial patterns. Indeed, difficulties exhibited by hippocampal lesioned rats on water maze tasks may be due to an inability to separate spatial patterns during encoding which lead to interference (Kesner & Hopkins, 2006). These authors also argue that topographical memory representation can be conceptualized as involving effective separation of spatial information so interference is overcome. Maguire, Burke, Phillips, & Staunton (1996) found that patients with lesions to their right temporal lobe were impaired in making proximity judgments about objects in the environment. Difficulties in perceiving and encoding the distance between two objects in the

environment may reflect a pattern separation deficit (Kesner & Hopkins, 2006). The hippocampus also supports pattern separation during the encoding of temporal information. For instance, DeCoteau and Kesner (2000) trained rats on a radial arm maze, where they had to visit the arms of the maze in a certain sequence. When hippocampal lesions were administered prior to learning, rodents were impaired relative to controls in acquisition of these sequences. However, when hippocampal lesions were administered after initial learning, rats were not impaired. This provides evidence that the hippocampus is important for the initial learning of sequence information. The hippocampus may be reducing interference between competing incoming information by performing temporal pattern separation at encoding (Kesner & Hopkins, 2006). Taken together, these animal and human studies suggest that the hippocampus may be necessary for adequate pattern separation of incoming information at encoding (Kesner & Hopkins, 2006), consistent with the aforementioned studies (Aimone et al., 2011; Bakker et al., 2008; Jerman et al., 2006; Kirwan & Stark, 2007; O'Reilly & McClelland, 1994).

However, pattern separation may also be engaged during the retention and retrieval of information. DiMattia & Kesner (1988) trained rodents on locating a spatial location in a water maze. Rats then underwent a lesion to the hippocampus or a control lesion. During test, rodents had to locate the same location they went to during study from four different locations. When hippocampal lesioned rats were tested from one of four locations, they showed a deficit, likely due to an inability to retain spatial information resulting in spatial interference operating during retrieval. Another possibility worthy of consideration is that the creation of a fine-grained representation at study separated from other similar input aided in the correct retrieval. However, the experimental evidence suggests susceptibility to interference can be augmented by intact

pattern separation abilities, and therefore pattern separation may also be operating at retrieval (Kirwan & Stark, 2007).

Human studies examining pattern separation have not systematically examined pattern separation at encoding and retrieval. For instance, Bakker et al. (2008) showed participants images of objects while undergoing MRI scanning. These objects may be identical to ones seen previously in the sequence, new items, or lures. Pattern separation was inferred when activity in certain subregions to lures was similar to initial presentation of the similar item. Pattern completion was inferred when activity in a certain subregion to lures was less pronounced than to the initial presentation. Because the lure is identified as novel in pattern separation, this suggests this subregion is also undergoing encoding, since it is identifying this lure as new. In contrast, in pattern completion the lure is "identified" by the subregion as being old, suggesting the subregion has undergone a retrieval process. Therefore, these subfield differentiations in activity may also reflect disparate stages in memory processing.

Contrary to the common view that pattern separation only operates at encoding, the reduction of interference is important at the retrieval stage as well, suggesting pattern separation could operate during retrieval. Whether the DG would be involved at the retrieval stage of pattern separation is another question however, and it has been suggested that the DG only operates during encoding (Becker, 2005). Therefore, the neural substrates of pattern separation at encoding and retrieval may differ.

Present Work

Although computational models have posited the existence of a pattern separation mechanism in the hippocampus for decades, research into pattern separation processes in humans is still in its infancy, and there are still questions that have yet to be addressed. First, the

involvement of extra-hippocampal structures, particularly those outside the MTL has not been systematically examined in humans, and rarely in non-human animals. This is an important direction for study, as the hippocampus does not function in isolation. Second, studies suggest pattern separation may operate at both encoding and retrieval. The neural substrates of pattern separation at encoding and retrieval have not yet been systematically examined in humans. Third, although animal researchers have dissociated between regions differentially involved in spatial and spatial-temporal pattern separation (Kesner & Hopkins, 2006), the manner in which pattern separation signals are influenced by information type has not been investigated in human studies (Yassa & Stark, 2011).

In this body of work, I utilize fMRI (Experiment 2) to investigate the neural correlates of spatial and temporal pattern separation. Although the importance of the subregions of the hippocampus in these processes has been established by rodent and human studies as well as computational models, these processes are not solely reliant on the subregions of the hippocampus (Yassa & Stark, 2011), and the extra-hippocampal regions involved merit study.

To date, no study has examined the neural networks involved in these processes, or specifically, the functional connectivity of these processes with the hippocampus. The present imaging analysis will employ a GLM subtraction analysis using SPM (Wellcome Department of Cognitive Neurology, London, UK) to investigate regional activations associated with spatial and temporal pattern separation as well as PLS (partial-least squares; McIntosh et al., 1996) to investigate the correlated networks involved in these processes.

Partial-least squares for neural network analysis. While univariate techniques such as univariate general linear modeling (GLM) using subtraction based analysis have focused on identifying signal changes at the voxel level at particular points in space or time, multivariate

analysis techniques combine information from space and time dimensions to identify signal changes (McIntosh & Lobaugh, 2004). Spatiotemporal PLS is a multivariate analysis technique developed by McIntosh et al. (1996) that identifies distributed patterns of activity that differ across experimental conditions and vary with time (McIntosh, Chau, & Protzner, 2004). Specifically, 'partial least squares' is a term referring to the maintenance of maximal covariances and minimization of residuals between a set of exogenous variables, such as conditions, behaviour, or seed activity, and the dependent measure (i.e., BOLD data; McIntosh & Lobaugh, 2004).

Generally, multivariate analyses such as PLS have increased sensitivity compared to univariate techniques like GLM, particularly when the dependent measures are correlated, as in neuroimaging data. McIntosh and colleagues (2004) compared results obtained using GLM analysis (using SPM) to PLS for the same dataset, and found reliable voxels using PLS that were not present at any threshold using the GLM analysis. Furthermore, they found there were no instances of SPM identifying voxels that were not already identified by PLS.

A factor that explains the sensitivity difference between PLS and GLM is that PLS requires no assumptions about the shape of the hemodynamic response function (HRF). In particular, in GLM analyses each voxel is convolved with a canonical HRF, and the degree of fit is further analyzed. If the difference in the voxel's response from the canonical HRF is large, the parameter estimate is weakened, resulting in reduced sensitivity (McIntosh & Lobaugh, 2004). Therefore, unlike univariate analyses, PLS allows for the examination of task-related changes in activity at different time lags (Addis, Pan, Vu, Laiser, & Schacter, 2009; McIntosh et al., 2004). Importantly, GLM and PLS analyses also differ with respect to the research questions they

address. In GLM analyses, subtraction methods are used to identify activated regions, whereas in PLS areas that correlate with one another are obtained.

The Mean-Centering Task PLS option allows for a preliminary examination into how brain activity and conditions covary within a task. A mean-centered analysis does not require a priori hypotheses. First, the cross-covariance of the design matrix and data matrix is computed. The design matrix contains vectors that code the different task conditions. The data matrix includes all voxels across each image for each event and for every participant and task. Singular value decomposition then delineates the matrix resulting from this cross-covariance computation, and gives rise to latent variables (LVs), which are distinct, nonoverlapping variables that provide an optimal relation between data sets. Every LV has two vectors that relate experimental design to brain activity (McIntosh et al., 2004). The singular value gives a measure of the amount of covariance accounted for by the LV, with each brain voxel having a salience or weight that is proportional to this covariance (Addis et al., 2009). A Non-Rotated Task PLS is similar, in that it yields LVs that best explain the effects of the experimental design on brain activity, except in this case a priori hypotheses are specified.

A component unique to PLS is permutation tests. The permutation test determines the statistical strength of the effect of a certain LV. Specifically it determines whether the effect is large enough to differentiate it from noise (McIntosh & Lobough, 2004). Permutation tests involve the random re-ordering of the rows and columns of a data matrix, and for each re-ordering, to generate new LVs. The value of the original LV is compared to that of the new LV, and a probability is calculated for the original LV depending on the number of instances a statistic from the permuted data is greater than the initial value (McIntosh et al., 1996; McIntosh & Lobaugh, 2004).

Bootstrapping randomly resamples elements with replacement and calculates the standard error of the saliences, or the weight of each brain voxel. In other words, while permutation tests determine the *significance* of each LV, bootstrapping approximates salience standard errors and then determines the *reliability* of the larger element saliences (McIntosh & Lobaugh, 2004). Bootstrap resampling in PLS reduces the influence of outliers that may influence SPM analyses (McIntosh et al., 2004).

A central question in my exploration of the neural correlates of spatial pattern separation and temporal pattern separation is how the hippocampus interacts with other brain regions during spatial pattern separation and temporal pattern separation. In other words, I aim to explore the functional connectivity (i.e., the correlation of activity among brain regions; Friston, 1994) of the hippocampus with other regions during spatial pattern separation and temporal pattern separation with a Seed Analysis in PLS. Functional connectivity differs from "effective connectivity," as the latter predicts activation of one region from another (Friston, 1994). Functional connectivity is useful for exploring associations between regions during a cognitive task (McIntosh, Nyberg, Bookstein, & Tulving, 1997).

Both SPM and PLS are utilized in the present study to address complementary questions. SPM will allow me to directly compare whole-brain activations unique to spatial and temporal pattern separation at encoding. The use of PLS will allow for the examination of neural networks involved in these processes, and also whether different neural networks are involved in the encoding versus retrieval of spatial or temporal information. Further, the functional connectivity of the hippocampus during spatial pattern separation and temporal pattern separation will be investigated using seed PLS.

Main Research Questions

The investigations in this largely exploratory body of work aim to shed light on the following questions:

1. Are the pattern separation tasks behaviourally sensitive to spatial and temporal manipulations?

    The goal of Experiment 1 is to establish behavioural sensitivities between separation manipulations to support the tasks' validity as measures of spatial and temporal pattern separation (as in Paleja et al., 2011). Specifically, items presented closer together spatially or temporally should require heavier engagement of pattern separation processes, and this should reflect in lower proportion correct and higher reaction times for items presented closer together than further apart.

2. Is the hippocampus more active when greater engagement of pattern separation processes is required for later successful retrieval?

    The majority of studies conceptualize pattern separation as a process that takes place during the initial encoding of an item (Bakker et al., 2008; Duncan, Sadanand, & Davachi, 2012; Kirwan & Stark, 2007; O'Reilly & McClelland, 1994; Wilson et al., 2006), although reduction of interference is also important for retrieval and therefore pattern separation may also be required at retrieval (Kesner & Hopkins, 2006). If behavioural differences between the separation manipulations are established, I aim to examine the neural correlates during encoding conditions requiring more engagement of pattern separation compared to those requiring less. Presumably, the encoding of a finer-grained memory (i.e., more pronounced

pattern separation) would be required for later successful retrieval of the correct item from two items presented closer together (more interference) than two items presented further apart (less interference). It is possible the hippocampus may be more heavily engaged during encoding for subsequently correct items requiring more pattern separation than items requiring less pattern separation. According to previous findings implicating the parahippocampal gyrus for fine temporal memory encoding and prefrontal cortices in coarse temporal memory encoding (Jenkins & Ranganath, 2010), we may expect these regions to be differentially involved in our close versus far conditions. This question was addressed by the univariate analysis using SPM (see Methods).

3. What are the areas uniquely involved in spatial and temporal pattern separation?

The univariate analysis will allow for the direct comparison between spatial and temporal pattern separation tasks, and will aid in identifying the unique neural substrates of each. Based on spatial and temporal encoding studies highlighted, we may expect the hippocampus, parahippocampus, and prefrontal cortices to be involved in both (e.g. Ekstrom & Bookheimer 2007; Ekstrom et al., 2011). However, the right hippocampus may be specific to spatial encoding (as per Bohbot et al., 1998; Burgess et al., 2002; Crane & Milner, 2005). Because spatial and temporal memory encoding have not been directly contrasted in the current literature, the findings will provide novel insight into spatial and temporal encoding and pattern separation at the whole-brain level.

4. What are the neural networks supporting pattern separation? Are the neural networks different depending on the type of information being processed?

If pattern separation is considered to be a core mechanism in episodic memory and hence spatial and temporal context memory, hypotheses can be drawn based on the large body of spatial and temporal context memory literature. For instance, we may expect the right or bilateral hippocampi and right parahippocampus to be involved in spatial pattern separation. In temporal pattern separation, activity in the left hippocampus and prefrontal cortices might be expected given the previous literature summarized above implicating these regions in temporal context memory.

5. Does heavier engagement of pattern separation involve a qualitatively different network than lesser engagement of pattern separation processes?

    Given that the hippocampus has been implicated in pattern separation (Kesner & Hopkins, 2006) it is possible that conditions requiring heavier reliance on pattern separation processing may require more recruitment of the hippocampus than conditions requiring less pattern separation. Further, if greater task difficulty is evidenced by lower accuracy and greater reaction time in conditions requiring greater pattern separation, additional recruitment of extra-hippocampal regions might be expected than when the condition requires less pattern separation.

6. Are there differences in neural network activity for *encoding* and *retrieval* in pattern separation? Are these regions similar to those involved in encoding and retrieval of spatial and temporal context memory?

As summarized above, pattern separation may operate at both encoding and retrieval to reduce interference from similar input (Kesner & Hopkins, 2006). Given that the majority of

studies have conceptualized and examined pattern separation only at encoding, the neural underpinnings of pattern separation at retrieval remain unknown. The hippocampus has been identified as having a prominent role in encoding and retrieval of episodic memories more generally, with some suggesting anterior hippocampal involvement at encoding and posterior hippocampal involvement at retrieval (Lepage et al., 1998; although the role of hippocampal involvement in very long-term retrieval has been controversial: see Nadel & Moscovitch, 1997; Squire, 1992; Zola-Morgan & Squire, 1990). Based on studies of spatial and temporal context memory, we may hypothesize slightly different regions involved in spatial pattern separation and temporal pattern separation during encoding, and different regions involved in spatial and temporal information during retrieval. In other words, the regions involved in pattern separation during different stages of memory processing may be a function of the type of information being processed. The previous literature would indicate a role for the hippocampus, parahippocampus and prefrontal cortex at spatial and temporal pattern separation during encoding. At retrieval, the hippocampus and prefrontal cortex are expected to be involved for both spatial and temporal pattern separation in line with previous literature summarized in the section above summarizing spatial and temporal memory retrieval. The parahippocampus may be selectively involved in temporal pattern separation during retrieval.

7. Given that the hippocampus has been identified as particularly important in pattern separation, how is the hippocampus *functionally connected* to other regions in the brain during pattern separation? Does this connectivity differ depending on whether spatial or temporal information is being retrieved?

Although the hippocampus has been implicated in pattern separation, functional connectivity between the hippocampus and the rest of the brain has not yet been examined. Accordingly, it is unclear what regions will be functionally correlated with the hippocampus during these tasks. Given the literature demonstrating the importance of more temporal regions in spatial processing compared to frontal regions in temporal processing, I expected a functional network between the hippocampus with other temporal lobe regions for spatial pattern separation and hippocampal connectivity with frontal lobe regions for temporal pattern separation. Questions 3-6 were addressed using the multivariate PLS analysis (see Methods).

As the analyses in this work are novel and exploratory, I expect this thesis will provide unique insight into whole-brain processes supporting pattern separation. Therefore, given that this work is the first of its kind to systematically assess how the entire brain is involved in pattern separation, the regions involved will likely diverge to some extent from the current literature examining spatial and temporal context memory more generally. However, the existing context memory literature provides a relevant and useful starting point for formulating hypotheses.

Chapter 3: Experiment 1 Methods and Results

Methods

Participants. Nineteen adults (12 female; M_{age}=31.9 years, *SD*= 13.96, Range 20-59 years) from the community with an average of 16.4 (*SD*= 3.02) years of education and no prior history of neurological or psychiatric impairment were recruited for participation in the behavioural study. Inclusion criteria included fluency in English, and normal or corrected-to-normal vision. Exclusion criteria included neurological impairment, Axis-I psychiatric disorder, history of drug/alcohol dependence or current abuse, or first degree relatives with a psychotic illness (Appendix I). Participants were tested at the Brain Imaging and Memory Lab at Ryerson University.

Behavioural tasks. All participants performed two computerized memory tasks: A spatial pattern separation (SPS) task and a temporal pattern separation (TPS) task. The order in which participants performed these tasks was counterbalanced.

These tasks were newly developed for use in this thesis. Tasks were piloted and modified to obtain behavioural differences between separation manipulations, as well as to achieve suitable overall performance levels (i.e., to avoid floor and ceiling effects). The spatial and temporal pattern separation tasks were designed similarly to studies using rodent and human tasks to examine spatial and temporal memory (see Kesner & Hopkins, 2006 for a review).

Spatial pattern separation. The SPS task design was based on a previous pattern separation task we had developed in our lab (see Paleja et al., 2011) using CG-Arena (Jacobs, Thomas, Laurance, & Nadel, 1998). The present task was modified to include spatial locations without the navigational component (screenshots from the Arena program were used) for the

sake of consistency in task structure between spatial and temporal tasks, and due to practical constraints such as time length of tasks. The present tasks were programmed using the software E-Prime 2.0 (Psychology Software Tools, Pittsburg, PA). Stimuli were displayed in a virtual bricked arena enclosed by four walls, each with a different fractal picture. The SPS task consisted of a study phase, a distractor letter task, and a recognition phase. In the study phase, participants were presented with a shape (e.g. circle) on the floor of the virtual arena for 6 s. This was followed by a 3-s distractor task, where participants were shown a letter and asked to indicate using a key press whether it was a vowel or consonant. This baseline task was similar to baseline tasks found to be optimal with studies examining medial temporal lobe-based processes (Stark & Squire, 2001), and is included for the purpose of the neuroimaging component in Experiment 2. Then during the subsequent 3.5s test phase, participants were shown two different shapes with either a "1" or "2" above them and asked to indicate which shape was in the same location as the one previously presented, using a button press of the "1" or "2" button on a keyboard (or the first or second key on the response box inside the scanner in Experiment 2). This was followed by a 1.5s fixation cross. Importantly the degree of separation between the test shapes were manipulated, such that in half the trials they were close together (NEAR condition; 2 area units apart, where 10 area units represents approximately 1 meter) and in the other half of the trials they were far apart (FAR condition; 4 area units apart). These distances were based on the furthest and closest distances from our previous study (Paleja et al., 2011). The viewpoint was altered slightly from study to test to encourage a more allocentric perspective that would involve processing of the location relative to the spatial cues in the environment, rather than just using absolute position on the screen. Within each run for the spatial task (two SPS runs in total),

40 trials were presented pseudorandomly, half in the NEAR condition and half in the FAR condition (Figure 5).

Figure 5

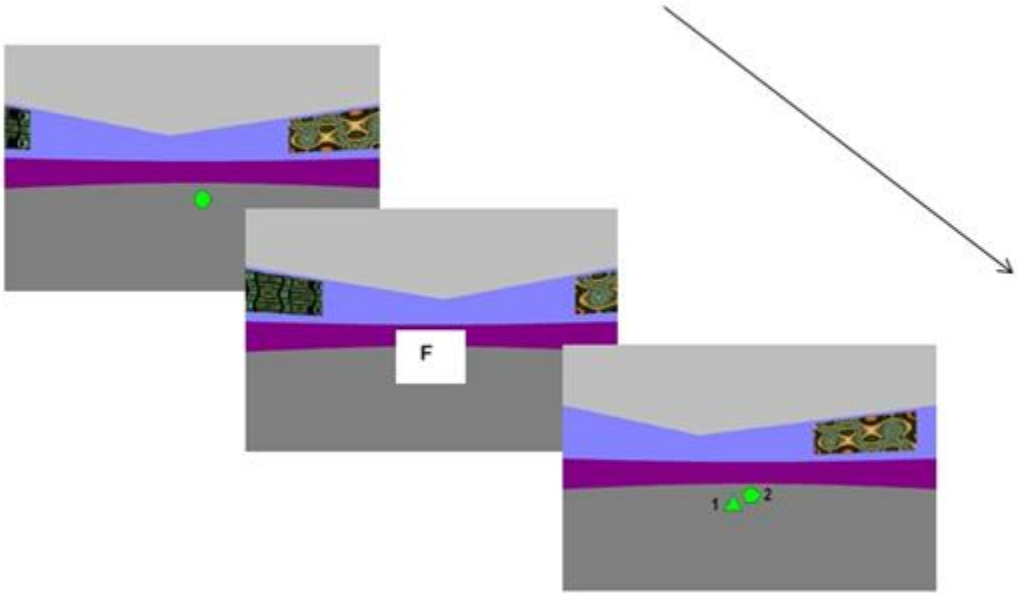


Figure 5. Spatial pattern separation task. During the study phase, participants were shown a shape in the scene. During a distractor phase, participants are shown a letter and asked to indicate with a key press whether it is a vowel or consonant. At recognition, participants will be shown two shapes at slightly different locations and asked to indicate with a key press, which shape is in the same location as the one observed during study.

Temporal pattern separation. Similar to the SPS task, the Temporal Pattern Separation (TPS) task consisted of a study phase, a distractor letter task, and a recognition phase. In the 6.5s study phase, participants were presented with a sequence of six geometric shapes presented for 0.5s each. The sequence was followed by a star, and then the same sequence repeated once. This

was followed by an identical 3s distractor task to that presented during SPS. Then, during the 3.5s test phase, participants were presented with two shapes and asked either “Which appeared later?” or “Which appeared earlier?” The degree of separation between the two items in the sequence was manipulated such that they were either presented relatively close together in the sequence (no intervening items in sequence; NEAR condition) or far apart in the sequence (two intervening items; FAR condition). The first and last items in the sequence were never presented in the retrieval phase to minimize primacy and recency effects. Within each run for the temporal tasks (two TPS runs in total), 40 trials were presented pseudorandomly, half in the NEAR condition and half in the FAR condition (Figure 6). The TPS task was embedded in the same virtual arena and using the same shapes as stimuli as in the SPS task to equate them as much as possible.

Figure 6

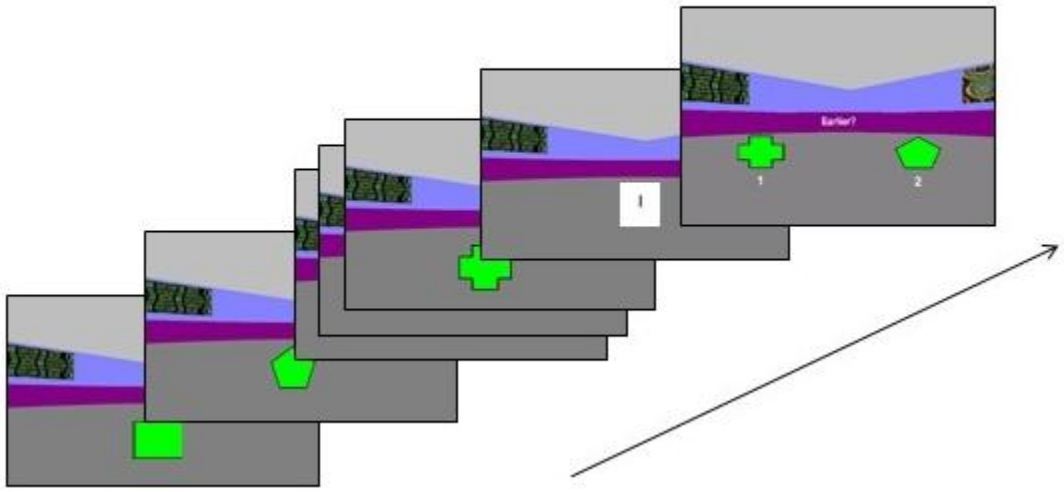


Figure 6. Temporal pattern separation task. In the study phase, participants were shown a sequence of six shapes. During a distractor phase, participants are shown a letter and asked to indicate with a key press whether it is a vowel or consonant. In the recognition phase,

participants will be shown two shapes that appeared in the sequence and asked to indicate using a key press, which appeared earlier or later, depending on the question posed on the screen.

Behavioural data analysis. Both accuracy and reaction time (RT) were assessed for both SPS and TPS tasks. Accuracy was assessed in each task by coding correct recognition as 1 and incorrect as 0. For each condition (near, far) within each task (SPS, TPS) the proportion of correct responses was calculated. Reaction time was measured in terms of the median response time (RT) per participant. These median RTs were averaged across participants to produce mean RTs for each separation condition for each task.

Results

Participants performed significantly above chance (50%) in every condition (Figure 7). A repeated-measures ANOVA with Task (SPS and TPS) and Separation (NEAR and FAR) as conditions revealed a main effect of Task with overall SPS proportion correct higher than TPS proportion correct, $F(1, 18)= 9.76$, $p=.006$, partial $\eta^2= .35$, and a main effect of Separation with a greater proportion correct in the FAR condition than in the NEAR condition, $F(1, 18)= 134.48$, partial $\eta^2= .88$. The interaction was nonsignificant, $F(1, 18)= 2.09$, $p=.166$, partial $\eta^2= .10$ (Figure 7). Contrary to some findings indicating better performance of males in spatial tasks compared to females, there were no sex differences in the two tasks, $F(1, 17)= 0.325$, $p= .58$, partial $\eta^2= .02$.

Figure 7

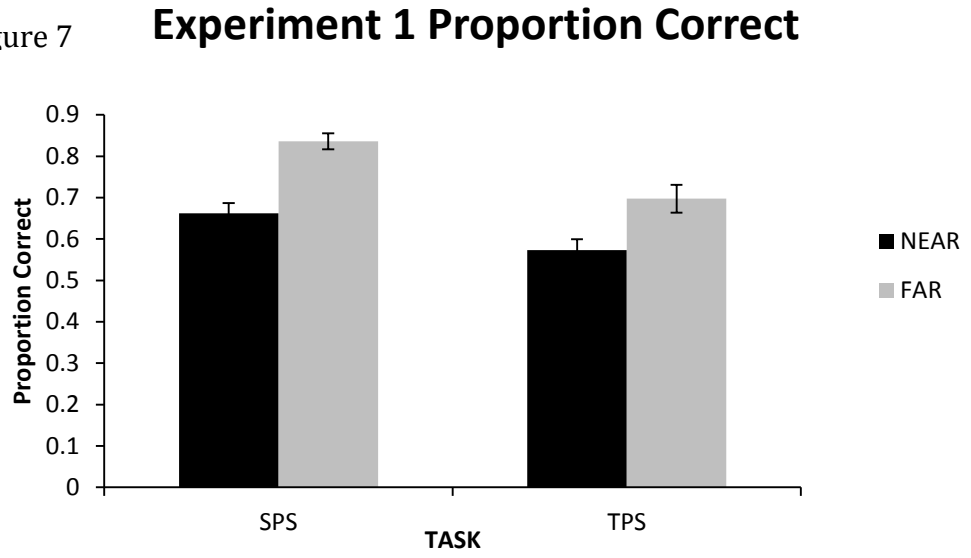


Figure 7. Experiment 1 proportion correct for SPS and TPS. There were significant differences in proportion correct between the NEAR and FAR conditions for both SPS and TPS. Overall, performance on SPS was higher than performance on TPS.

RT results were consistent with accuracy results such that there was a main effect of Task, with higher overall RTs for TPS compared to SPS, $F(1, 18)= 62.09$, $p<.001$, partial $\eta^2= .775$, and main effect of Separation with longer RTs for the NEAR condition, $F(1, 18)= 29.81$, $p<.001$, partial $\eta^2= .623$ (Figure 8).

Figure 8

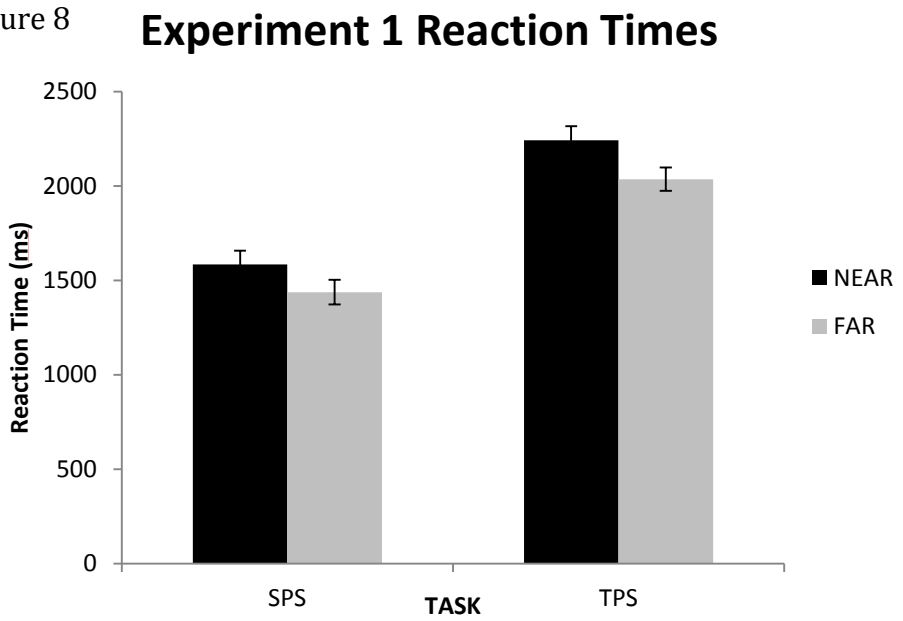


Figure 8. Experiment 1 reaction time for SPS and TPS. There were significant differences in reaction time between the NEAR and FAR conditions for both SPS and TPS. Overall, reaction time was lower for SPS than TPS.

Chapter 4: Experiment 2 Methods and Results

Methods

Participants. Fourteen healthy young adults from the community with no prior history of neurological or psychiatric impairment were recruited for participation in the fMRI portion of this study (9 female; M_{age}=27.4 years, *SD*= 9.22, Range 18-55 years). Average years of education for this sample was 17.4 (*SD*= 2.59). Inclusion criteria include an age requirement of 18-59, fluency in English, normal or corrected-to-normal vision, and meeting MRI scanning requirements. Exclusion criteria included neurological impairment, Axis-I psychiatric disorder, history of drug/alcohol dependence or current abuse or first degree relatives with a psychotic illness (Appendix I). Imaging took place at the St. Joseph's Healthcare Brain-Body Institute Imaging Research Centre in Hamilton, ON.

Pre-scanning cognitive/neuropsychological testing. In Experiment 2, participants were scanned while performing the SPS and TPS tasks outlined in Experiment 1. Participants also performed additional cognitive tests and practice tasks outside of the scanner.

Prior to scanning, participants underwent a series of three cognitive measures used to characterize the sample administered by either a trained Research Assistant or myself. These are the WAIS-III Information and Matrix Reasoning subtests (Wechsler, 1997), the Mental Rotation Test (MRT; Peters et al., 1995), and Spatial Span (Rowe, Hasher, & Turcotte, 2008).

The WAIS-III is a well-validated and reliable test of general intelligence containing 14 subtests (Wechsler, 1997). Full-Scale IQ is computed from 11 of these subtests. Two subtests, Information and Matrix Reasoning, were used to calculate a reliable prorated estimate of IQ (Sattler & Ryan, 1998). Participants had an estimated IQ of 118 (*SD*= 13.2), indicating this sample IQ is above the population average.

The MRT is a modification of Vandenberg and Kuse (1978) classic test of spatial abilities. In this paper and pencil test, participants are shown a geometric object with four objects next to it. They are asked to determine which two of the four objects are rotated versions of the target stimulus (Peters, et al., 1995). This test was used to characterize general spatial abilities in our sample. Participants obtained an average Mental Rotations test score of 10.9 (*SD*= 5.13). This score is consistent with the average performance of the sample of undergraduates tested by Peters et al. (1995).

Spatial span is a measure of visuospatial working memory (Rowe et al., 2008). Because of the possible visuospatial working memory component in the SPS and TPS tasks, the spatial span is a useful measure for characterizing the general visuospatial working memory abilities in our sample. On a given trial in this computerized task, participants view a sequence of nine gray squares on a monitor presented one at a time. After the presentation, participants were required to touch the squares in the order they were presented. In the ascending condition, the number of squares presented in the sequence would increase with each trial. In the descending condition, the number of blocks presented would decrease with each trial. The current sample obtained an average ascending proportion correct percentage of 82.0% (*SD*=19.2%), and descending proportion correct percentage of 78.3% (*SD*= 17.4%). Rowe et al. (2008) reported young adults performed at 71% (*SD*= 20) in the ascending condition, and at 57% (*SD*= 16) on the descending condition.

Subsequent to completing the neuropsychological tests, participants completed practice versions of the SPS and TPS tasks on a laptop computer. Practice sessions took place in a room adjacent to the suite containing the MRI scanner, and 10 study-test trials were performed in this room that were similar to those participants later performed in the MRI scanner. The practice

session ended once participants reached a criterion of 80% on both spatial and temporal pattern separation tasks. This criterion was set to ensure participants understood the task instructions and were able to perform the task adequately before entering the scanner.

Scanning session. In the scanning environment, participants lay in the scanner with an adjusted padded holder to minimize movement. Visual stimuli were projected onto a screen at the back of the scanner and a mirror in front of the participants allowed them to see the stimuli. Participants responded using one of two keys on an MR-compatible five-button response box. Four runs of functional neuroimaging were administered in total. Each of the SPS and TPS tasks were administered in two runs. Each run was approximately 10 minutes in duration. The task order was counterbalanced. Total time in the scanner was approximately one hour.

fMRI data acquisition. Images were acquired with a 3T MRI scanner. Detailed anatomical data were collected using a multiplanar rapidly acquired gradient echo (MP-RAGE) sequence. Functional images were acquired using a T2*-weighted echo planar imaging (EPI) sequence (TR=3000ms, TE= 30ms, FOV=192mm, slice thickness= 4mm, flip angle= 90 degrees). The first four scans were collected prior to the task trials. These were dummy scans required for scanner equilibrium, and were discarded. Forty axial slices parallel to the long axis of the hippocampus providing whole-brain coverage (voxel size: 3x3x4 mm^3) were acquired in an interleaved fashion. Axial slices were selected to minimize signal loss in the inferior frontal lobe, and also to prevent overheating that can be caused by other slice acquisition methods. A voxel size was selected that would be small enough to allow a fine enough resolution to visualize the hippocampus but large enough to prevent overheating as well as noise-related artifacts, and thick enough to provide whole brain coverage within a 3s TR. Our choice of in-plane resolution was approximately in line with other studies examining spatial (Summerfield, Hassabis, &

Maguire, 2010) and temporal processing (Jenkins & Ranganath, 2010) and the hippocampus. T1-weighted anatomical images were acquired with a spatial resolution of 1x1x1 mm^3 and TR= 6ms. B0 maps were acquired at the end of the scanning session to use in preprocessing to correct for magnetic field inhomogeneities.

fMRI data analysis. Standard preprocessing of functional images was performed using SPM8 (Wellcome Department of Cognitive Neurology, London, UK). This included slice timing correction, rigid-body motion correction and unwarping, coregistration of the anatomical image with functional images, segmentation of the coregistered anatomical image, spatial normalization of the realigned and unwarped functional images to the Montreal Neurological Institution (MNI) template, spatial normalization of the anatomical image to the MNI template based on segmentation, and spatial smoothing, using an 8mm full-width half maximum isotropic Gaussian kernel (see Appendix II for detailed step-by-step preprocessing procedure).

Univariate analysis using SPM8. SPM uses a general linear modeling (GLM) approach to analyze neuroimaging data. Individual participant data were analyzed with first level (fixed-effects) contrasts entered for each task: Encoding subsequently correct versus Letter, Encoding NEAR subsequently correct versus Letter, Encoding FAR subsequently correct versus Letter, Encoding versus Letter, Retrieval versus Letter. Encoding was broken down into four contrasts and retrieval collapsed across all conditions because my aim here was to examine activity when pattern separation was engaged at encoding, as per question 2 under the subsection Main Research Questions. Group results were analyzed with a random-effects model in SPM, with each of the contrasts above as well as a 2 (TASK: SPS vs. TPS) x 2 (SEPARATION: subsequently correct NEAR vs. FAR) repeated-measures ANOVA. This analysis, unlike the PLS analysis below, allowed for the direct comparison of activation between SPS and TPS tasks, in

identifying regions unique to each task during successful encoding with the removal of the effects of the baseline task. All reported *p* values are corrected for multiple non-independent comparisons based on the false discovery correction at 10^{-7}, and extent threshold of 5 voxels. Data were visualized and localized using xjview (Ciu, X., http://www.alivelearn.net, Stanford, United States of America), which localizes MNI coordinates using the MNI Space Utility (PET Lab of Institute of the Human Brain, St. Petersburg, Russia) and WFU_PickAtlas (Department of Radiological Sciences, Wake Forest University, Winston-Salem, USA) databases.

Multivariate analysis using PLS. A Mean-Centering Task PLS allows for a preliminary examination into how brain activity and conditions covary within a task, without a priori hypotheses. For each LV, statistical significance is determined with permutation tests (McIntosh et al., 1996). In this study, 500 permutations were performed. Bootstrap estimation assesses reliability of the saliences for brain voxels within a LV. This bootstrap estimation was conducted 100 times. A 16s temporal window (i.e., 5 TRs) was specified. A temporal window is the expected length of the hemodynamic response.

An analysis was conducted to determine whether encoding and retrieval conditions show a differing pattern of activity in SPS and TPS tasks. Since the mean-centered analysis clustered the letter task with retrieval (see Results), I ran a non-rotated task analysis that allowed me to specify *a priori* contrasts removing the letter condition. As with the above mean centered analysis, 500 permutations and 100 bootstraps were carried out, and the temporal window was set at 5 TRs. The 5 TR temporal window setting presents the pattern of correlated activity for a certain LV for each of 0, 1, 2, 3, and 4 lags.

The non-rotated task analysis identified right posterior hippocampal clusters in both tasks (see Results), and these clusters were inputted into a seed analysis in order to examine functional

connectivity between regions. Here I aimed to assess whether the hippocampal seeds exhibited distinct patterns of functional connectivity with the rest of the brain for SPS and TPS. As with prior analyses, 500 permutations and 100 bootstrap sampling procedures were carried out. For all PLS analyses, MNI coordinates were obtained and were converted to Talairach space. The Talairach Space Utility toolbox (PET Lab of Institute of the Human Brain, St. Petersburg, Russia) based on a stereotaxic atlas (Talairach & Tournoux, 1988) was used for localization of regions.

Results

Behavioural data. I ran identical analyses to those of Experiment 1 for Experiment 2 behavioural data. Again, accuracy in all conditions was higher than chance (Figure 9). Other findings differed slightly from those seen in Experiment 1, with a main effect of Separation, $F(1, 13)= 17.99$, $p=.001$, partial $\eta^2= .580$ and a Task x Separation interaction observed, $F(1, 13)= 15.63$, $p=.002$, partial $\eta^2= .546$, but no main effect of Task, $F(1, 13)= 3.28$, $p=.093$, $\eta^2=.201$. Follow-up paired samples t tests revealed significant differences in proportion correct between NEAR and FAR conditions in SPS, $t(13)= -5.845$, $p<.001$, $d= 1.56$, but not TPS, $t(13)= -2.68$, $p=.312$, $d= 0.28$. Furthermore, performance in NEAR SPS and TPS were equivalent, $t(13)= 0.00$, $p=1.00$,$d= 0.00$, while performance in FAR SPS was significantly better than in FAR TPS, $t(13)= 3.20$, $p=.007$, $d= 0.86$ (Figure 9). As in Experiment 1, there were no sex differences in the tasks, $F(1, 12)= 0.363$, $p= .558$, partial $\eta^2= .029$.

Correlations between SPS proportion correct, TPS proportion correct, eFSIQ, MRT, Ascending Spatial Span, and Descending Spatial Span were examined. TPS proportion correct showed a high positive correlation with the MRT, $r= .633$, $p= .015$. The reason for this relationship is not clear, but one possibility is that the two may share the characteristic of being

more cognitively demanding than the other tasks. Overall, the general paucity of relationships between SPS and TPS tasks confirms the divergent nature of these tasks, both between each task, and with the other measures. Therefore, these tasks may be tapping into unique processes not assessed by other commonly used neuropsychological measures.

Figure 9

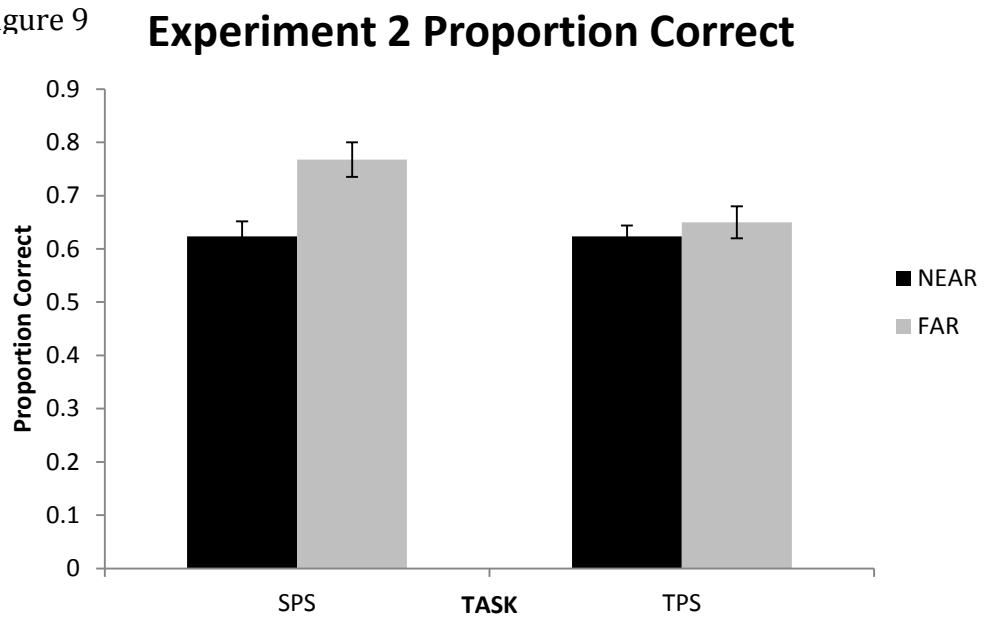


Figure 9. Experiment 2 proportion correct for SPS and TPS. There were significant differences in proportion correct between NEAR and FAR conditions for SPS, but not for TPS. Error bars represent standard error.

RT results more closely mirrored those seen with Experiment 1. In particular, there was a main effect of Task *(F*(1, 13)= 28.92, *p*<.001, partial η^2= .690), and main effect of Separation (*F(*1, 13)= 28.46, *p*<.001, partial η^2= .686, but no interaction between Task and Separation, *F*(1, 13)= .024, *ns*. T tests revealed greater overall RTs for TPS compared to SPS, *t(*13)= -5.38, *p*<.001, and significantly shorter RTs for the FAR condition compared to the NEAR condition for both SPS, *t*(13)= 2.62, *p*=.021, *d*=0.70, and TPS, *t*(13)= 3.86, *p*=.002, *d*=1.02 (Figure 10).

Figure 10

Figure 10. Experiment 2 reaction time for SPS and TPS. There were significant differences in reaction time between NEAR and FAR for both SPS and TPS tasks. Overall, reaction time was lower in SPS compared to TPS. Error bars represent standard error.

fMRI data. ***SPM univariate analysis.*** Activation for SPS and TPS was assessed using a univariate random-effects analysis with SPM 8. Contrasts from the fixed-level analysis (see Methods) were first run as a Random Effects group analysis. However, these failed to yield suprathreshold activity in medial temporal lobe areas of interest, and therefore these results are not discussed here further. The SPS and TPS successful encoding trials minus baseline letter were inputted into a 2 x 2 repeated-measures ANOVA, with Task (SPS and TPS) and Separation (Near and Far) as factors. Due to robust activation throughout the brain with one or more very large clusters spanning a large area of the brain with a corrected *p* of .001, the *p* value was reduced to 10^{-8} (with a False Discovery Rate correction). This analysis yielded main effects of Task. The main effect of Task showed differences in activation between SPS and TPS. Although

there were significant differences in activation between the NEAR and FAR conditions collapsed across tasks, there was no significant activation within each task when separation distances were directly compared, contrary to predictions. The main effect of Task will be discussed further.

Two large clusters uniquely activated for SPS were found. These had peak voxels in the lingual gyrus and the cuneus. A cluster in the left hippocampus emerged with a relaxed threshold at p=.05 FDR-corrected and this cluster is indicated in the table because it is an a priori region of interest. Sites of peak activation uniquely involved in TPS included the middle occipital gyrus, fusiform gyrus (BA 19), and the superior temporal gyrus (Table 1; Figure 11).

Table 1

Activations unique to each task using SPM univariate analysis

k	Brain Region	*x*	*y*	*z*	*t*
SPS>TPS					
585	R Lingual Gyrus	20	-58	-8	10.81
44	L Cuneus	-14	-86	20	8.00
6	L Hippocampus	-22	-28	-6	3.42
TPS>SPS					
2152	R middle occipital gyrus	50	-66	-10	10.85
1750	L fusiform gyrus (BA 19)	-60	-48	30	12.39
23	L superior temporal gyrus (BA 38)	-54	10	-6	6.91
2638	R supramarginal gyrus	52	-28	36	10.01
237	R caudate	22	12	14	7.64
874	L postcentral gyrus (BA 6)	-54	-8	36	11.06
34	L insula (BA 13)	-34	-10	20	6.84
41	R cingulate gyrus	12	0	30	6.88
24	L cingulate gyrus	-14	-28	30	7.16
103	R paracentral lobule (BA 5)	12	-36	54	7.88
112	R medial frontal gyrus (BA 6)	12	-16	58	7.79

Table 1. All clusters are significant at $p<.0000001$, with FDR correction for multiple comparisons. Only clusters with an extent (*k*) of 20 or more voxels are reported, with the exception of the hippocampus since this was an a priori region of interest. MNI, Montreal Neurological Institute; BA, Brodmann area, L, left; R, right.

Figure 11

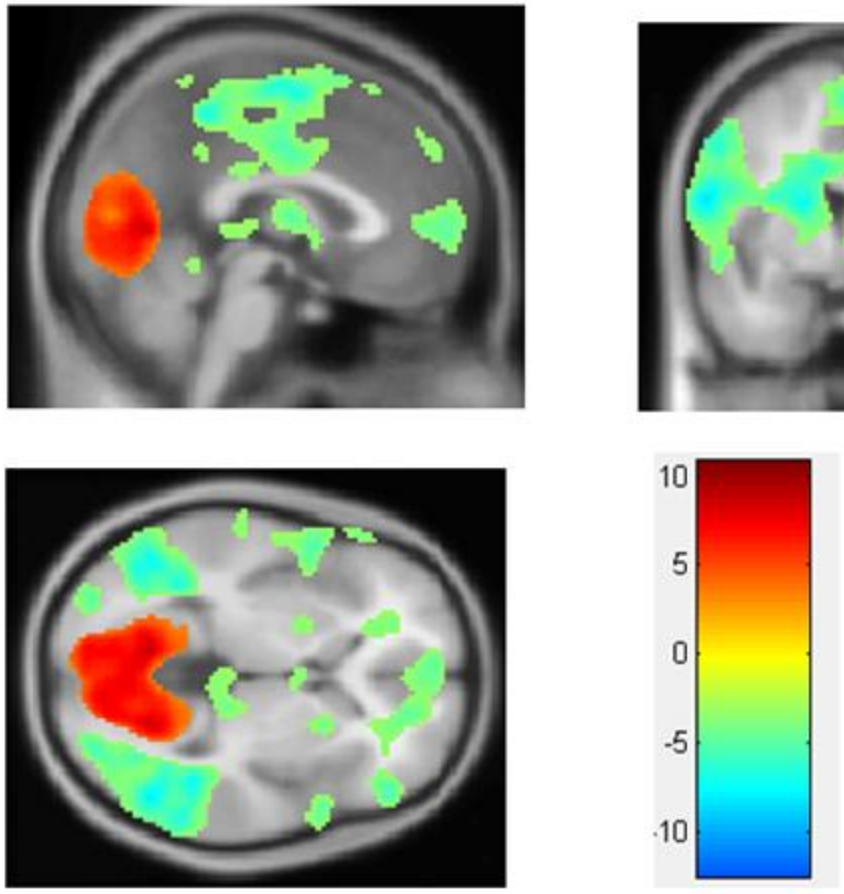


Figure 11. The contrast SPS>TPS displays areas uniquely activated by SPS (warm colours) and TPS (cool colours). Activation unique to SPS is largely confined to the lingual gyrus and cingulate, whereas activation unique to TPS shows a larger area of activation spanning throughout the brain. Areas of activation superimposed over a mean anatomical image. Scale of colourbar reflects arbitrary intensity differences.

PLS multivariate analysis. Seven conditions were entered into the PLS analysis for both SPS and TPS: Encoding near subsequently correct, Encoding far subsequently correct, Encoding subsequently incorrect, baseline Letter, Retrieval near correct, Retrieval far correct, and

Retrieval incorrect. These contrasts were based on expected differences in activation between the NEAR and FAR conditions. Specifically, I suspected more pronounced hippocampal activation might support successful performance on a NEAR retrieval condition, and less hippocampal activation may be required to support successful performance in the FAR retrieval condition. In addition, I expected correlated networks might differ between the encoding and retrieval conditions, in line with the previous literature summarized above that suggests different patterns of activation for encoding versus retrieval. Further, correctly answered items may produce more hippocampal involvement compared to incorrectly answered items given different cognitive processes may be underlying each, and therefore there were additional conditions specified in these cases as well.

Mean-centered PLS: SPS. The mean-centered analysis yielded one significant LV accounting for 45.19% of the covariance in the data. This LV ($p<.0001$; singular value= 61.82) distinguished between all encoding conditions (encoding near subsequently correct, encoding far subsequently correct, encoding subsequently incorrect) and the letter and retrieval conditions (retrieval near correct, retrieval far correct, and retrieval incorrect).

There was extensive activity throughout the brain that characterized the letter and retrieval conditions, compared to the encoding condition including the frontal pole (BA 10), bilateral inferior frontal gyri (BA 47), parahippocampal gyrus (BA 36), hippocampus, caudate nucleus, and thalamus (Figure 12).

The involvement of some of these regions changed throughout the trial. For example, the right hippocampus (MNI: X=24, Y= -14, Z= -18) was active during the first lag, and the positive bootstrap ratio indicates it was positively activated for the letter and retrieval conditions. During the second lag, no hippocampal activity was present. However, in the third lag, left hippocampal

activity was positively related to the encoding conditions. In the first lag, left frontal pole (BA10) activity was related to letter and retrieval, and right frontal pole activity was related to encoding. In the second lag, the opposite pattern was evident, with right frontal pole activity for letter and retrieval, and left frontal pole activity for encoding. In the third lag, there was bilateral frontal pole activation for the letter and recognition conditions, and left frontal pole activation for the encoding conditions. While not apparent during the first three lags, caudate activity was seen in the fourth lag. In particular, caudate head activity was related to letter and recognition, and caudate body activity was related to encoding. For full table of coordinates, see Appendix III.

Figure 12

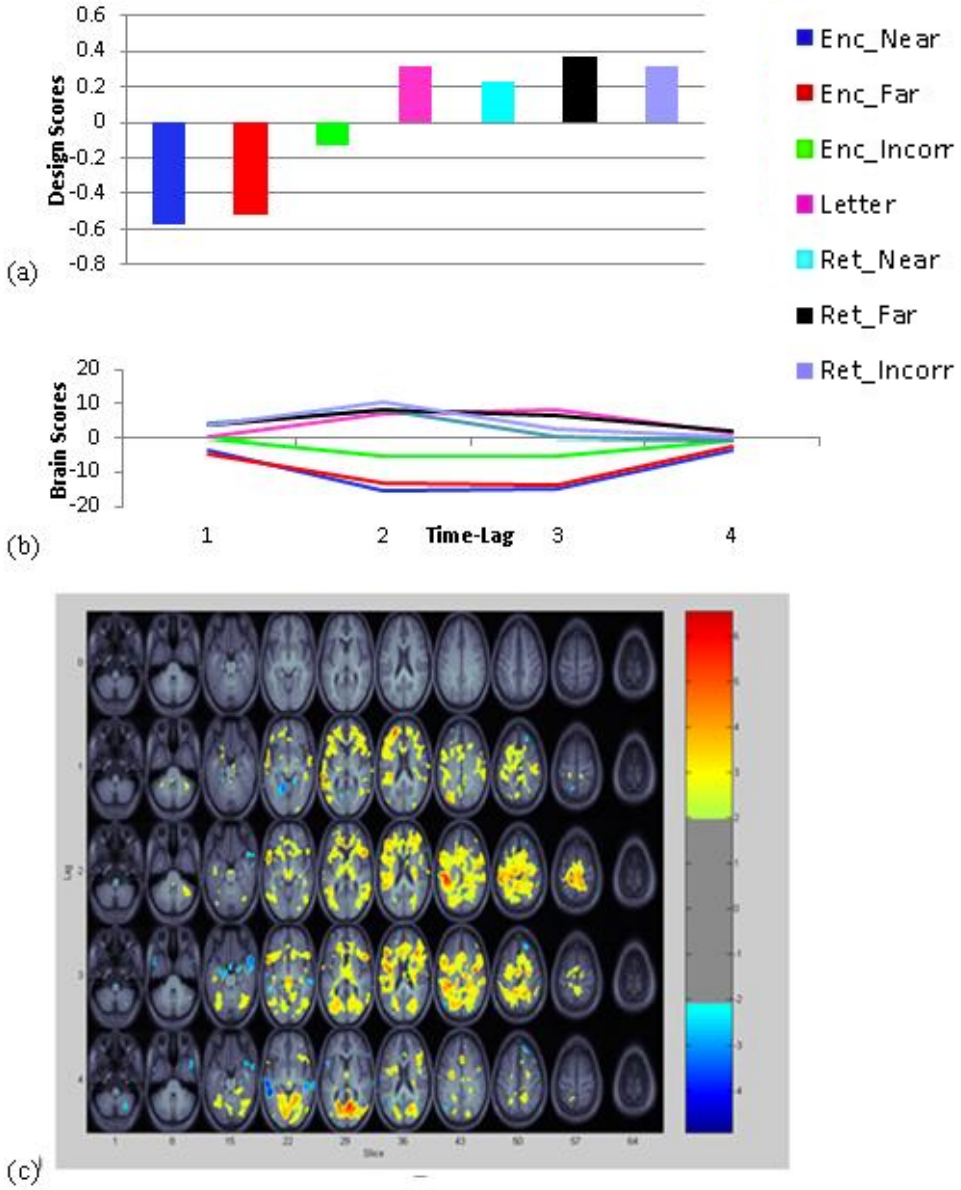


Figure 12. Results from SPS mean-centered PLS analysis. (a) This graph illustrates activation for the significant LV (SPS encoding versus letter/recognition). (b) Brain scores for each condition (i.e., the weighted average of activation for all subjects across all voxels through the duration of the experimental tasks). The Retrieval conditions (turquoise, black, purple) peak during Lag 2, while the Encoding conditions (blue, red, green) peak during Lag 2 and Lag 3. (c)

Pattern of activation distinguishing letter/recognition (warm colours) from encoding (cool colours).

Mean-centered PLS: TPS. For TPS, the mean-centered analysis yielded two significant LVs. The first accounted for 81.3% of the variance in the data. Similar to SPS, the first LV differentiated between the encoding conditions and letter/retrieval ($p<.001$; singular value= 203.81).The second LV accounted for 13.0% of the variance in the data. This LV distinguished between activation for the letter versus retrieval near, retrieval far, and retrieval incorrect ($p<.002$, singular value=81.42) indicating that PLS was sensitive to the difference between activations during the letter baseline and retrieval processes. Because this latter contrast is not relevant to the a priori hypotheses, it will not be discussed here.

Widespread activity characterized the first LV. Active regions included the frontal pole (BA10), bilateral medial frontal gyri (BA 6), the right hippocampus, and the caudate (Figure 13). Similar to the SPS task, the involvement of some regions changed as the trial progressed. For instance, the right hippocampus was active during the first lag for letter/recognition, but there was no hippocampal involvement after this initial lag. This differs from SPS, where right hippocampal activity was evident for the first lag (retrieval) and left hippocampal activity was seen in the third lag (encoding). Bilateral frontal pole activity was apparent in the fourth lag for letter/recognition. In comparison, in SPS frontal pole activity was evident throughout lags 1-3. There was left caudate head and right caudate body activation for letter/recognition, and right caudate body activation for encoding, but this caudate involvement was only evident in the first lag. This contrasts to the SPS task, where caudate activity was isolated to the fourth lag. For full table of coordinates, see Appendix IV.

Figure 13

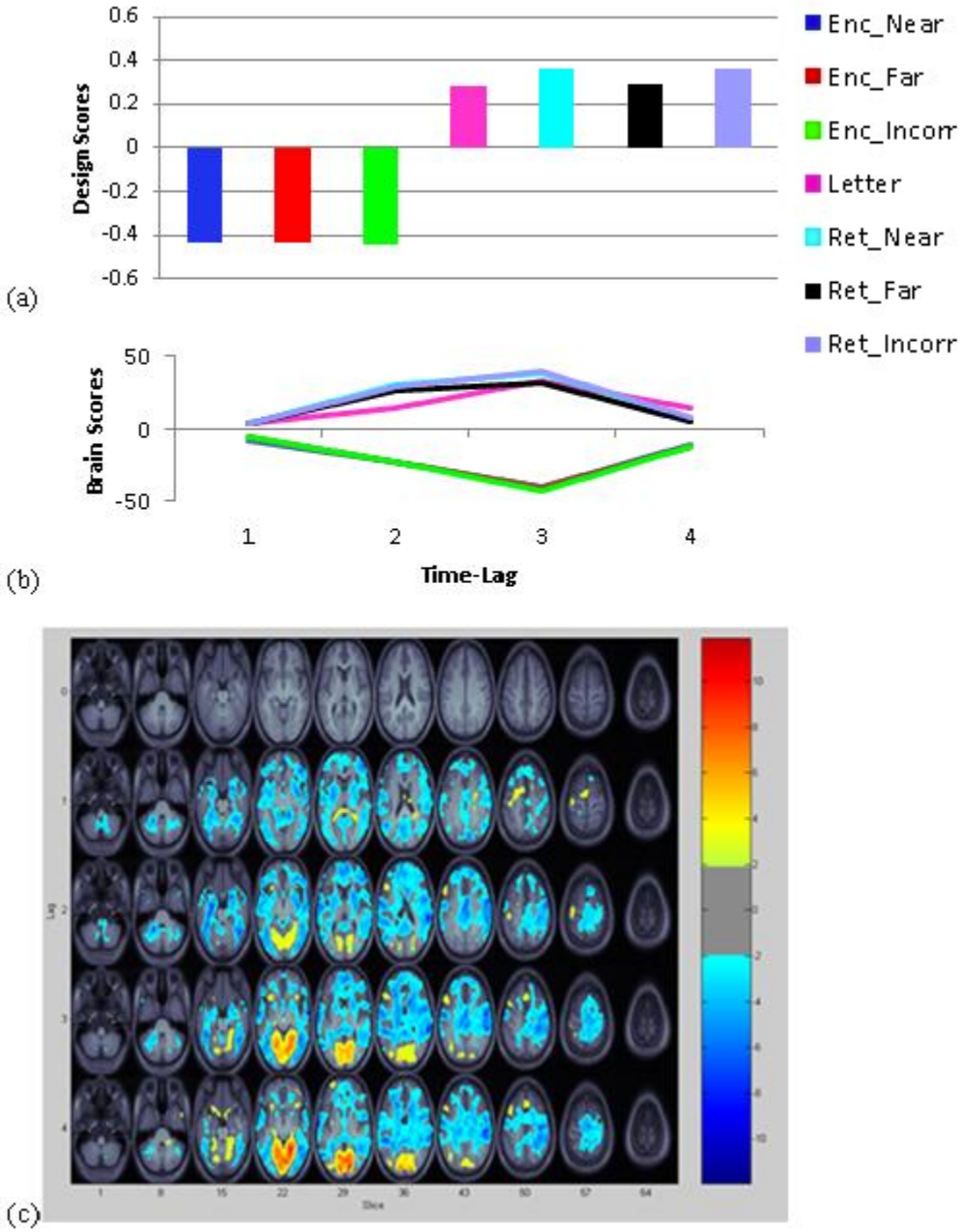


Figure 13. Results from TPS mean-centered PLS analysis. (a) This graph illustrates activation for LV1 (TPS letter/recognition versus encoding) (b) Brain scores for each condition (i.e., the weighted average of activation for all subjects across all voxels through the duration of the experimental tasks). Both retrieval (turquoise, black, purple) and Encoding (blue, red, green)

conditions peak during Lag 3. c) Regions where activation was associated positively (warm colours: letter/recognition) and negatively (cool colours: encoding).

Non-rotated task PLS: SPS. I compared NEAR and FAR conditions for both encoding and retrieval. These contrasts did not reveal a unique pattern of activity for each of NEAR and FAR. This was the case for both encoding (p<1.00, singular value= 30.61) and retrieval (p<1.00, singular value= 29.00). This nonsignificant finding may be due to insufficient power as a result of the small number of trials within each condition.

A non-rotated analysis was conducted that directly compared the encoding conditions to the retrieval conditions, and this contrast was significant (p<.001, singular value= 57.09), and explained 40.1% of the variance in the data. The sole difference between this analysis and the mean-centered analysis was that the letter task was removed from the analysis in order to directly compare the encoding and retrieval conditions. This analysis revealed a network involving bilateral anterior hippocampal activation associated with encoding, and right posterior hippocampal activation associated with retrieval. Other regions active for the encoding vs. retrieval contrast were similar to those in the mean-centered analysis, including the frontal pole (BA10), caudate, and parahippocampal gyrus (BA 36), and showed similar activations across lags as in the mean-centered analysis (Figure 14). For full table of coordinates, see Appendix IV.

Contrary to expectations, this pattern of activation did not hold up when unsuccessful trials were removed from the analysis. Although the LV was significant for this contrast and explained 36.5% of the variance in the data, (p<.004, singular value= 54.48), no hippocampal activity was present. This may have to do with the reduced power due to the smaller number of trials in each condition.

Figure 14

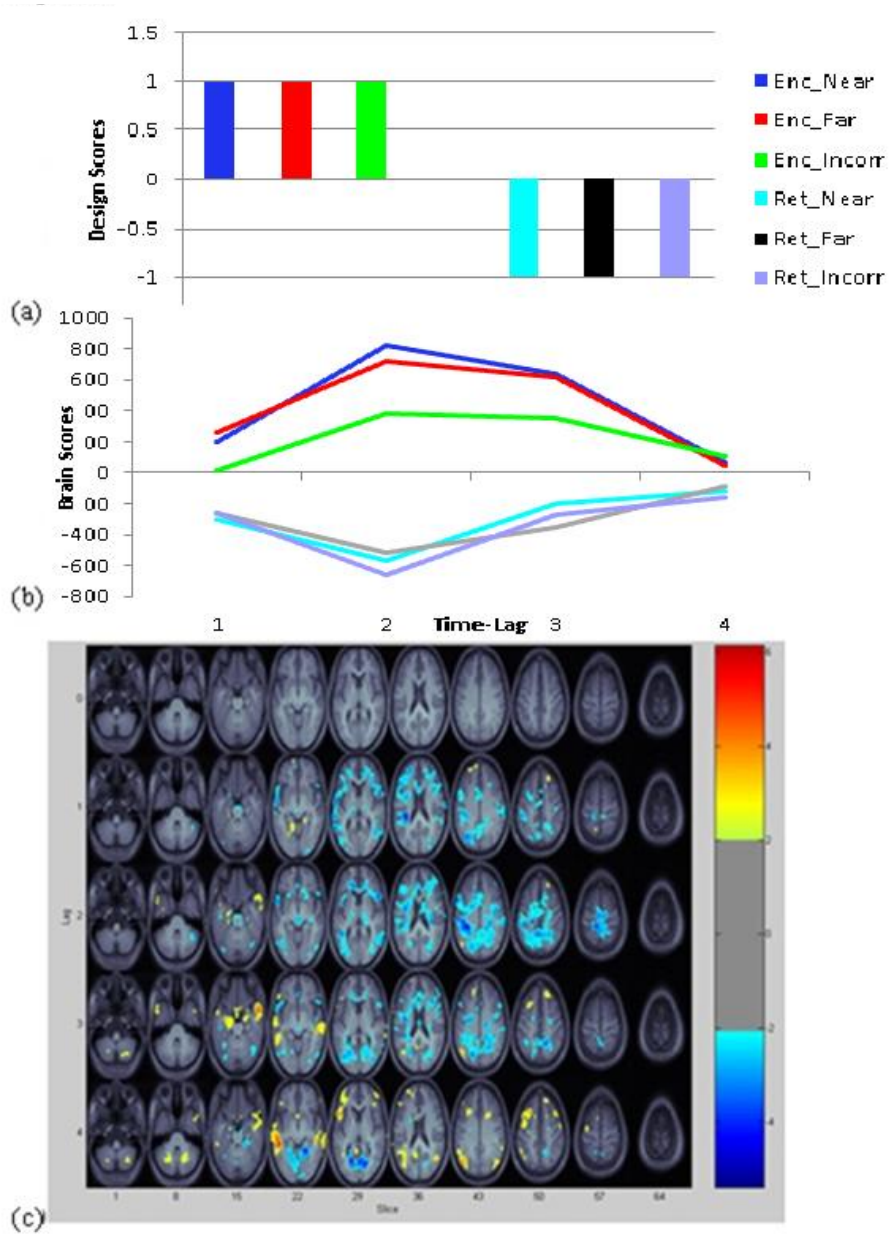


Figure 14. Results from SPS non-rotated task analysis. (a) This graph illustrates contrast for LV1 (SPS encoding versus retrieval) (b) Brain scores for each condition (i.e., the weighted average of activation for all subjects across all voxels through the duration of the experimental tasks). Both retrieval (turquoise, black, purple) and encoding (blue, red, green) conditions peak during Lag 2. (c) Regions where activation was associated positively (warm colours: encoding) and negatively (cool colours: retrieval).

Non-rotated task analysis: TPS. A non-rotated task analysis compared NEAR and FAR conditions for both encoding and retrieval. Contrary to expectations, these contrasts were nonsignificant for both encoding (p<.738, singular value= 29.29) and retrieval (p<.424, singular value= 32.31).

As in SPS, a non-rotated analysis with a contrast comparing encoding to retrieval was performed. This contrast was significant, p<.001, singular value= 195.13. Results were consistent with the mean-centered results, such that the right hippocampus was more active for retrieval. Interestingly, a cluster in the right posterior hippocampus was active during retrieval in a similar location to the right anterior hippocampal cluster in SPS retrieval. Unlike SPS however, hippocampal activation was not apparent for encoding. Similar regions to the mean-centered analysis were activated and showed similar patterns of activation across lags, such as the frontal pole (BA 10), bilateral medial frontal gyri (BA 6), and the caudate. However the caudate only showed a single cluster of activation for this contrast, which was left sided activation for the retrieval condition in the first lag, whereas it showed multiple clusters in lag 1 when the letter task was grouped with the retrieval conditions (Figure 15). For full table of coordinates of peak activation, see Appendix V.

Similar to SPS, the contrast comparing only subsequently correct encoding trials to correct retrieval trials resulted in a significant LV (p<.001, singular value= 157.04). The same peak voxel was active in the right hippocampal cluster as when the incorrect trials were included in the contrast. However, the size of the cluster was substantially reduced and the p value was larger when the incorrect trials were removed from the analysis.

Figure 15

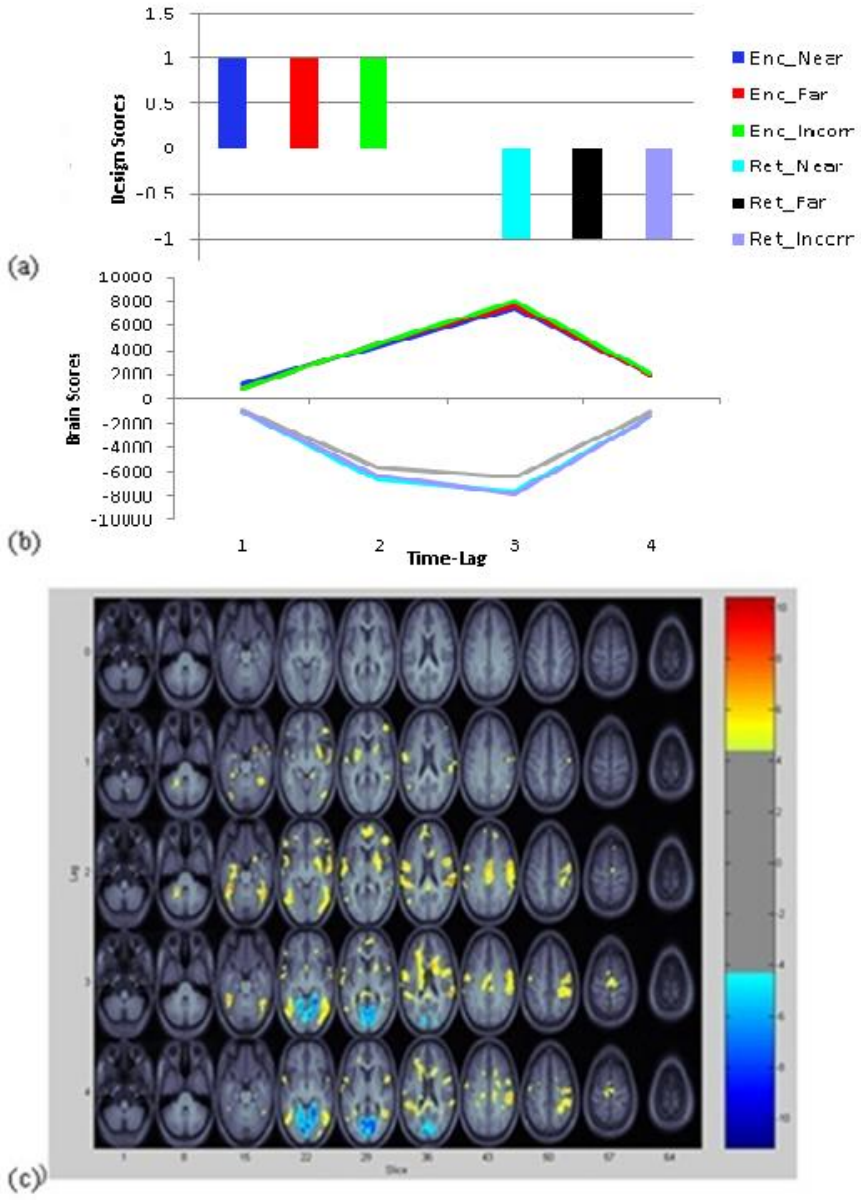


Figure 15. Results from TPS non-rotated task analysis. (a) This graph illustrates the pattern of activation for LV1 (TPS encoding versus retrieval) from the PLS non-rotated task analysis. (b) Brain scores for each condition (i.e., the weighted average of activation for all subjects across all voxels through the duration of the experimental tasks). Both Encoding (blue, red, green) and Retrieval (turquoise, black, purple) conditions peak during Lag 3. (c) Regions where activation was associated positively (warm colours: encoding) and negatively (cool colours: retrieval).

Seed analysis: SPS. Two separate seed PLS analyses were conducted on the SPS data using hippocampal seeds identified in the encoding versus retrieval contrast in the nonrotated task analysis (previous section). One seed analysis was conducted with three hippocampal seeds, and the other from a single hippocampal seed. For the three seed analysis, two of these seeds were in the right hippocampus (MNI coordinates: X=30, Y=-6, Z=-28; X=30, Y=24, Z=-10) and one in the left hippocampus (MNI: X=-32, Y=-12, Z=-26).Although the three seed analysis may be informative in that it displays general functional connectivity in SPS between the hippocampus and other extra-hippocampal regions, a complicating factor is that two of these seeds are associated with the encoding phase of the task, while one is associated with the retrieval phase. Thus when comparing it to the TPS task that has a single right hippocampal cluster yielded by the nonrotated analysis, it would not be a direct comparison of hippocampal connectivity during the same phase of memory processing for SPS and TPS. Therefore, the single seed analysis allowed for the comparison of hippocampal functional connectivity during the retrieval phase for both SPS and TPS. Tables and figures for the analysis using all three seeds can be found in Appendix VI.

The second analysis used a single seed from the posterior right hippocampus that was engaged during SPS retrieval (MNI coordinates: X=30, Y=-24, Z=10), in order to compare it to the single posterior hippocampal seed identified for TPS during retrieval (MNI: X=30, Y=-46, Z=6). One LV that accounted for 62.71% of the summed squared crossblock covariance (SSCC) was significant out of the seven LVs identified at a significance level of .001. Regions of peak activation included the left inferior temporal gyrus (BA 37), the left and right middle temporal gyri (BA 21), and the left anterior lobe of the cerebellum (Table 2; Figure 16; Figure 17).

Note that the cluster tied to the seed region is quite large, spanning over 60,000 voxels. Because increasing the threshold was not successful at separating this cluster into smaller regions, I used the Anatomy Toolbox in SPM (Institut for Medicine, Juelich, Germany) to better characterize regions within that cluster. The Anatomy Toolbox uses a probabilistic cytoarchitectonic atlas from human histological studies for the localization of activation maps from functional neuroimaging studies (Eickhoff et al., 2005). Regions throughout the brain were identified as part of this large cluster, including the right CA fields of the hippocampus, the right subiculum, the left CA fields, the left entorhinal cortex, the left subiculum, and the left DG. Outside of the medial temporal lobe, the cluster extended throughout the brain into the insula, bilateral frontal areas (BA 6), as well as bilateral occipital areas (BA 17/18). The seed voxel itself was identified as being in the CA fields of the HC.

Table 2

Regions with functional connectivity to the right hippocampal seed region in SPS.

k	Brain Region	*x*	*y*	*z*	BSR	*p*
61210	R hippocampus (seed)	30	-24	-7	-8248129	<.0001
101	R declive	44	-71	-18	-5.38	<.0001
34	L inferior temporal gyrus	-57	-44	-16	-4.49	<.0001
18	L middle temporal gyrus (BA 21)	-69	-35	0	-3.74	.0002
71	L anterior lobe	-8	-38	-30	-3.70	.0002
18	R middle temporal gyrus (BA 21)	51	10	-36	-3.55	.0004
42	L superior parietal lobule (BA 7)	-32	-62	49	-3.37	.0007

Table 2. Only clusters in the timepoint (Lag 2) where the seed cluster showed activation with a bootstrap ratio of greater than +/- 3 (roughly p=.0027) and a cluster size of at least 15 voxels are reported. Coordinates are in MNI space. BA, Brodmann area; MNI, Montreal Neurological Institute; BSR, bootstrap ratio (i.e., voxel's parameter estimate divided by the standard error and proportional to *z* score, Addis, McIntosh, Moscovitch, & McAndrews, 2004); L, left; R, right.

Figure 16

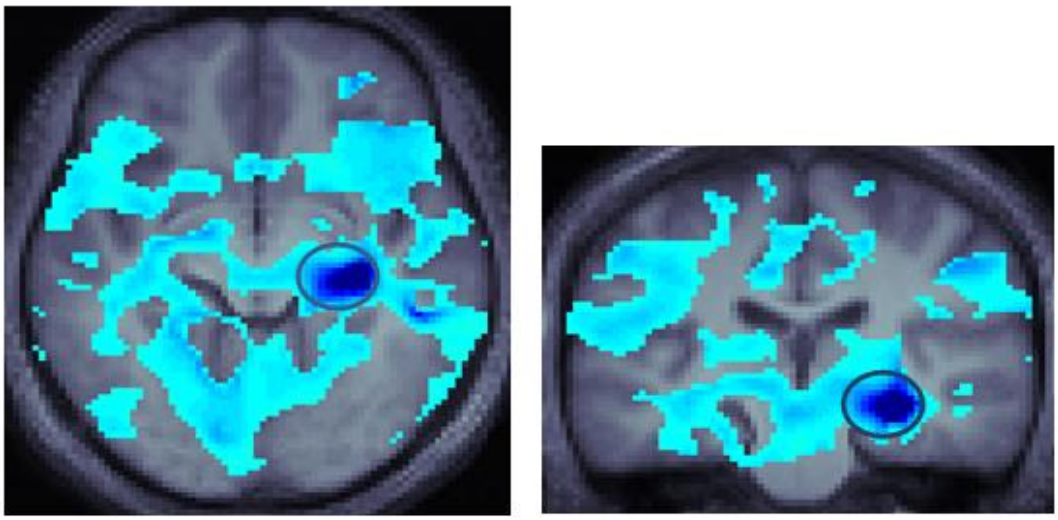


Figure 16. Regions of activation correlated with right hippocampal seed in SPS at Lag 2 superimposed over a mean anatomical image. Location of seed region indicated by circle. Areas functionally connected to seed region represented in blue.

Figure 17

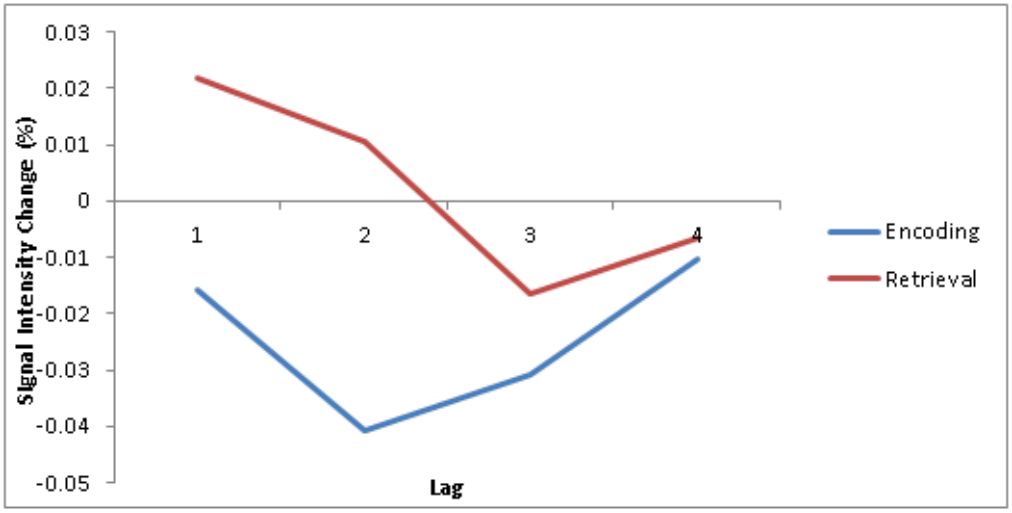


Figure 17. BOLD signal response function plot for right hippocampal seed voxel for SPS. This voxel shows a peak negative signal intensity change at lag 2 associated with encoding, and a peak positive signal intensity change at lag 1 associated with retrieval.

Seed analysis: TPS. The peak voxel from the active right hippocampal cluster identified from the nonrotated analysis at lag 1 (MNI: X=30, Y=-46, Z=6) was used in the seed analysis. The functional connectivity of this region with others in the brain was visually assessed for overlapping and unique patterns of activation compared to SPS. At a significance level of .001, one LV was significant out of seven LVs yielded. This LV accounted for 45.5% of the SSCC. Regions functionally connected to the right hippocampus seed region in TPS included clusters with peak activations in the left inferior frontal gyrus (BA 47), the right medial frontal gyrus (BA 6), the left parahippocampal gyrus (BA 30) and the right fusiform gyrus, cerebellum, among other regions (Table 2; Figure 18; Figure 19).

As with the SPS task, there was one large cluster that extended bilaterally from the seed region. To elucidate the precise areas active in this cluster, Anatomy Toolbox was again utilized. This analysis revealed activation in the bilateral CA fields, bilateral subiculum, and bilateral DG. Similarly to SPS the seed voxel was localized to the CA fields of the hippocampus, but activation in the hippocampus was less lateralized than in SPS. Regions in this cluster outside of the hippocampus included bilateral entorhinal cortices, bilateral frontal regions (BA 6/1/2/4), the insula, bilateral amygdala, and bilateral occipital regions (BA 17/18).

Table 3

Regions with functional connectivity to hippocampal seed region in TPS.

k	Brain Region	*x*	*y*	*z*	BSR	*p*
44	L cerebellum	26	-28	-12	7.19	<.0001
12046	Hippocampus (seed)	30	-46	6	19117540	<.0001
337	L parahippocampal gyrus (BA 30)	-22	-30	-10	15.07	<.0001
139	L medial frontal gyrus (BA 32)	-66	-34	-12	5.81	<.0001
77	L superior temporal gyrus (BA 39)	-2	62	20	5.78	<.0001
171	R medial frontal gyrus (BA 6)	30	18	54	5.60	<.0001
104	L inferior frontal gyrus (BA 47)	-60	-48	30	5.46	<.0001
30	Hypothalamus	58	8	-18	5.21	<.0001
34	R fusiform gyrus (BA 37)	-36	18	-28	4.58	<.0001
27	Postcentral gyrus (BA 2)	32	-50	58	4.51	<.0001

Table 3. Only clusters in the timepoint (Lag 1) where the seed region showed activation with a bootstrap ratio of greater than $\pm$ 4.5 (roughly $p<.0001$) and a cluster size of at least 30 voxels are reported. Because activation was so robust throughout the brain for TPS, a higher bootstrap ratio was used than in SPS. Coordinates are in MNI space. BA, Brodmann area; MNI, Montreal Neurological Institute; BSR, bootstrap ratio; L, left; R, right.

Figure 18

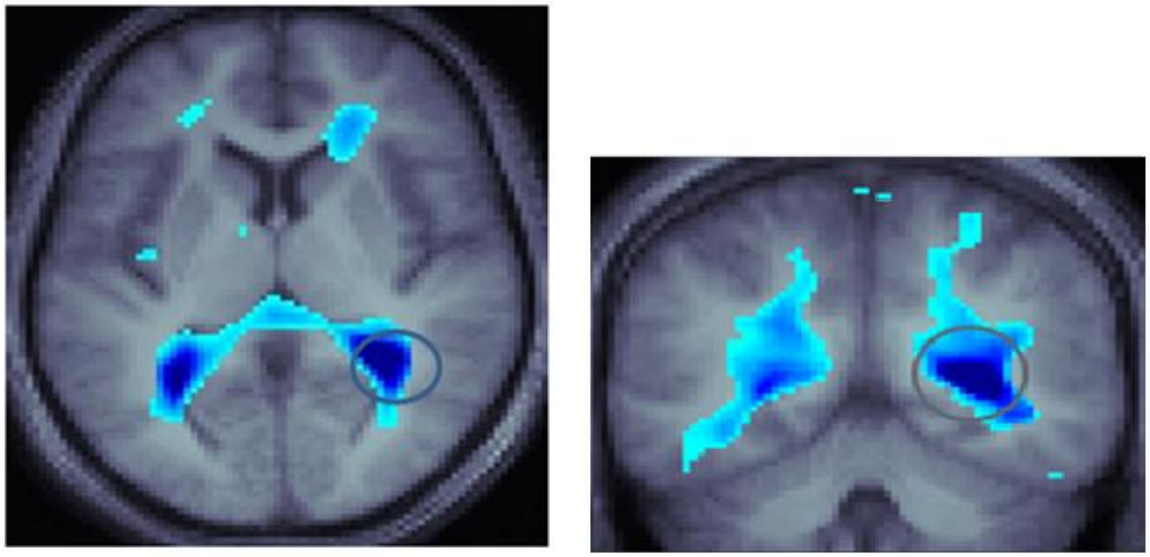


Figure 18. Regions of activation correlated with right hippocampal seed in TPS at Lag 1 superimposed over a mean anatomical image. Location of seed region indicated by circle. Areas functionally connected to seed region represented in blue.

Figure 19

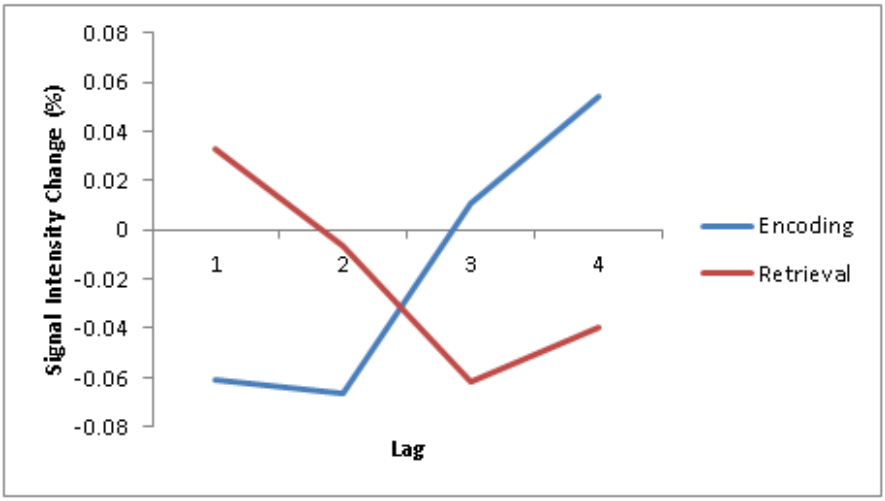


Figure 19. BOLD signal response function plot for right hippocampal seed voxel for TPS. This voxel shows a high negative signal intensity change at lag 1and 2 and a high positive signal

intensity change at lag 4 associated with encoding. The opposite pattern can be found for retrieval, where this voxel displays a high positive signal intensity change at lag 1, and a high negative signal intensity change at lags 3 and 4.

Chapter 5: Discussion

In this section, I will provide a general overview of the results of the current work, and also discuss these findings in relation to the current literature. First, several specific discussion sections pertaining to each analysis will be provided, and my findings will be addressed in relation to relevant literature and prominent theoretical frameworks. Subsequently in a general discussion section I will draw general conclusions and consider overarching themes of the work, as well as address limitations of the current studies and consider future directions for further study. A short section with concluding remarks will follow.

Experiment 1

The goal of this experiment was to demonstrate behavioural sensitivity to separation manipulations; I expected differences in both proportion correct and accuracy between the NEAR and FAR conditions in each task. In the SPS task, participants were presented with a single item in a certain location. At test, the distance between the target and foil object varied, such that the two objects may be relatively near to each other or far from each other. In the temporal pattern separation task, participants were presented with a sequence of objects during the sample phase, and the distance between two test items presented at test was varied, such that the items may have appeared close to one another in the sequence or far apart in the sequence. At closer target-foil distances, a more pronounced reliance on pattern-separation processes is required to discriminate the two locations/points in time (Paleja et al., 2011). This separation manipulation was successful, in that participants showed accuracy and reaction time differences for both the NEAR and FAR conditions in both SPS and TPS tasks. Moreover, in all conditions, performance was significantly better than chance. These findings demonstrate the behavioural sensitivity of these tasks to separation manipulations.

Experiment 2: Behavioural

The data were generally in line with those of Experiment 1. Performance was significantly better than chance for all conditions. Separation effects were seen for SPS and TPS in both proportion correct and reaction time that were generally consistent with those in the previous experiment. In the second experiment however, there was not a significant separation effect for near versus far in TPS, although it was nonsignificantly in the predicted direction. This difference between the two experiments may be due to the increased power resulting from the larger sample size in Experiment 1. It is also possible that training to the 80% criterion before the scanning session in Experiment 2 somehow led to disproportionate gains in the TPS NEAR condition compared to the FAR condition. Comparison of data from behavioural studies to behavioural data from imaging studies may pose an inherent difficulty, in that imaging studies often require training to criterion in practice tasks. As in our study, this is a common practice used to ensure participants are familiar with the task prior to entering the scanner. Generally however, the behavioural results from Experiment 1 and Experiment 2 are in line, and further reinforce the behavioural sensitivity of our SPS and TPS tasks to separation manipulations.

Experiment 2: SPM Univariate Analysis

The aim of the univariate analysis in SPM was two-fold. One goal was to establish whether the hippocampus or other regions were more engaged at encoding for subsequently successfully identified stimuli, when a target stimulus required a finer-grained representation (NEAR condition) versus a coarser representation (FAR condition) in order to separate it from a foil. The lack of differences between separation conditions within each task could have to do with the low statistical power resulting from too few trials within each task for each separation condition.

The second aim of the univariate analysis was to directly compare activations unique to each of successful spatial pattern separation and temporal pattern separation encoding throughout the brain. As mentioned previously, the majority of studies conceptualize pattern separation as a process that occurs primarily during the encoding of information (Bakker et al., 2008; Jerman et al., 2006; Kirwan & Stark, 2007; O'Reilly & McClelland) in the creation of a fine-grained representation (Aimone et al., 2011). Although the hippocampus appears to be important for pattern separation more generally, how this is influenced by information type throughout the brain has not been studied until now.

Regions uniquely involved in spatial pattern separation compared to temporal pattern separation included the right lingual gyrus, the cuneus, and left hippocampus. A study by Menon, White, Eliez, Glover, & Reiss (2000) examined the role of the lingual gyrus, the parahippocampus, and the hippocampus in spatial information processing. They found the largest spatial information processing effects in the lingual gyrus compared to the parahippocampal gyrus and the hippocampus (although all three were involved in the processing of spatial information). This is consistent with previous findings implicating the right lingual gyrus as a "place area" that is particularly important for coding topographical landmarks (Aguirre, Zarahn, & D'Esposito, 1998). Therefore, activation of the right lingual gyrus at encoding might reflect an attempt to code landmarks in the spatial environment for later retrieval.

The cuneus also showed activation in spatial pattern separation. Studies have found the involvement of the cuneus in tasks requiring spatial memory or attention. For instance, Moscovitch, Kapur, Kohler, and Houle (1995) found bilateral cuneus activation in a spatial location memory task contrasted with a baseline perceptual task. A recent study found that spatial learning modulated by individual fitness level is related to activation in the cuneus

(Holzchneider, Wolbers, Roder, & Hotting, 2012). Others suggest the cuneus may have a role in shifting attentional resources based on spatial information (Simpson et al., 2011). Our findings are in line with literature documenting a role for the cuneus in the encoding of spatial information.

In this analysis comparing spatial versus temporal pattern separation we identified the left hippocampus as being important for spatial pattern separation at encoding. This finding is consistent with Ekstrom and Bookheimer's (2007) results, where the left hippocampus was more active for a spatial task than a temporal task, whereas there was no difference in the right hippocampus for the two conditions. Importantly however, Ekstrom and Bookheimer did find bilateral hippocampal activations in both tasks. Traditionally, the right hippocampus has been deemed important for spatial memory and the left hippocampus for verbal or temporal memory (Burgess et al., 2002; Igloi, Doeller, Berthoz, Rondi-Reig, & Burgess, 2010), but there have been suggestions that both the left and right hippocampus play complementary roles in the encoding of spatial information (Maguire et al., 1996; Maguire et al., 1998). The differing roles of the left and right hippocampus in spatial information processing will be discussed in more detail in a later section when I consider the findings from the nonrotated task analysis in PLS below.

When regions more active for temporal pattern separation compared to spatial pattern separation were examined, a number of regions throughout the brain including the left fusiform gyrus, the left insula, bilateral cingulate gyrus, and right middle occipital gyrus were active. Interestingly, activation of the left fusiform gyrus as a region that was unique to temporal versus spatial encoding is paralleled by findings from a study by Nyberg et al. (1996), where the encoding of time information compared to location information was found to involve a region in the left fusiform gyrus. Other than the Nyberg et al. (1996) study, clear parallels are not evident

in other work, as the left fusiform gyrus has been noted in the literature primarily for its role in word recognition and reading (McCandliss, Cohen, & Dehaene, 2003). Paradoxically, Daselaar, Prince, and Cabeza (2004) found that activation of the left insula was associated at encoding with items that were later forgotten. The current analysis considered only subsequently correct items, so the activation of the left insula is inconsistent with the findings of Daselaar et al. (2004). The findings from our study with those of Daselaar et al. (2004) suggest the insula may have a more general role in encoding that might not necessarily be related to encoding success. Bilateral cingulate gyrus activity was also present in our study. The cingulate gyrus may have a role in temporal memory, although it may have to do with violations in repeating sequence patterns in particular (Huettel, Mack, & McCarthy, 2002). The paracentral lobule showed activation on the right side, and this may be related to the heightened attentional demands of this task (Mayer, Roebroeck, Maurer, & Linden, 2010). The right middle occipital area was activated during this task, and this is consistent with its role in the encoding of pictures (Vaidya, Zhao, Desmond, & Gabrieli, 2002).

Contrary to expectations, activation of the orbitofrontal cortex region of the prefrontal cortex was not observed, as it was in previous studies examining temporal versus spatial memory in both patients with orbitofrontal lesions (Duarte et al., 2010) as well as using neuroimaging techniques in healthy young participants (Duarte et al., 2010; Fujii et al., 2004). Likewise, I failed to find any medial temporal lobe involvement uniquely associated with temporal pattern separation compared to spatial pattern separation. As noted previously, the hippocampus appears to play a role in the encoding of temporal information (Tubridy & Davachi, 2010).

This analysis examined the neural regions uniquely involved in spatial and temporal pattern separation. In particular, the regions supporting successful encoding of later-remembered

spatial and temporal information was investigated. Although the spatial pattern separation task found regions activated that were consistent with the spatial memory encoding literature, this was not the case for temporal pattern separation with respect to the temporal memory encoding literature. While a cluster of the hippocampus was uniquely involved in spatial encoding success, this was not the case for temporal encoding success. Notably, studies examining temporal memory encoding are relatively sparse (Jenkins & Ranganath, 2010), and the neural correlates of these tasks have not been as thoroughly investigated as they have for spatial memory encoding. The bulk of studies directly contrasting spatial and temporal memory have primarily examined neural activations at the retrieval stage. Accordingly, this analysis provides insight into the unique neural correlates supporting the successful encoding of each of spatial and temporal information.

Experiment 2: PLS Mean-Centered Analysis

As noted, PLS is a multivariate analysis technique that identifies patterns of neural activity differing across experimental conditions and time. This method allows for an examination of correlated activity across a network of regions involved in spatial and temporal pattern separation at encoding and retrieval. Moreover, because this technique has heightened sensitivity compared to univariate methods such as GLM methods using SPM, it may yield regions of activation that are unidentified by standard univariate analyses (McIntosh et al., 2004). Notably, when I discuss "activation" here it is in regards to correlated activity within a network rather than a single region per se. In this respect, the use of this term differs from when it is used in reference to a GLM analysis employing a subtraction method. Therefore it is important to note that many of the studies reviewed in this work have employed GLM methods in their analyses.

For each of spatial pattern separation and temporal pattern separation tasks, this analysis yielded a pattern of activation that distinguished encoding conditions from the baseline letter task and retrieval conditions. The spatial pattern separation mean centered analysis found a network of regions that differentiated the letter/retrieval conditions from the encoding conditions, including the frontal pole (BA 10), middle frontal gyrus (BA 6), parahippocampal gyrus (BA 34), hippocampus, as well as superior, middle and inferior temporal gyri (BA 21/22/37/18). Both the left and right frontal poles were active for encoding and letter/retrieval but at different lags, suggesting the two hemispheres are involved at different points in time to facilitate encoding and retrieval in spatial pattern separation. The right parahippocampus was also involved in both retrieval and encoding, but again at different lags, indicating that at earlier timepoints over the course of the trial it may support encoding, whereas later on it may support retrieval (or be involved in the baseline letter task). Hippocampal involvement, as expected, was also observed, and appeared to be important at both the encoding and letter/retrieval phases. A region in the left anterior hippocampus was associated with encoding. A region in the right anterior hippocampus was associated with letter/retrieval early on in the trial.

The temporal pattern separation task identified a network differentiating encoding from letter/retrieval. In this case, activity was apparent in the frontal pole (BA 10), the precentral gyrus (BA 4), the inferior frontal gyrus (BA 47), the parahippocampal gyrus (BA 19), the hippocampus, and the cingulate gyrus. Although the frontal pole was also involved in the spatial pattern separation task, the right frontal pole was involved for letter/retrieval and only towards the end of the trial, suggesting the frontal pole may be involved in spatial and temporal memory, but at different stages of memory processing. In contrast to the involvement of the right parahippocampus in the spatial pattern separation task at encoding and retrieval, the temporal

pattern separation task involved only the left parahippocampus and only at retrieval, suggesting possible laterality differences in the parahippocampus for spatial versus temporal information. Like the parahippocampus, the hippocampus also showed activity only on the left side for temporal pattern separation retrieval.

While the regions involved are consistent with prior studies, an obvious drawback of this analysis is that the letter baseline task is combined with the retrieval task. To isolate the regions active in retrieval, I ran a non-rotated task analysis. This allowed me to directly compare encoding to retrieval excluding the baseline letter task.

Experiment 2: Non-Rotated Task Analysis

A Non-Rotated Task Analysis was conducted to examine whether heavier engagement of pattern separation processes might engage qualitatively distinct neural networks that recruit additional regions. This hypothesis was not supported; there was no differing pattern of neural activation for conditions requiring more pattern separation compared to conditions requiring less. This finding was consistent across both tasks as well as across both encoding and retrieval conditions.

The neural networks involved in the encoding versus retrieval in pattern separation are still unknown. Furthermore, whether these differ based on the type of information processed (i.e., spatial versus temporal) has not been studied. To examine whether the areas involved at encoding and retrieval in spatial and temporal pattern separation are different from those identified in the spatial and temporal context memory literature, I ran a non-rotated task analysis that allowed me to contrast encoding and retrieval in spatial and temporal pattern separation. For both spatial pattern separation and temporal pattern separation, a unique network was identified that differentiated between encoding and retrieval. For the sake of clarity, I will discuss the

regions involved in spatial encoding, spatial retrieval, temporal encoding, and temporal retrieval in separate subsections.

Spatial pattern separation encoding. The spatial pattern separation task at encoding activated a number of regions throughout the brain. These included bilateral parahippocampal gyri, frontal pole (BA 10), and other parts of the bilateral prefrontal cortex (BA 8/9/46/47), bilateral anterior hippocampi, bilateral caudate, and bilateral precuneus (BA 7/39). Importantly, the regions involved in pattern separation encoding are similar to those in the literature involved in the encoding of spatial information in general.

Hippocampal activation was bilateral, and traditional views of hippocampal function in spatial memory posit the importance of the right side. Generally the left hippocampus has been attributed to verbal or temporal memory (Burgess et al., 2002; Igloi, Doeller, Berthoz, Rondi-Reig, & Burgess, 2010), and the right hippocampus to spatial memory (Burgess et al., 2002; Bohbot et al., 1998; Crane & Milner, 2005; Igloi et al., 2010; Kessels et al., 2001; Maguire et al., 2003; Piekema et al., 2006; Smith & Milner, 1981; 1989). However, others have suggested that while spatial memory is highly lateralized to the right hippocampus, the left also plays a role (Maguire et al., 1996; Maguire et al., 1998; Stepankova, Fenton, Pastalkova, Kalina, & Bohbot, 2004). Other studies have found evidence for bilateral medial temporal lobe involvement in spatial tasks (Aguirre, Detre, Alsop, & D'Esposito, 1996; Maguire et al., 1996). For instance, Maguire et al. (1996) found that both right and left medial temporal lobe lesioned patients exhibited topographical disorientation that was equivalent to one another and greater than in a normal control group. The right hippocampus may be particularly important for an allocentric spatial representation that aids in directing one to a particular location from a starting location. The role of the left hippocampus in spatial memory may have to do with the active maintenance

of a memory trace of a certain location or destination. Alternatively, the left hippocampus may be involved in the recollection of paths previously taken when learning how to get to a goal location, even if this was not a direct path (Maguire et al., 1998). Therefore the two hippocampi may have complementary functions that optimize the encoding of spatial information.

Parahippocampal gyrus activation in this study was observed bilaterally. Similar to the hippocampus, right parahippocampal activity is typically associated with spatial information processing. However, given that the parahippocampal gyri provide input to the hippocampus, and that here I observed bilateral hippocampal activation, it is not surprising that bilateral parahippocampal gyri are active. Parahippocampal activation is consistent with previous studies implicating bilateral parahippocampal regions in encoding for later successful retrieval of object-location associations (Sommer et al., 2005a, b), and also with its role in the processing of spatial scenes (Burgess et al., 2002).

Spatial pattern separation retrieval. Spatial pattern separation at retrieval involved a network composed of a number of regions throughout the brain including the right posterior hippocampus, bilateral parahippocampal gyri (BA 36/30/34), bilateral prefrontal cortices (BA 46/47) and bilateral precuneus (BA 7).

Medial temporal lobe activity in this analysis is in line with findings implicating the right medial temporal lobes in spatial context retrieval. Specifically, authors have noted the importance of both the right hippocampus (Hayes et al., 2004; Smith & Milner, 1989) as well as bilateral parahippocampi (Burgess et al., 2001; Ekstrom & Bookheimer, 2007) in the retrieval of spatial information. Still, others have found evidence for only right parahippocampal involvement in spatial context retrieval (Hayes et al., 2004). An interesting finding was the relatively posterior activation of the hippocampus during retrieval compared to the anterior

bilateral hippocampal activation involved at encoding, and this will be discussed in greater detail below.

Regions activated outside the medial temporal lobe were also consistent with those from the literature. The present study identified regions in the prefrontal cortex that were active, and studies have implicated the prefrontal cortices in spatial memory retrieval (McCarthy et al., 1994; Rajah, Languay et al., 2010). In addition the precuneus has been noted for its involvement in both the encoding as well as the retrieval of a spatial location (Frings et al., 2006), and this is consistent with the present findings of precuneus involvement in spatial pattern separation encoding and retrieval.

Temporal pattern separation encoding. Regions involved in temporal pattern separation encoding included the left and right prefrontal cortices (BA 9/11/47). These areas have been implicated in the encoding of general temporal context information (Jenkins & Ranganath, 2010). Consistent with findings from Duarte et al. (2010) that identified a role for the orbitofrontal cortex in temporal but not spatial context memory encoding, the prefrontal cortex activation in this study included parts of the orbitofrontal cortex (BA 11/47). Contrary to the findings of Jenkins and Ranganath (2010) and Tubridy and Davachi (2010) who found medial temporal lobe involvement in the encoding of temporal information, medial temporal lobe activation was not evident during the encoding phase of temporal pattern separation.

Temporal pattern separation retrieval. While medial temporal lobe activation was not observed in the encoding of temporal information, it did have a role during retrieval along with other regions outside of the medial temporal area. Specifically, the right posterior hippocampus, the right parahippocampal gyrus (BA 19), as well as bilateral prefrontal regions (BA 8/9/10/11/47) were involved in temporal pattern separation retrieval. This is consistent with a

large body of literature pointing to the importance of prefrontal (Cabeza et al., 2000; Ekstrom et al., 2011; Eyler et al., 1996; Konishi et al., 2002; Rajah, Languay, et al., 2010) and medial temporal lobe regions (DeVito & Eichenbaum, 2011; Ekstrom et al., 2011) in temporal context memory retrieval.

Hippocampal Activity in Spatial and Temporal Pattern Separation Encoding versus Retrieval

As emphasized throughout this work, the hippocampus plays a central role in pattern separation processes. This analysis yielded interesting patterns of hippocampal activation for spatial and temporal pattern separation at encoding and retrieval. The spatial pattern separation and temporal pattern separation tasks showed differing hippocampal involvement at encoding, but similar activation at retrieval. Specifically, encoding of spatial information involved bilateral hippocampi, but hippocampus activity was not observed in the encoding of temporal information. Retrieval of both spatial and temporal information involved the right posterior hippocampus. The finding of bilateral hippocampal activation during the spatial task is consistent with other studies that found bilateral medial temporal lobe activations for scenes (see Henson, 2005 for a review). Further, my data are aligned with those from other studies positing a greater overall role for medial temporal lobe regions in spatial memory compared to temporal memory (Ekstrom et al., 2011).

Interesting findings were observed with respect to the anterior-posterior differentiation of the hippocampus between encoding and retrieval. Both the left and right hippocampal clusters activated during spatial encoding were relatively anterior (MNI coordinates: 30, -6, -28 for right cluster, and -32, -12, -26 for left cluster) to the hippocampal cluster activated during spatial retrieval (MNI coordinates: 30, -24, -10). In addition, although the temporal task did not show

hippocampal activation during the encoding phase, the cluster activated during the retrieval phase was relatively posterior (MNI coordinates: -34, -46, 6). These data are in line with the HIPER model (Lepage et al., 1998).

This pattern of activation suggests that anterior hippocampal regions support the encoding of spatial information, and this view is further in line with the notion that spatial memory, and our spatial task in particular, may just be particularly relational hence involving the anterior hippocampus (Eichenbaum & Cohen, 2001; Schacter & Wagner, 1999). The right posterior hippocampus appears to be important in the retrieval of a memory, regardless of information type.

My finding implicating the posterior hippocampus in the retrieval of spatial and temporal information is in contrast to another study that found that anterior hippocampal volume predicted both spatial and temporal context memory retrieval. The authors attributed this to the role of the anterior hippocampus in flexible relational binding, and suggested that spatial and temporal context memory retrieval were associatively demanding (Rajah, Kromas, Han, & Pruessner, 2010). However, our findings fit the framework put forth by Lepage and colleagues (1998) and further suggest differential roles of the anterior hippocampus in encoding based on information type, but a role of the posterior hippocampus in retrieval regardless of information type.

Experiment 2: Seed Analysis

Retrieval for both spatial and temporal pattern separation was associated with activity in the right posterior hippocampus. To examine the extent to which the connectivity of the right posterior hippocampus differed based on information type, I ran a seed analysis in PLS. As expected, these right posterior hippocampal clusters had different patterns of functional connectivity for spatial and temporal pattern separation.

For spatial pattern separation, the right hippocampal seed showed functional connectivity with regions of the cerebellum, the superior parietal lobule, left inferior temporal gyrus, and bilateral middle temporal gyri. The large cluster that included the hippocampal seed encompassed regions of the medial temporal lobe including bilateral entorhinal cortices, CA fields, left dentate gyrus, and bilateral subiculum. Outside the medial temporal lobe, the cluster included the bilateral frontal and occipital areas as well as the insula. The seed voxel was located in the right CA field of the hippocampus.

The right posterior hippocampal seed for temporal pattern separation also showed functional connectivity with other regions throughout the brain. The left parahippocampal gyrus, bilateral medial frontal gyri, and the left inferior frontal gyri were functionally connected to the seed. As with spatial pattern separation, there was a large cluster that extended bilaterally that included the seed region. Areas within this cluster in the medial temporal lobe included the bilateral CA fields, bilateral dentate gyrus, bilateral subiculum, bilateral entorhinal cortices, and bilateral amygdala. Regions outside the medial temporal lobe that were part of this large cluster included bilateral frontal regions, bilateral occipital regions, and the insula. As in spatial pattern separation, the seed voxel was located in the right CA field of the hippocampus.

This analysis yielded some interesting differences and similarities between the spatial and temporal pattern separation tasks. Interestingly, although regions outside of hippocampus functionally connected to the right hippocampal seeds were quite different for spatial and temporal pattern separation, the regions activated within the hippocampus were similar with some notable differences.

First, for both spatial and temporal pattern separation, similar regions within the hippocampi were active, but these differed in laterality. Both right hippocampal seeds involved

in spatial and temporal pattern separation retrieval were found in the CA subfields. Bilateral CA field and subiculum were active for both tasks, but the temporal task also showed bilateral dentate gyri activity and the spatial task showed only left dentate gyrus activity. As discussed in a previous section, the activation of this structure along with the right CA field is consistent with computational models (Becker, 2005; Leutgeb et al., 2007; Rolls, 1996; Treves & Rolls, 1994) and rodent studies (Goodrich-Hunsaker et al., 2008) implicating the dentate gyrus in pattern separation. In addition, the fact that the dentate gyrus projects to the CA3 to engage pattern separation processes (Leutgeb et al., 2007) and that in some circumstances CA3 may be performing pattern separation (Lee et al., 2004; Leutgeb et al., 2007; Vazdarjnova & Guzowski, 2004; Yassa & Stark, 2011), it is not surprising that in this analysis both the CA fields (Anatomy Toolbox does not distinguish between CA fields) and dentate gyrus are active. The differences in dentate gyrus activity between spatial and temporal tasks are unexpected and interesting. To my knowledge, there are no studies examining laterality differences in the dentate gyrus and memory in humans. It is possible, and my findings suggest, that based on the type of information input the different hemispheres of the dentate gyrus are engaged differently in pattern separation processing. This is an interesting question for future study and warrants further research. Bilateral activation of the subiculum was evident as well. Activity in the subiculum has been associated with the retrieval of spatial information (O'Mara, Sanchez-Vives, Brotons-Mas, & O'Hare, 2009; Suthana et al., 2009), and it is possible that this region may also have a more general role in episodic recollection (Viskontas, Carr, Engel, & Knowlton, 2009) and memory (O'Mara et al., 2009).

Second, outside of the hippocampus, while some regions were similarly active for both spatial and temporal tasks, such as bilateral frontal and occipital areas, the temporal task

recruited additional regions. For instance, the hippocampal seed associated with the temporal task recruited extra-hippocampal regions including the left parahippocampus, left prefrontal cortex, bilateral entorhinal cortices, and bilateral amygdala, regions that did not show peak activations in spatial pattern separation. The finding of prefrontal cortex involvement in temporal pattern separation is in line with a large body of literature emphasizing the importance of the prefrontal cortex in temporal order or recency judgments (Cabeza et al., 2000; DeVito & Eichenbaum, 2011; Ekstrom et al., 2011; Eyler Zorrilla et al., 1996; Hayes et al., 2004; Konishi et al., 2002; McAndrews & Milner, 1991; Milner et al., 1991). The finding of left parahippocampal activation for temporal pattern separation retrieval was not expected, given that the parahippocampus has generally been associated with the retrieval of spatial information rather than temporal information (Ekstrom et al., 2011; Ekstrom & Bookheimer, 2007). However, the parahippocampus has been implicated in the encoding of temporal information (Jenkins & Ranganath, 2010; Tubridy & Davachi, 2010). It is possible that these differences in extra-hippocampal connectivity are supporting the retrieval of different types of pattern separated information.

Overall, the findings from the nonrotated task and subsequent seed analyses suggest that the right posterior hippocampus may be involved in pattern separation retrieval regardless of information type. This finding is in line with a theory proposed by Lepage and colleagues (1998) suggesting a rostrocaudal gradient within the hippocampus for the encoding and retrieval of information. Interestingly, the present study found that functional connectivity with extra-hippocampal structures differed for spatial and temporal pattern separation, suggesting that while pattern separation retrieval generally involves the hippocampus, the regions functionally

connected to the hippocampus as well as activation in hippocampal subregions during pattern separation differ when different types of information are being retrieved.

Chapter 6: General Discussion and Conclusions

This body of work had two main goals: to develop spatial and temporal pattern separation tasks that are behaviourally influenced by separation manipulations, and to uncover the whole-brain activity and neural networks involved in pattern separation and whether this is influenced by information type (i.e., spatial versus temporal). To this extent, the objectives were met.

Both behavioural and neuroimaging methodologies were utilized in this effort to gain a more complete picture of pattern separation in the brain. Behavioural results revealed separation manipulations do influence how well and how fast people perform for both spatial and temporal information processing. Moreover, the neuroimaging analyses shed light on the neural underpinnings of spatial and temporal pattern separation.

Univariate analyses were used to directly compare spatial and temporal pattern separation at encoding for subsequently retrieved memories. The left hippocampus was uniquely involved in spatial pattern separation, and although spatial processing is typically related to the right hippocampus, the left also plays a role and may be contributing to the successful encoding of spatial information here. This is also in line with another study that found left hippocampal involvement when directly comparing activation between a spatial and temporal memory task (Ekstrom & Bookheimer, 2007). Other regions specific to the encoding of spatial and not temporal information included the lingual gyrus and the cuneus, both of which are involved in spatial information processing. Although the analysis of regions unique to temporal pattern separation encoding did not identify the hippocampus, there were a number of regions including the insula and cingulate gyrus that may have unique roles in temporal pattern separation, and warrant further study.

Multivariate analyses were used to assess the neural networks involved in spatial and temporal pattern separation, as well as the functional connectivity of the hippocampus with the rest of the brain during the engagement of these processes. These analyses identified unique neural networks characterizing encoding versus retrieval in both spatial and temporal pattern separation, suggesting distinct networks support encoding and retrieval of spatial and temporal information.

The neural network supporting spatial pattern separation encoding included bilateral parahippocampi, bilateral hippocampi, precuneus, and bilateral prefrontal cortices. The neural network at retrieval included some of the same regions, including bilateral parahippocampi, bilateral prefrontal cortices, and precuneus. However, only the right posterior hippocampus was activated during the retrieval of spatial information, suggesting the bilateral hippocampi might be important for spatial encoding, but only the right hippocampus is involved in the retrieval of a spatial memory.

Unique neural networks for encoding versus retrieval in temporal pattern separation were also identified. At encoding, bilateral prefrontal cortices were active, consistent with the literature identifying the importance of these structures in the encoding of temporal information (Duarte et al., 2010; Jenkins & Ranganath, 2010). These regions were also involved in the retrieval of temporal information. Although regions in the medial temporal lobe were not involved during the encoding phase, the right posterior hippocampus and right parahippocampus were associated with the retrieval of temporal information. This suggests that other extra-hippocampal regions are sufficient to support the encoding of temporal sequence information, but the retrieval of temporal sequence information involves the hippocampus.

An interesting finding was the relative location of the hippocampal clusters involved in encoding and retrieval. The spatial pattern separation task at encoding involved anterior hippocampal regions and at retrieval involved the posterior hippocampus. The temporal pattern separation task did not involve the hippocampus at encoding, but required the posterior hippocampus at retrieval. This finding is partially consistent with an influential model initially proposed by Lepage et al. (1998) suggesting anterior hippocampal regions may be preferentially involved in the encoding of information, while posterior hippocampal regions may be involved at retrieval. However, in the present findings hippocampal activation was not associated with temporal encoding. This suggests other extra-hippocampal regions may be sufficient to support the encoding of some types of information.

Because a similar region in the right posterior hippocampus was involved in the retrieval of both spatial and temporal information, the functional connectivity of these respective regions with the rest of the brain was examined to assess how the hippocampus may interact differently with other regions to support the retrieval of spatial versus temporal information. Functional connectivity with the hippocampal seed in the spatial task included temporal and superior parietal regions. The large cluster containing the hippocampal seed included left dentate gyrus and bilateral subiculum, and extended to frontal regions (although there were no independent activations in the frontal regions). The hippocampal seed in the temporal task was functionally connected largely to frontal regions, as well as the left parahippocampus, and regions within the hippocampus showed less laterality than in the spatial task, with bilateral dentate gyrus activation. These findings suggest a similar pattern of activation within the hippocampus, with some laterality differences but considerable differences in extra-hippocampal functional connectivity. Therefore while hippocampal structures may be processing spatial and temporal

information similarly, extra hippocampal structures may be differentially involved depending on information type.

The neuroimaging portion of this work aimed to assess whole-brain patterns of activation during the engagement of spatial and temporal pattern separation processes. First, I examined the neural regions uniquely involved in the successful encoding each of spatial and temporal information. Then, neural networks involved in these processes were assessed, and findings of anterior versus posterior hippocampal differences in spatial and temporal encoding and retrieval were found to be in line with a model proposed by Lepage et al (1998). Both spatial and temporal retrieval similarly involved the right posterior hippocampus, and the functional connectivity of this region was assessed to see how extra-hippocampal structures may be supporting differences in information type. Extra-hippocampal structures functionally connected to the hippocampus included predominantly temporal lobe regions for spatial information, and frontal regions for temporal information. Although care was taken to remove potential experimental confounds, some limitations to this work should be addressed.

Limitations and Future Directions

One possible limitation of this set of studies is the differences in task structure between tasks, which may explain differences in neural activation and performance. Although the retrieval phase of both our spatial and temporal tasks have similar demands, such that a forced-choice decision is required between two shapes, the demands during encoding are different. Specifically, during spatial encoding, participants are presented with a *single* location to remember. During temporal encoding, participants are presented with a *sequence* of shapes.

Rajah et al. (2011) equated task demands and performance in spatial and temporal context memory tasks. Generally, the left prefrontal cortex is associated with spatial context

retrieval, whereas the right prefrontal cortex is associated with temporal context retrieval (Rajah et al., 2010), but the authors questioned whether these task differences would exist if task structure and difficulty were equated. Participants encoded three faces for each of three separate time blocks. After a delay, they were shown three faces previously presented and asked to indicate either the face that was initially presented in a certain location (spatial easy condition), or to order the three shapes either "from left to right" or "from right to left (spatial difficult condition)." In the temporal conditions, participants were asked to either select the face presented during a certain block (temporal easy condition), or to order the faces "from most to least recent" or from "least to most recent (temporal difficult condition)." In this way, a similar categorical-based task structure was used for both tasks. Participants reported using the same strategies for both tasks, and performance was equal between spatial easy and temporal easy, as well as spatial difficult and temporal difficult conditions. Contrary to previous findings, prefrontal cortex activity was similar for spatial and temporal context memory when structure and performance were equated (Rajah et al., 2011).

These results by Rajah et al. (2011) suggest that neural differences observed between my spatial and temporal tasks may be due to different demands and difficulty levels, especially since there were overall performance differences between tasks with temporal tasks showing worse performance than spatial. In particular, the greater difficulty level in TPS compared to SPS in the current study (as evidenced by overall higher reaction time in TPS), may have resulted in the more extensive activation noted in the TPS task. It also may have influenced the increased activation of frontal regions compared to the SPS task due to more effortful cognition. In the future, equating difficulty and task structure between spatial and temporal tasks would be beneficial in reducing potential experimental confounds.

A potentially important issue that requires addressing is whether the present tasks tap into episodic memory or whether they primarily reflect short-term working memory. It is possible that the short delay between our sample and choice phase may not engage what is termed long-term episodic memory in a strict sense. Numerous studies suggest shorter-term memory involves the hippocampus as well (Carr, Viskontas, Engel, & Knowlton, 2010; Kesner & Hopkins, 2001; Piekema, Kessels, Mars, Petersson, & Fernandez, 2006). Controls and hypoxic patients with bilateral hippocampal pathology were tested on short-term memory for an item, spatial item distance, or temporal duration. Hypoxic participants were impaired in short-term memory for duration and spatial distance information but showed less impairment for visual item information (Kesner & Hopkins, 2001). The right hippocampus, in particular, may be important for the maintenance of object-location associations over a short duration, consistent with its function over a longer duration (Piekema et al., 2006).

In fact, different portions of the medial temporal lobe may support memory over different durations. Carr et al. (2010) examined the contribution of different medial temporal lobe structures at encoding for subsequently remembered items at a short delay (10 minutes) and longer delay (one week). Items recalled across both shorter and longer delays involved a hippocampal subfield that included the dentate gyrus and CA3 fields as well as the perirhinal cortex. In contrast, the parahippocampal cortex was preferentially involved in the encoding of items successfully recollected after 10 minutes. This suggests the hippocampus is involved in memory with shorter and longer delays, while the parahippocampus has a role in memory for shorter delays.

Both theoretical and logistical factors influenced my choice of shorter delays between encoding and retrieval. A theoretical factor was the preponderance of rodent studies examining

spatial and temporal pattern separation that had shown a clear role of the hippocampus (see Kesner & Hopkins, 2006 for a review). My aim was to create tasks that followed an analogous format for use in humans in order to tap into these same processes (see Paleja et al., 2011). Logistically, scanner time restrictions limited my delay period, especially given that we wanted to have an adequate amount of data for two manipulations within each of two tasks. While some research indicates the hippocampus may similarly be involved for shorter- and longer- term memories, a large body of literature has supported the notion that short-term and long-term memory are separable cognitive processes (Buchsbaum, Padmanabhan, & Berman, 2010). An interesting direction for further study may be how performance and neural activity in spatial and temporal pattern separation changes as a result of shorter versus longer delays between study and test, and whether this influences one information type more than another.

Although our tasks showed behaviour separation effects, neural differences for NEAR and FAR conditions were not apparent in our imaging contrasts. A main effect of separation overall collapsed across tasks was observed, but within each task this effect did not hold. It is possible that due to the lack of statistical power associated with the low number of trials in the PLS analysis, I did not observe significant differences between my separation conditions. A separation effect with imaging data is critical to claiming that a given region's activation is separation-related, and future studies should include a large number of trials for each separation condition in order to avoid possible Type II errors. Indeed this limitation is not trivial, and it is difficult to make a case for pattern separation processes occurring when there is no corresponding neural sensitivity to separation manipulations.

The present examination of neural networks in spatial and temporal pattern separation could be extended to study older adult populations. For instance, pattern separation declines have

been documented in the aging literature (Stark, Yassa, & Stark, 2010; Toner, Pirogovsky, Kirwan, & Gilbert, 2009; Wilson et al., 2006; Yassa, Lacy, et al., 2010; Yassa, Stark, et al., 2010), but thus far the effect of information type has not been addressed. Older adults may demonstrate difficulty with the encoding or maintenance of fine-grained representations of one type of information more than another. This difficulty may cause more pronounced deficits in adequate separation of one type of stimuli more than another and this difficulty in lower level processing may in turn account for more global memory changes in older adults. The dysfunction of the hippocampus' connection to the prefrontal cortex in aging has been well-established. Given that the present study has identified a prominent role for frontal regions that are functionally connected to the hippocampus in temporal pattern separation, it is possible older adults demonstrate lessened temporal pattern separation abilities related to alterations in hippocampus-prefrontal connectivity. There is already evidence to suggest spatial and temporal context retrieval may each involve different portions of the prefrontal cortex in older adults (Rajah, Languay, Valiquette, 2010), and therefore we might expect that neural differences may also be observed in older adults during the pattern separation of spatial and temporal information.

Concluding Remarks

The present findings confirm and extend results from previous literature suggesting a critical role of the hippocampus in pattern separation. Here I clearly demonstrate hippocampal involvement in pattern separation for both spatial and temporal pattern separation. Importantly however, hippocampal involvement may vary based on the stage of memory processing (i.e., encoding or retrieval) for each of spatial and temporal pattern separation. Furthermore the hippocampus may display differing patterns of functional connectivity with extra-hippocampal

structures based on information type. In other words, I provide evidence that the hippocampus is not uniformly involved throughout the stages of spatial and temporal pattern separation memory processing and that regions functionally connected to the hippocampus display differing patterns of activity based on whether spatial or temporal memory processing is taking place.

These findings set the stage for valuable future directions. Further research may examine these processes when task structure and function are equated to account for potential confounds. Also future studies may apply longer durations between study and test to ensure long-term episodic memory is being "tapped into" rather than short-term, or working memory. Another interesting direction would be the examination of these processes as a function of aging. Given that pattern separation may show a decline with older age, and that hippocampal-prefrontal connectivity is involved in temporal pattern separation in the present study, the adequate separation of temporal information may be particularly affected.

Appendix I: Telephone Screen (Experiment 1)

TELEPHONE Interview

Date: _____ Interviewer: _____

The purpose of this study is to develop computerized tasks that will measure different types of memory thought to be related to different brain systems. Performance on these tasks will help us to fine-tune these tasks for future studies aimed at understanding what parts of the brain might be affected in clinical disorders like Schizophrenia. Participation will require answering some questions concerning lifestyle and health and experimental tasks. The risks involved in participating in this study are small. At times you may become "mentally fatigued" or feel frustrated or a little disappointed with your performance. However, whenever possible, you will be provided with rests. It is also noted that the difficultly level of some tasks are designed such that most people will make errors on the more difficult items. In addition, the personal nature of the questions during the interview or questionnaires may bring to mind unpleasant memories. If you feel uncomfortable, you have the right to discontinue participation, either temporarily or permanently, at any time. Total study duration is expected to be 1 hr. You will receive 1% course credit for your participation. The results of this study are expected to lay groundwork for research that may benefit patients with forms of mental illness in the future.

That is, you have the right to refrain from answering any questions or participating in any aspects of the study, at any time. Are you interested in participating in the study that I described? (if yes) Great! I have a few more questions to ask you right now. (if not, politely offer them a 'walk through' of the methods, briefly show the tasks)

Your answers will be kept under lock and key, and separately from your identifying information. Right now, I am asking for your *verbal consent* to take part in this brief interview. If you are eligible for the study, then written informed consent will be sought before participation in the next stage of the study. If, for whatever reason, you do not fit the eligible profile we are seeking for this study, then your responses to the following questions will be destroyed. However, in order to track reasons for exclusion, a coded list (with only ID codes and abstract codes representing reasons) will be kept securely and separately from any identifying information. Moreover, your information will not be disclosed.

DO YOU WISH TO CONTINUE? Y / N

What is your full name? _____

How old are you? _____ Date of Birth: _____

Gender: **F** **M**

The remaining questions will be stored securely and separately from your identifying information and only linked through an arbitrary code #.

Now I'd like to ask you some questions about your background (i.e., medical, academic history):

[If do not meet criteria listed below, STOP interview. Where unsure, ask for more details. Important NOT to indicate explicitly the reasons that they do not qualify. Just that they don't meet the right profile – then can offer the walk-through option. They get a credit either way.]

1. Do you speak English fluently?

_____

2. Do you have normal or corrected-to-normal vision? Y / N

3. Are you colourblind? Y / N
[**of relevance to seeing the cues and target; some forms of CB may not interfere with this, so we could proceed and see from the practice trials etc. – or if they are later seen as an outlier this may be a reason; i.e., perhaps a 'flag', but not outright reason to exclude]**

4. Have you ever been diagnosed with a learning disability? Y / N

5. Have you ever lost consciousness (passed out or blacked out) for more than one hour? Y / N
If yes: How long did it last? _____

6. Have you ever been diagnosed with a neurological condition (e.g., seizures, traumatic brain injury, dementia, etc.)? Y / N

7. Are you currently taking any medications to treat/help with mental health issues (e.g., antidepressants, anti-anxiety medications, etc.)? Y / N

8. Have you ever been diagnosed with a mental health disorder? Y / N
[Must NOT have previous diagnosis of any kind.]

9. Has anyone in your immediate family ever been diagnosed by a professional as having schizophrenia or a schizophrenia-spectrum disorder? Y / N
[Must not have first-degree relative with a schizophrenia-spectrum disorder]

10. How many drinks containing alcohol have you had in the last 4 weeks?

11. Have you used street or party drugs like marijuana, cocaine, heroine, Ecstacy, Special K, or any others in the last 4 weeks? Y / N

12. Have you ever participated in another research study? Y / N
If yes: What study and where/ with whom? _____

Appendix II: Preprocessing in SPM

Getting started

Opening SPM

- Open matlab
- In the matlab command window (at the >> prompt), open SPM
  >>spm fmri
- On Menu window, click the drop-down menu "Utils" and click "CD." Select the directory you will be obtaining your imaging files from (e.g., Whole brain data) or your specific subject folder (e.g., Whole brain data\Subject 101).

DICOM Import

This step converts your raw scanner DICOM files (.dcm) to SPM-friendly ANALYZE format (.img and *.hdr).*

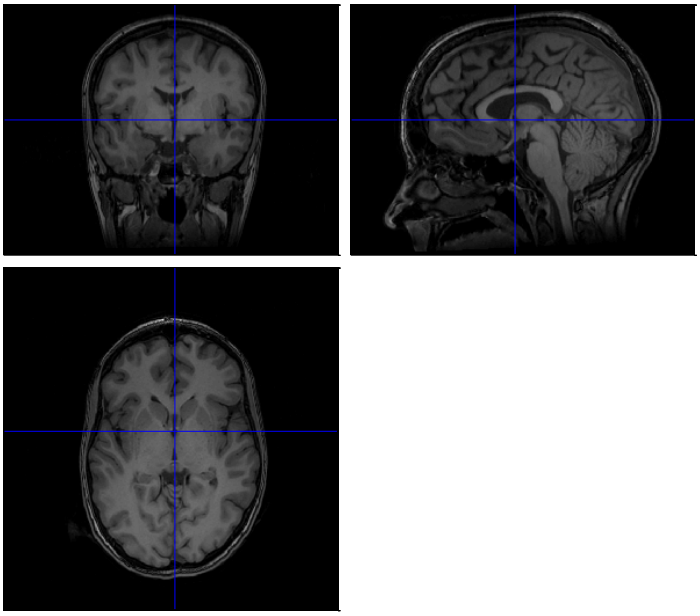
- Click on **DICOM import**
- This opens the spm_get window (where you select your files)
- Select all dcm images (on the right hand section of the window) by either:
  - right clicking in the box listing the files, and choosing "select all"
  - holding shift key and click the last image to select all images
- Selected images should appear in the lower section of this window; click Done
- Choose where you want your files to be saved, i.e., the "Output Directory". Select the main subject folder
- The red bar should appear …..
- You need to make a directory for each sequence in Windows Explorer: AX 3D Obl to HC, SPS1, SPS2,…etc.
- Then move the relevant files to the folder. You should have a series_INFO text file in your DICOM folder that will tell you the series number for each sequence.

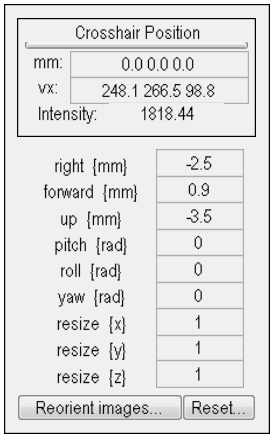
Display, Reorient, Check Reg

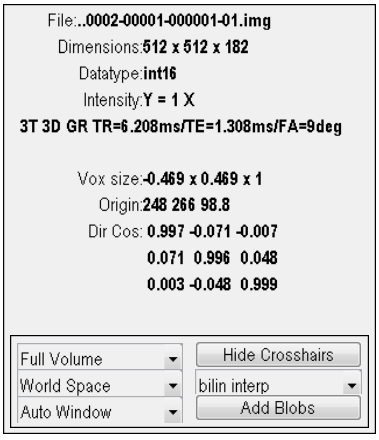
This step is to check that your data are oriented correctly and that your AC is at crosshair position 0 0 0 for all images before you begin pre-processing.

- Click **DISPLAY**
- Select a structural scan, by going to the anatomical directory (AX3D) and selecting your high-resolution anatomical image.
- It should be oriented in the following ways:
  - Sagittal: Frontal cortex should be on the left
  - Axial: Frontal cortex should be on the top
  - Coronal: Occipital cortex is facing you
- Functional scans should be similarly oriented

- Click on the AC (anterior commissure) so the crosshairs are over it. The horizontal line should go through the PC.
- Look at the “mm” field under Crosshair Position
- Multiply each of the coordinates by -1 and enter the first number into the “right” field, and the second number into the “forward” field, and the third into the “up” field
- You can also adjust pitch, roll, and yaw to make sure the brain is oriented properly in all three views.
- To apply these rotations, click **Reorient Images** (bottom left); select structural (AX 3D Obl to HC directory), raw functional scans (from the **task** directories- SPS1/2, TPS1/2), B0 scans (B0_map05, B0_map08), and T2/PD scans (Axial Dual Echo) to apply these translations; select all files then click **Done.**
- **Check Reg**: Check that the functional, B0, and T2/PD scans line up with the anatomical.



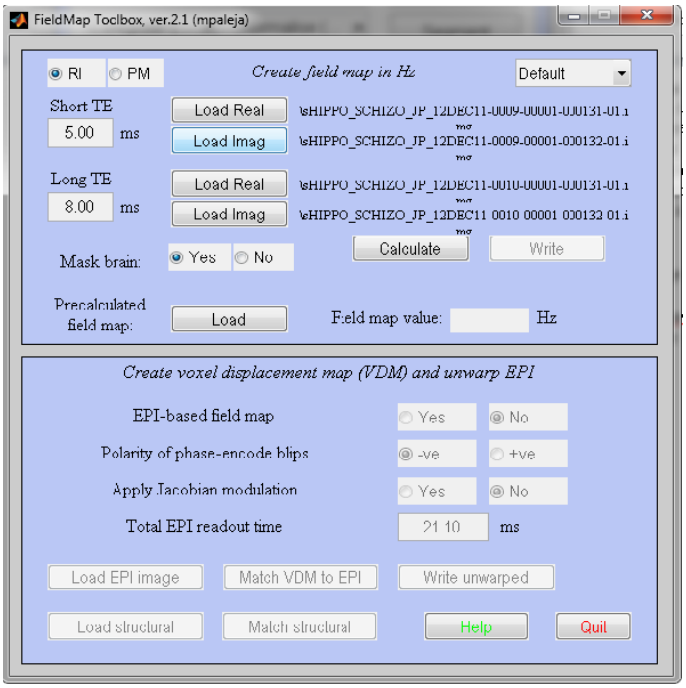




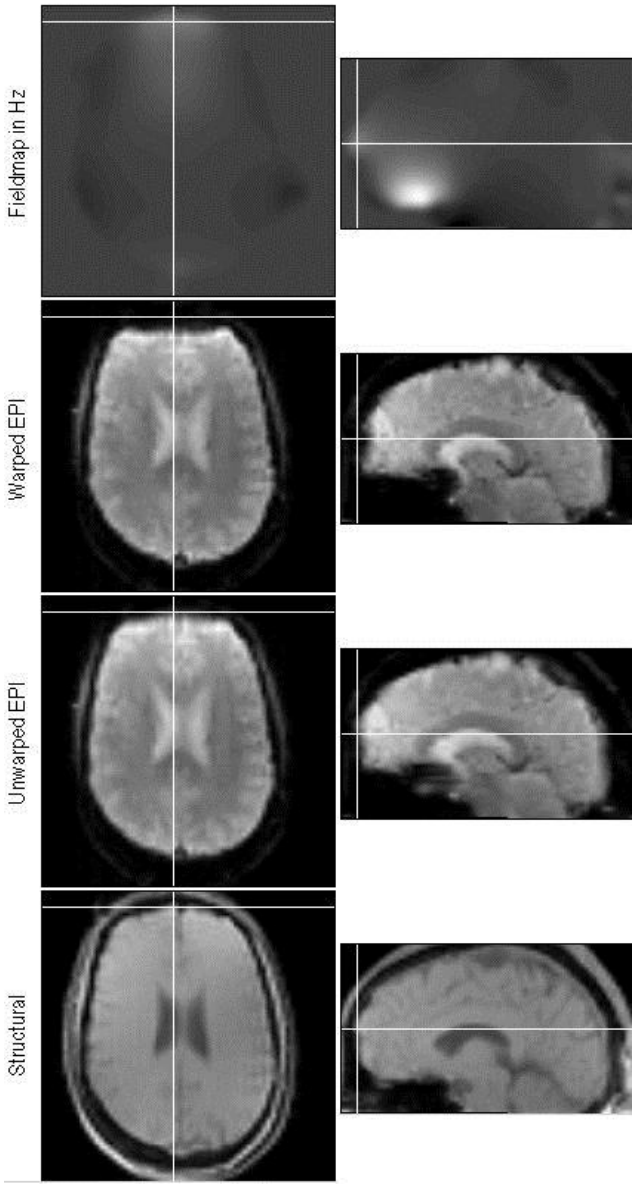
Field Map Generation

There is normally signal dropout associated with magnetic field inhomogeneity in EPI images. This is particularly problematic in regions such as the medial temporal lobe (esp hippocampus), frontal pole, and orbito-frontal cortex. Homogeneity errors result in both signal loss and spatial distortion. Unwarping techniques help reduce spatial distortion, but they cannot correct for signal loss. This step is highly recommended and should be used as a standard part of the preprocessing pipeline, particularly if the susceptible regions mentioned are of interest.

- Choose **Toolbox→Fieldmap** from SPM's menu window.
- On the top left "**RI**" should be selected (for **R**eal and **I**maginary).
- Make sure to set your '**Short TE**' and '**Long TE**' to the correct values (5.00 and 8.00 for this study).
- Press '**Load Real**' and choose your real image for your shorter TE from the B0_map5 folder. The images in the folder should be in the order Phase, Magnitude, Real, Imaginary, so you would select the third image.
- You will be asked if you want to have this scaled to radians – select Yes. A new version of the fieldmap (with prefix s) will be created that has an intensity range of –pi…+pi.
- Press '**Load Imaginary**' and select one of your imaginary images (should be fourth image in folder).
- Load Real and Imaginary images for the long TE the same way.
- Check "yes" for "**Mask brain**."
- Press '**Calculate**' – after a couple minutes a fieldmap is displayed. You can interactively click on the display and the amount of inhomogeneity for that voxel will appear in the 'Field map value
- Hz' field. Several new image files are created, including a voxel displacement image (.vdm).



- Press '**Load EPI image**' and select your functional data, and make sure the **Total EPI readout time** is set correctly. The **total EPI readout time= # phase encode steps*echo spacing**. The number of phase encode steps refers to the matrix size (e.g., if you have a 96x96 matrix, you have 96 echoes). There's a MATLAB script created by Norm Konyer to calculate echo spacing (The value for the whole brain SPS TPS study is 64*0.656= 41.984.
- Press '**Load structural**' and select one of your structural (anatomical) images.
- Press '**Write unwarped**' – a new undistorted image is created (u*.*).
- The image below shows the SPM graphics window at this stage – the 'Unwarped EPI' should have a more similar shape to the 'Structural' then the 'Warped EPI'. If the error is worse, change -ve to +ve.



Preprocessing

Preprocessing job file is saved in the main whole_br directory (preprocess_job). The steps below use the "Dependency" option in SPM8 to create job files. To add each step when creating your own preprocessing job file, go to the SPM tab and select the appropriate steps in the order that you wish to run them. Save the job file.

Slice Timing

Because slices are collected at slightly different times, the slice timing step interpolates the data as if all slices were collected at the same time. This step is particularly important if you have an event-related design and/or your TR is less than 2 seconds.

- Under **Data**, enter all s* functional scans from each session (e.g. SPS1 for the first session, SPS2 for the second, etc.)

- **Number of Slices**: enter the number of slices per TR (I had 40).
- **TR**: enter TR (I had 3).
- **TA**: this is TR-(TR/nslices) (mine was 2.925).
- **Slice order**: enter your slice order. The bottom slice is 1. If you have an ascending sequence you would enter [1:1:nslices]. This means you started at 1 and went up by 1 until you got to the final slice. A descending sequence would be [nslices:-1:1]. An interleaved sequence is the most common and the one used in this study, [1:2:39 2:2:40].
- Slice timed files will have the filename prefix a*.

Realign and Unwarp

This step corrects for head motion that can occur in six different ways (x, y, z, pitch, roll, yaw; Realign), and for motion by magnetic field inhomogeneity distortions (Unwarp). Generally, even when you have multiple runs, you should realign them together in a single session. However, here I have put them in separate sessions for simple entry of my rp files during 1st level analysis. Note that contrary to popular belief it is not necessary to exclude participants who have more than 3mm or 3 degrees of movement within a run. Realign corrects for up 10mm of motion as long as it is slow movement across runs and not sudden.

- Click **Data** and from the **Current Item** menu, click "**New: Session**" until you have 4 sessions (or however many functional runs you have in your study). In my case, this was 4 sessions (SPS1, SPS2, TPS1, TPS2).
- Under **Data→Session→Images**, include your session 1 slice-timed images by clicking **Dependency** and then "**Slice Time: Session 1**"
- Plug in the slice-timed images for the other sessions/runs.
- Under **Data→Session→Phase maps**, include the vdm file created in the Fieldmap toolbox (see above). This should be in your B0 maps folder.
- Leave everything else according to defaults.
- Realigned and unwarped files will have the filename prefix u*.

Coregister: Estimate

Coregistration allows us to align images from different modalities (i.e., our anatomical with functionals).

- For **Reference Image**, click **Dependency** and select "**Realign and Unwarp: Unwarped Mean Image.**" This is the mean functional image to which we will align to the anatomical.
- For **Source Image**, select your anatomical.
- Under **Other Images**, select your anatomical.

Segment

Segmenting breaks up your anatomical image into gray matter, white matter, and CSF.

- **Data**: click **Dependency** and select "**Coregister: Estimate: Coregistered Images**."

Normalize: Write (functionals)

Here we spatially normalize the functionals to an MNI template (standard anatomical space). This step allows us to get group averages and label our regions.

- **Data→Subject→Parameter file**: Select **Dependency** and then "**Segment: Norm Params Subj->MNI**"
- **Images to Write**: Click **Dependency** and select all of your realigned and unwarped images (e.g., "**Realign & Unwarp: Unwarped Images (Sess 1),**" "**Realign & Unwarp: Unwarped Images (Sess 2),**" "**Realign & Unwarp: Unwarped Images (Sess 3),**" "**Realign & Unwarp: Unwarped Images (Sess 4).)**"
- Normalized files will have the file prefix w*.

Normalize: Write (anatomical)

This step spatially normalizes the anatomical to an MNI template.

- **Data→Subject→Parameter file**: Select **Dependency** and then "**Segment: Norm Params Subj->MNI**"
- **Images to Write**: **Dependency**, then "**Coregister: Estimate: Coregistered Images**."
- Normalized files will have the file prefix w*.
-

Smoothing

Smoothing is performed to compensate for between-subject variability after normalization, and to permit the application of Gaussian random field theory at the statistics inference stage. FWHM stands for full-width half-maximum and it defines the size of the Gaussian kernel used for smoothing.

- Your smoothing **FWHM** value should be approximately twice the size of your voxels or more. So for example, if you collected at 3 x 3 x 3 your FWHM should be [6 6 6]. For this study, the voxels were at 3 x 3 x 4 so I selected a FWHM of [8 8 8].
- Leave everything else at default values.
- Smoothed files will have the prefix s*.

Save the batch job file.
Press the bright green arrow at the top to run the batch.
Check Reg to make sure the swaus images are aligned and not "wonky" before starting 1st level analyses.

Appendix III: Regions of activation for mean-centered SPS analysis.

Table 4.

Activations in MNI coordinates for SPS mean-centered analysis (letter/retrieval vs. encoding).

k	Brain Region	*x*	*y*	*z*	BSR	*p*
Lag 1						
Enc>Ret						
979	R Superior Temporal Gyrus (BA21)	50	-26	-4	6.55	<.0001
13753	L Middle Temporal Gyrus (BA 22)	-66	-34	4	5.79	<.0001
4684	L Superior Frontal Gyrus (BA 10)	-22	50	18	5.63	<.0001
4999	R Inferior Frontal Gyrus	50	16	2	5.47	<.0001
97	L Superior Temporal Gyrus (BA 38)	-44	12	-30	5.21	<.0001
1547	R Inferior Frontal Gyrus (BA 9)	44	2	24	3.90	0.0001
345	R Postcentral Gyrus (BA 4)	42	-20	48	3.72	0.0002
474	R Middle Temporal Gyrus (BA 37)	44	-62	4	3.51	0.0005
155	L Middle Temporal Gyrus (BA 19)	-44	-82	18	3.42	0.0006
84	R Middle Occipital Gyrus (BA 18)	32	-92	-4	3.36	0.0008
107	L Culmen	-36	-46	-34	2.84	0.0045
125	R Insula (BA 13)	44	-36	20	2.82	0.0048
68	R Putamen	24	-4	-10	2.76	0.0058
50	R Cuneus (BA 19)	28	-88	20	2.52	0.0116
306	L Precuneus (BA 7)	-4	-68	46	2.52	0.0118
47	**R Hippocampus**	**24**	**-14**	**-18**	**2.46**	**0.0141**
127	R Declive	34	-68	-30	2.40	0.0164
Ret>Enc						
797	L Lingual Gyrus (BA 19)	-14	-54	-4	-3.94	0.0001
80	L Fusiform Gyrus (BA 20)	-36	-8	-32	-2.94	0.0033
192	R Culmen	16	-38	-16	-2.73	0.0063
115	R Middle Frontal Gyrus (BA 6)	22	34	46	-2.60	0.0092
Lag 2						
Enc>Ret						
52025	L Postcentral Gyrus (BA 2)	-56	-24	34	6.45	<.0001
400	R Culmen	38	-56	-34	3.37	0.0007
123	L Declive	-40	-76	-26	3.32	0.0009
261	R Fusiform Gyrus (BA 37)	46	-36	-10	3.22	0.0013
Ret>Enc						
196	R Superior Temporal Gyrus (BA 38)	58	16	-26	-3.81	0.0001
68	R Superior Frontal Gyrus (BA 8)	22	38	44	-2.44	0.0146
Lag 3						

Enc>Ret						
49161	R Precentral Gyrus (BA 6)	38	-8	34	6.12	<.0001
81	R Caudate Tail	36	-26	-6	4.20	<.0001
265	L Fusiform Gyrus (BA20)	-44	-22	-22	4.15	<.0001
56	L Anterior Cingulate (BA 32)	-2	36	-8	3.61	0.0003
Ret>Enc						
623	R Middle Temporal Gyrus (BA 21)	52	2	-30	-4.92	<.0001
137	L Middle Temporal Gyrus (BA 21)	-64	-14	-16	-3.61	0.0003
131	L Middle Temporal Gyrus (BA 21)	-54	4	-40	-3.39	0.0007
227	R Middle Temporal Gyrus (BA 21)	50	-28	-10	-3.03	0.0024
189	R Superior Frontal Gyrus (BA 8)	18	32	52	-2.98	0.0029
167	**L Hippocampus**	**-30**	**-12**	**-22**	**-2.893**	**0.0038**
54	L Inferior Parietal Lobule (BA 39)	-46	-66	36	-2.79	0.0053
46	L Superior Temporal Gyrus (BA 38)	-56	24	-24	-2.70	0.0069
84	R Parahippocampal Gyrus (BA 34)	20	-8	-22	-2.63	0.0084
77	L Middle Temporal Gyrus	-48	-38	-6	-2.40	0.0164
Lag 4						
Enc>Ret						
14050	R Cuneus (BA 30)	10	-64	4	5.85	<.0001
806	R Cingulate Gyrus (BA 32)	2	20	38	4.64	<.0001
950	L Insula (BA 13)	-38	-2	20	4.38	<.0001
1026	R Middle Frontal Gyrus (BA 46)	40	28	24	4.27	<.0001
115	R Thalamus	2	-10	8	3.62	0.0003
341	R Inferior Frontal Gyrus (BA 47)	28	26	-6	3.52	0.0004
506	L Precuneus (BA 7)	-14	-54	56	3.29	0.001
45	L Caudate Head	-6	6	0	3.19	0.0014
44	R Parahippocampal Gyrus (BA 34)	12	-14	-28	3.00	0.0027
68	R Superior Frontal Gyrus (BA 6)	4	0	70	2.93	0.0034
40	L Transverse Temporal Gyrus (BA 41)	-32	-36	8	2.90	0.0037
108	R Middle Frontal Gyrus (BA 6)	26	-8	48	2.67	0.0076
53	R Cingulate Gyrus (BA 23)	4	-18	34	2.63	0.0086
Ret>Enc						
680	R Superior Temporal Gyrus (BA 21)	48	-28	-10	-3.66	0.0002
512	R Middle Temporal Gyrus (BA 21)	56	10	-32	-3.63	0.0003
92	R Superior Frontal Gyrus (BA 9)	14	52	30	-3.12	0.0018
94	R Superior Frontal Gyrus (BA 8)	20	34	52	-3.04	0.0024
40	R Inferior Frontal Gyrus (BA 45)	62	28	8	-2.92	0.0035
44	L Middle Frontal Gyrus (BA 6)	-44	-2	56	-2.80	0.0052
88	R Inferior Semi-Lunar Lobule	28	-68	-50	-2.78	0.0055
263	L Precuneus (BA 39)	-42	-72	36	-2.76	0.0058
69	L Middle Frontal Gyrus (BA 8)	-30	16	42	-2.69	0.0071
107	L Pyramis	-32	-68	-42	-2.58	0.01

51	L Posterior Cingulate (BA 31)	-10	-56	22	-2.45	0.0144

Table 4. Only clusters with a bootstrap ratio of greater than +/-2.40 (roughly *p*=.01) and a cluster size of at least 40 voxels are reported. BA, Brodmann area; BSR, bootstrap ratio; MNI, Montreal Neurological Institute; L, left; R, right.

Appendix IV: Regions of activation for mean-centered TPS analysis.

Table5.

Activations in MNI coordinates for TPS mean-centered analysis (letter/retrieval vs. encoding).

k	Brain Region	*x*	*y*	*z*	BSR	*p*
Lag 1						
Enc>Ret						
1346	L Precentral Gyrus (BA 4)	-16	54	-46	5.03	<.0001
1241	L Hippocampus	-46	8	30	3.85	0.0001
140	R Caudate Head	10	2	0	3.40	0.0007
44	L Cingulate Gyrus (BA 24)	-8	22	0	3.24	0.0012
67	L Paracentral Lobule (BA 6)	-36	72	6	3.18	0.0015
82	R Medial Frontal Gyrus (BA 32)	10	44	16	2.87	0.0041
Ret>Enc						
39011	L Middle Temporal Gyrus (BA 21)	-8	-12	63	-10.50	<.0001
24160	L Cuneus (BA 7)	-78	28	14	-8.55	<.0001
280	R Medial Frontal Gyrus (BA 25)	14	-18	2	-6.25	<.0001
65	L Postcentral Gyrus (BA 3)	-34	70	-20	-2.64	0.0082
Lag 2						
Enc>Ret						
115	R Inferior Frontal Gyrus (BA 47)	22	-6	-30	5.17	<.0001
334	L Precentral Gyrus (BA 4)	-16	62	-38	4.83	<.0001
4909	L Fusiform Gyrus (BA 19)	-64	-12	-26	4.78	<.0001
480	R Middle Frontal Gyrus (BA 46)	22	26	-48	3.77	0.0002
75	L Superior Occipital Gyrus (BA 19)	-78	20	-34	3.45	0.0006
53	R Inferior Frontal Gyrus (BA 47)	22	-4	32	3.36	0.0008
Ret>Enc						
56660	L Amygdala	-10	-16	-28	-11.95	<.0001
16225	R Inferior Frontal Gyrus (BA 47)	36	0	57	-10.09	<.0001
11811	L Postcentral Gyrus (BA 40)	-30	22	61	-9.47	<.0001
811	L Fusiform Gyrus (BA 19)	-76	-18	42	-7.60	<.0001
212	R Medial Frontal Gyrus (BA 25)	14	-18	2	-5.75	<.0001
43	R Middle Temporal Gyrus (BA 21)	14	-38	-48	-3.56	0.0004
Lag 3						
Enc>Ret						
12211	L Parahippocampal Gyrus (BA 19)	-56	-10	-18	8.14	<.0001
326	R Inferior Frontal Gyrus (BA 47)	20	-12	-30	7.91	<.0001
874	R Middle Frontal Gyrus (BA 9)	14	40	-53	3.78	0.0002
161	R Inferior Frontal Gyrus (BA 47)	22	-4	32	3.75	0.0002

276	R Medial Frontal Gyrus (BA 8)	22	48	4	3.03	0.0024
Ret>Enc						
74542	L Middle Temporal Gyrus (BA 21)	-6	-8	63	-11.32	<.0001
3204	L Fusiform Gyrus (BA 19)	-78	-18	40	-8.75	<.0001
2196	L Culmen	-42	-26	-40	-8.67	<.0001
260	R Anterior Cingulate (BA 25)	6	-12	0	-4.86	<.0001
Lag 4						
Enc>Ret						
13734	L Cuneus (BA 17)	-82	8	16	11.91	<.0001
92	L Middle Temporal Gyrus (BA 39)	-76	20	-42	4.59	<.0001
65	L Postcentral Gyrus (BA 3)	-34	68	-24	4.06	<.0001
401	R Inferior Frontal Gyrus (BA 47)	20	-14	-26	3.64	0.0003
493	R Middle Frontal Gyrus (BA 8)	18	50	-42	3.56	0.0004
167	L Precuneus (BA 39)	-66	36	-38	3.40	0.0007
41	R Middle Frontal Gyrus (BA 11)	38	-14	-44	3.40	0.0007
375	R Middle Frontal Gyrus (BA 10)	54	-4	34	3.30	0.001
355	R Medial Frontal Gyrus (BA 8)	24	48	4	3.29	0.001
110	R Superior Frontal Gyrus (BA 10)	60	4	-28	3.21	0.0013
67	R Middle Temporal Gyrus (BA 21)	6	-34	51	3.15	0.0016
Ret>Enc						
69858	L Cingulate Gyrus (BA 31)	-30	40	10	-9.07	<.0001
59	R Superior Temporal Gyrus (BA 38)	10	-28	38	-3.84	0.0001
70	R Inferior Frontal Gyrus (BA 47)	36	-12	-57	-3.77	0.0002
249	L/R Amygdala	0	-16	22	-3.72	0.0002
137	R Putamen	6	-12	-20	-3.34	0.0008

Table 5. Only clusters with a bootstrap ratio of greater than +/-2.40 (roughly p= .01) and a cluster size of at least 40 voxels are reported. BA, Brodmann area; BSR, bootstrap ratio; MNI, Montreal Neurological Institute; L, left; R, right.

Appendix IV: Regions of activation for SPS nonrotated task analysis.

Table 6.

Activations in MNI coordinates for SPS nonrotated task analysis (encoding versus retrieval).

k	Brain Region	*x*	*y*	*z*	BSR	*p*
Lag 1						
Enc>Ret						
77	L Parahippocampal Gyrus (BA 36)	-28	-14	-28	3.43	0.0006
310	L Culmen	-14	-52	-6	3.18	0.0015
45	L Superior Frontal Gyrus (BA 9)	-24	50	36	2.88	0.004
103	R Parahippocampal Gyrus (BA 30)	20	-40	-8	2.64	0.0083
134	R Middle Frontal Gyrus (BA 8)	22	34	46	2.54	0.0112
Ret>Enc						
6279	L Medial Frontal Gyrus (BA 10)	-20	52	16	-5.29	<.0001
3644	L Insula (BA 13)	-34	-34	20	-5.25	<.0001
2770	R Inferior Frontal Gyrus	52	16	2	-4.61	<.0001
685	R Postcentral Gyrus (BA 43)	70	-16	16	-3.88	0.0001
106	R Middle Occipital Gyrus (BA 18)	30	-94	-4	-3.75	0.0002
2270	L Precuneus (BA 19)	-34	-70	36	-3.68	0.0002
147	L Postcentral Gyrus (BA 3)	-20	-30	60	-3.47	0.0005
616	R Middle Temporal Gyrus (BA 39)	46	-58	4	-3.33	0.0009
364	R Paracentral Lobule (BA 5)	8	-48	56	-3.28	0.001
60	L Superior Temporal Gyrus (BA 38)	-42	12	-30	-3.15	0.0016
51	L Sub-Gyral (BA 20)	-38	-12	-18	-2.98	0.0028
85	L Declive	-34	-76	-30	-2.89	0.0038
321	L Thalamus	-12	-20	-2	-2.86	0.0042
97	L/R Culmen	0	-38	-16	-2.81	0.005
336	L Middle Frontal Gyrus (BA 6)	-32	10	46	-2.74	0.0061
61	R Precentral Gyrus (BA 6)	48	-12	32	-2.63	0.0085
95	L Culmen	-38	-42	-32	-2.57	0.0103
70	L Postcentral Gyrus (BA 5)	-32	-46	58	-2.46	0.0139
87	R Paracentral Lobule (BA 6)	10	-34	64	-2.46	0.0141
55	R Superior Temporal Gyrus (BA 22)	60	-40	22	-2.43	0.0152
159	R Middle Occipital Gyrus (BA 19)	30	-90	18	-2.35	0.0186
Lag 2						
Enc>Ret						
286	R Superior Temporal Gyrus (BA 38)	58	16	-26	3.89	0.0001
96	L Middle Temporal Gyrus (BA 21)	-50	6	-40	3.73	0.0002
134	L Parahippocampal Gyrus (BA 36)	-24	-30	-18	2.84	0.0045
43	L Medial Frontal Gyrus (BA 10)	-14	60	-4	2.68	0.0074
31	**R Hippocampus**	**30**	**-6**	**-28**	**2.61**	**0.009**

65	L Angular Gyrus (BA 39)	-44	-68	36	2.61	0.0091
120	R Superior Frontal Gyrus (BA 8)	22	38	44	2.60	0.0093
Ret>Enc						
24823	L Inferior Parietal Lobule (BA 40)	-30	-36	34	-5.05	<.0001
1770	R Inferior Frontal Gyrus (BA 47)	58	20	0	-4.10	<.0001
290	L Superior Temporal Gyrus (BA 38)	-54	4	-10	-3.77	0.0002
190	L Parahippocampal Gyrus (BA 36)	-40	-34	-14	-3.68	0.0002
918	R Red Nucleus	6	-24	-6	-3.32	0.0009
781	R Middle Temporal Gyrus (BA 37)	50	-58	0	-3.23	0.0012
112	L Declive	-38	-76	-26	-3.05	0.0023
583	R Inferior Parietal Lobule (BA 40)	62	-30	28	-2.93	0.0034
52	L Middle Frontal Gyrus (BA 6)	-34	0	58	-2.81	0.0049
119	R Tuber	42	-56	-36	-2.70	0.0069
64	R Middle Occipital Gyrus (BA 18)	30	-88	-8	-2.48	0.0131
98	**R Hippocampus**	**30**	**-24**	**-10**	**-2.38**	**0.0171**
Lag 3						
Enc>Ret						
814	R Middle Temporal Gyrus (BA 21)	54	8	-24	6.16	<.0001
499	L Superior Frontal Gyrus (BA 8)	-16	18	54	4.95	<.0001
389	L Middle Temporal Gyrus (BA 21)	-62	-14	-16	4.25	<.0001
701	R Superior Temporal Gyrus (BA 21)	48	-30	-8	4.21	<.0001
456	**L Hippocampus**	**-32**	**-12**	**-26**	**4.15**	**<.0001**
395	L Subcallosal Gyrus (BA 25)	-6	10	-14	4.14	<.0001
386	L Inferior Parietal Lobule (BA 39)	-46	-66	38	4.09	<.0001
268	L Middle Temporal Gyrus (BA 21)	-48	14	-40	3.51	0.0005
316	L Middle Temporal Gyrus (BA 37)	-54	-48	-10	3.41	0.0007
91	L Inferior Frontal Gyrus (BA 47)	-50	30	-8	3.23	0.0012
290	R Superior Frontal Gyrus (BA 8)	20	32	54	3.11	0.0019
120	R Parahippocampal Gyrus (BA 28)	18	-8	-24	2.87	0.0041
139	R Inferior Semi-Lunar Lobule	26	-68	-50	2.81	0.0049
146	R Inferior Frontal Gyrus (BA 47)	26	8	-20	2.75	0.0059
46	L Inferior Semi-Lunar Lobule	-24	-64	-48	2.51	0.0121
164	L Posterior Cingulate (BA 29)	-8	-50	8	2.48	0.013
Ret>Enc						
5848	L Precentral Gyrus (BA 6)	-38	-12	36	-4.45	<.0001
8961	R Cingulate Gyrus (BA 31)	24	-44	30	-4.30	<.0001
213	L Superior Temporal Gyrus (BA 22)	-54	10	-6	-3.58	0.0003
74	L Parahippocampal Gyrus (BA 36)	-42	-22	-22	-3.42	0.0006
227	R Postcentral Gyrus (BA 2)	60	-24	34	-3.42	0.0006
238	L Middle Frontal Gyrus (BA 46)	-52	22	26	-3.21	0.0013
507	R Declive	-32	-76	-24	-3.04	0.0024
161	R Superior Temporal Gyrus (BA 22)	64	-54	8	-2.88	0.004

48	L Red Nucleus	-2	-26	-8	-2.83	0.0047
68	L Cingulate Gyrus (BA 24)	-16	-8	50	-2.65	0.0081
57	L Postcentral Gyrus (BA 40)	-58	-26	20	-2.61	0.009
235	R Inferior Occipital Gyrus (BA 18)	30	-84	-10	-2.49	0.0128
139	R Fusiform Gyrus (BA 37)	44	-64	-22	-2.47	0.0136
39	R Caudate Tail	32	-36	6	-2.39	0.0168
78	R Superior Frontal Gyrus (BA 9)	44	38	32	-2.36	0.0185
Lag 4						
Enc>Ret						
1496	L Middle Temporal Gyrus (BA 21)	-48	-36	-8	5.39	<.0001
2933	L Middle Frontal Gyrus (BA 8)	-30	22	50	5.15	<.0001
1703	L Angular Gyrus (BA 39)	-42	-64	38	5.13	<.0001
293	L Precentral Gyrus (BA 44)	-52	16	8	5.02	<.0001
340	R Superior Temporal Gyrus (BA 21)	46	-30	-10	4.89	<.0001
464	R Precuneus (BA 39)	44	-76	34	4.41	<.0001
69	R Middle Frontal Gyrus (BA 8)	46	16	48	4.08	<.0001
73	R Inferior Frontal Gyrus (BA 47)	58	40	-14	3.88	0.0001
588	R Middle Temporal Gyrus (BA 21)	46	6	-32	3.86	0.0001
335	R Middle Temporal Gyrus (BA 21)	68	-30	-8	3.65	0.0003
304	R Dentate	16	-64	-32	3.44	0.0006
103	R Inferior Frontal Gyrus (BA 46)	48	50	6	3.39	0.0007
173	R Superior Frontal Gyrus (BA 9)	14	52	26	3.30	0.001
99	R Superior Frontal Gyrus (BA 6)	20	12	52	3.28	0.001
238	L Inferior Frontal Gyrus (BA 47)	-16	28	-18	3.20	0.0014
388	L Pyramis	-20	-64	-38	3.19	0.0014
145	R Cingulate Gyrus (BA 24)	18	12	32	3.04	0.0024
176	R Inferior Semi-Lunar Lobule	32	-66	-50	2.94	0.0033
52	L Caudate	-8	8	18	2.89	0.0039
54	L Posterior Cingulate (BA 29)	-6	-50	6	2.80	0.0051
51	R Caudate	20	16	12	2.72	0.0065
150	L Posterior Cingulate (BA 31)	-10	-54	20	2.70	0.0069
47	R Superior Frontal Gyrus (BA 8)	20	40	48	2.57	0.0102
60	R Inferior Parietal Lobule (BA 40)	42	-32	28	2.56	0.0103
47	L Precuneus (BA 7)	-12	-72	44	2.56	0.0105
60	L Anterior Cingulate (BA 25)	-2	12	-8	2.44	0.0146
Ret>Enc						
4129	R Parahippocampal Gyrus (BA 30)	14	-46	-4	-5.39	<.0001
80	L Parahippocampal Gyrus (BA 34)	-8	-8	-24	-4.35	<.0001
40	L Paracentral Lobule (BA 5)	-10	-48	64	-3.78	0.0002
282	L Caudate Body	-18	4	24	-3.33	0.0009
189	R Lingual Gyrus (BA 18)	26	-94	-12	-3.28	0.001
58	L/R Anterior Cingulate (BA 24)	0	28	14	-3.27	0.0011

62	R Caudate Body	22	-14	28	-3.05	0.0023
108	R Precuneus (BA 7)	16	-50	48	-2.71	0.0067

Table 6. Activations in MNI coordinates for SPS nonrotated task analysis (encoding versus retrieval). Only clusters with a bootstrap ratio of greater than +/-2.35 (roughly p=.02) and a cluster size of at least 40 voxels are reported. BA, Brodmann area; BSR, bootstrap ratio; MNI, Montreal Neurological Institute; L, left; R, right.

Appendix V: Regions of activation for TPS nonrotated task analysis.

Table 7.

Activations in MNI coordinates for TPS nonrotated task analysis (encoding versus retrieval).

k	Brain Region	*x*	*y*	*z*	BSR	*p*
Lag 1						
Enc>Ret						
42346	R Middle Temporal Gyrus (BA 21)	62	-8	-12	10.39	<.0001
18128	L Declive	-38	-74	-22	6.76	<.0001
384	R Subcallosal Gyrus (BA 25)	4	14	-16	5.82	<.0001
227	R Inferior Semi-Lunar Lobule	8	-66	-50	4.86	<.0001
57	L Cuneus (BA 19)	-26	-84	24	4.31	<.0001
96	L Inferior Semi-Lunar Lobule	-8	-60	-50	3.91	0.0001
51	L Precuneus (BA 7)	-16	-58	50	3.03	0.0025
Ret>Enc						
899	L Precentral Gyrus (BA 4)	-46	-16	54	-3.53	0.0004
330	**R Hippocampus**	**30**	**-46**	**6**	**-3.06**	**0.0022**
Lag 2						
Enc>Ret						
43275	R Inferior Frontal Gyrus (BA 47)	58	36	-2	9.82	<.0001
26028	R Amygdala	26	2	-16	9.74	<.0001
13093	R Superior Temporal Gyrus (BA 42)	62	-32	20	8.98	<.0001
2849	R Fusiform Gyrus (BA 19)	42	-78	-18	7.29	<.0001
152	R Superior Frontal Gyrus (BA 6)	12	26	62	4.98	<.0001
172	R Medial Frontal Gyrus (BA 25)	2	14	-18	4.41	<.0001
40	L Middle Temporal Gyrus (BA 21)	-48	12	-40	3.74	0.0002
Ret>Enc						
7053	R Lingual Gyrus	16	-78	-6	-4.69	<.0001
102	L Inferior Frontal Gyrus (BA 47)	-30	22	-6	-4.48	<.0001
88	L Precentral Gyrus (BA 4)	-38	-18	62	-4.09	<.0001
87	L Superior Occipital Gyrus (BA 19)	-34	-78	22	-3.91	0.0001
505	L Middle Frontal Gyrus (BA 46)	-48	22	28	-3.86	0.0001
67	R Inferior Frontal Gyrus (BA 47)	32	22	-4	-3.64	0.0003
Lag 3						
Enc>Ret						
6814	L Middle Frontal Gyrus (BA 11)	-30	38	-16	10.01	<.0001
68036	R Superior Temporal Gyrus (BA 42)	62	-34	20	8.82	<.0001
2206	L Culmen	-38	-44	-28	8.46	<.0001
Ret>Enc						
13040	R Parahippocampal Gyrus (BA 19)	22	-52	-8	-8.11	<.0001

359	L Inferior Frontal Gyrus (BA 47)	-30	22	-14	-6.91	<.0001
1037	L Middle Frontal Gyrus (BA 9)	-48	16	38	-4.17	<.0001
60	L Lateral Geniculum Body	-22	-24	-6	-3.34	0.0008
149	R Inferior Frontal Gyrus (BA 47)	34	22	-8	-3.25	0.0011
385	R Medial Frontal Gyrus (BA 8)	4	24	48	-3.24	0.0012
Lag 4						
Enc>Ret						
1459	L Inferior Occipital Gyrus (BA 18)	-34	-88	-14	7.59	<.0001
1311	L Superior Temporal Gyrus (BA 22)	-48	8	0	6.39	<.0001
154	R Superior Frontal Gyrus (BA 9)	4	56	34	3.91	0.0001
47	R Superior Temporal Gyrus (BA 38)	38	12	-28	3.83	0.0001
Ret>Enc						
14716	R Cuneus (BA 17)	16	-84	10	-11.15	<.0001
530	L Superior Frontal Gyrus (BA 8)	-2	22	56	-5.29	<.0001
128	L Middle Temporal Gyrus (BA 39)	-42	-74	20	-4.82	<.0001
427	L Middle Frontal Gyrus (BA 8)	-44	18	48	-3.93	0.0001
115	R Middle Temporal Gyrus (BA 21)	54	6	-32	-3.79	0.0001
41	L Postcentral Gyrus (BA 3)	-24	-34	68	-3.55	0.0004
42	L Middle Frontal Gyrus (BA 11)	-44	38	-14	-3.27	0.0011
116	R Inferior Parietal Lobule (BA 39)	50	-66	38	-3.24	0.0012
310	L Superior Temporal Gyrus (BA 39)	-54	-58	26	-3.18	0.0015
111	L Superior Frontal Gyrus (BA 10)	-26	62	4	-3.11	0.0018

Table 7. Only clusters with a bootstrap ratio of greater than +/-3.00 (roughly p=.002) and a cluster size of at least 40 voxels are reported. BA, Brodmann area; BSR, bootstrap ratio; MNI, Montreal Neurological Institute; L, left; R, right.

Appendix VI: SPS functional connectivity analysis using three hippocampal seeds.

A seed analysis was conducted to assess the functional connectivity of three hippocampal seeds that were identified in the nonrotated task analysis. Two of these seeds were in the right hippocampus (MNI coordinates: X=30, Y=-6, Z=-28; X=30, Y=24, Z=-10) and one in the left hippocampus (MNI: X=-32, Y=-12, Z=-26). This analysis was performed to assess the pattern of functional connectivity between the hippocampus and the rest of the brain for spatial pattern separation.

The seed analysis yielded 21 LVs, of which two were significant at .001. Each LV determined accounts for progressively less of the summed squared crossblock covariance (SSCC), which is considered a measure of importance (McIntosh et al., 1997). The first LV accounted for 49.4% of the SSCC, and the second accounted for 9.1%. Because of the drastically higher SSCC accounted for by the first LV compared to all other LVs, only this first LV will be discussed.

This LV is characterized by widespread activation through bilateral parahippocampal gyri, the frontal pole (BA10), right superior (BA 8) and left inferior (BA 47) frontal gyri, and bilateral precentral gyri (BA 4/6; Table 8; Figure 20).

Table 8.

Regions with functional connectivity to hippocampal seed regions.

		MNI coordinates				
k	Brain Region	*x*	*y*	*z*	BSR	*p*
7767	R parahippocampal gyrus (BA 35)	26	-28	-12	10.43	<.0001
15053	R inferior frontal gyrus (BA 47)	50	24	0	9.53	<.0001
3973	L parahippocampal gyrus (BA 27)	-22	-30	-10	7.86	<.0001
55	L middle temporal gyrus (BA 21)	-66	-34	-12	6.29	<.0001
122	L medial frontal gyrus (BA 10)	-2	62	20	6.28	<.0001
144	R superior frontal gyrus (BA 8)	30	18	54	6.27	<.0001
62	L supramarginal gyrus (BA 40)	-60	-48	30	6.11	<.0001
114	R middle temporal gyrus (BA 21)	58	8	-18	5.75	<.0001
41	L superior temporal gyrus (BA 38)	-36	18	-28	5.64	<.0001
42	R superior parietal lobule (BA 7)	32	-50	58	5.43	<.0001
32	L medial frontal gyrus (BA 10)	0	64	-6	5.36	<.0001
43	L precentral gyrus (BA 6)	-60	0	28	4.80	<.0001
35	R middle temporal gyrus (BA 19)	44	-80	14	4.72	<.0001
31	L superior temporal gyrus (BA 38)	-54	10	-16	4.56	<.0001
30	R precentral gyrus (BA 4)	22	-22	52	4.53	<.0001

Table 8. Only clusters in the peak timepoint (Lag 2) with a bootstrap ratio of greater than +/- 4.5 (roughly $p<.0001$) and a cluster size of at least 30 voxels are reported. BA, Brodmann area; MNI, Montreal Neurological Institute; BSR, bootstrap ratio, L, left; R, right.

Figure 20

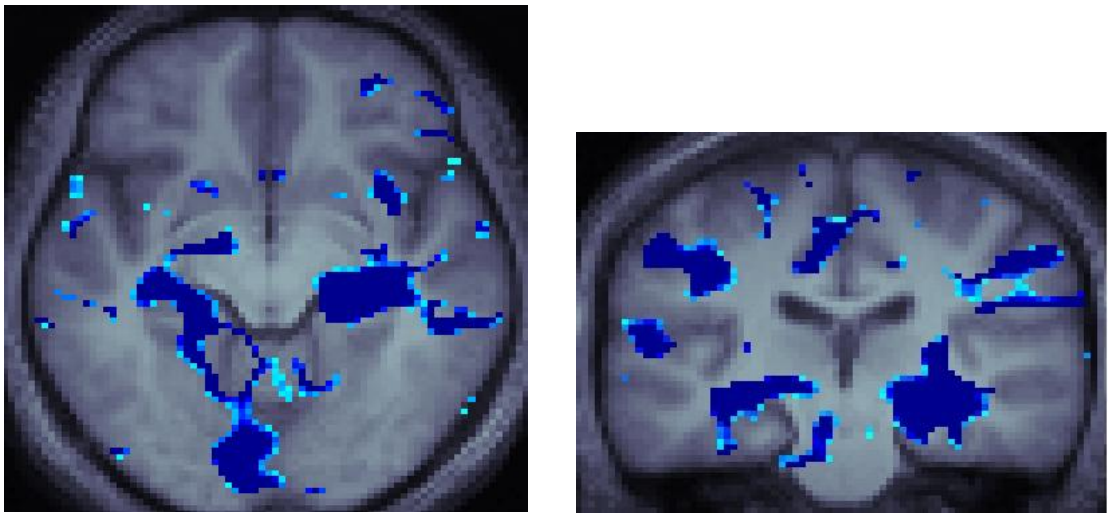


Figure 20. Regions of activation correlated with hippocampal seeds in SPS at Lag 2 superimposed over a mean anatomical image.

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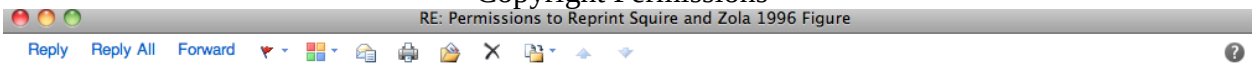

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