UNIVERSITY OF CALIFORNIA, SAN DIEGO

Associative Encoding in Episodic Memory: Binding Items Across Time

A Dissertation submitted in partial satisfaction of the requirement for the degree
Doctor of Philosophy

in

Neurosciences

by

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2011

The dissertation of Jena Bresnihan Hales is approved, and is acceptable in quality and form for publication on microfilm and electronically:

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University of California, San Diego

2011

DEDICATION

I dedicate this dissertation to my family and friends. To my loving husband Tyler- thank you for your unwavering support and confidence in me and for your endless love and encouragement throughout the last eleven years. To my mom, dad, and sister Ariana - thank you for always believing in me and for your unconditional love and support; despite the distance, I have known that you were here with me every step of the way. To my friends, old and new, near and far- thank you for always being there for me either in person or in spirit. To my friend Jen- thank you for your invaluable advice, love, and friendship over the past few years; Tyler and I feel lucky to have made such lifelong friends as you and Paul. To my undergraduate advisor Seth- thank you for seeing the researcher in me even before I did and for helping me believe that I could achieve whatever I set my mind to. To my labmates- thank you for all of your daily and limitless guidance, support, knowledge, and friendship; you all have made coming to lab each and every day so enjoyable. To Sarah- thank you for taking me under your wing and teaching me so much about science, research, life, and friendship; you have made a permanent impact on my life, and I cannot imagine it without you. To Jim- thank you for taking a chance on a new graduate student coming straight from undergrad with no imaging or programming experience; while I have gained so much knowledge and scientific understanding from working with you over the past five years, I have learned even more about how to be an effective P.I. and successful researcher, for which I am forever grateful.

TABLE OF CONTENTS

ACKNOWLEDGMENTS

I would like to acknowledge Dr. James Brewer for his invaluable support and guidance throughout graduate school and for being the chair of my dissertation committee. Additionally, I would like to acknowledge Drs. David Salmon, John Serences, Larry Squire, and John Wixted for the guidance and wisdom they have shared with me.

I would also like to acknowledge the members of the Human Memory Laboratory, Sarah Gimbel, Tyler Seibert, Elizabeth Murphy, Emilie Schwager, and Erik Kaestner, for their endless support, constant guidance, and lasting friendship.

Chapter 2, in full, is a reprint of the material as it appears in Journal of Cognitive Neuroscience, 2009. Hales, Jena B.; Israel, Sarah L.; Swann, Nicole C.; Brewer, James B. The dissertation author was the primary investigator and author of this paper.

Chapter 3, in full, is a reprint of the material as it appears in Neuropsychologia, 2010. Hales, Jena B.; Brewer, James B. The dissertation author was the primary investigator and author of this paper.

Chapter 4, in full, is a reprint of the material as it appears in Journal of Neurophysiology, 2011. Hales, Jena B.; Brewer, James B. The dissertation author was the primary investigator and author of this paper.

Chapter 5, in full, is a reprint of the material as it was submitted for consideration for publication. Hales, Jena B.; Brewer, James B. The dissertation author was the primary investigator and author of this paper.

Chapter 6, in full, is a reprint of the material as it was submitted for consideration for publication as a brief communication. Hales, Jena B.; Brewer, James B. The dissertation author was the primary investigator and author of this paper.

This work was supported by the National Institute of Neurological Disorders and Stroke NINDS K23 NS050305, the General Electric Medical Foundation, and the University of California, San Diego Departments of Neurosciences and Radiology. JBH was supported by the National Science Foundation through the Graduate Research Fellowship Program.

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Hales, J. B., & Brewer, J. B. The path to memory is guided by strategy: distinct networks are engaged in associative encoding under visual and verbal strategy and influence memory performance in healthy and impaired individuals. (In review).

Hales, J. B., & Brewer, J. B. Distinct parietal and frontal contributions to sequential object-location associative encoding. (In review).

Schwager, E.T., Gimbel, S.I., **Hales, J. B.**, & Brewer, J. B. Search-related suppression of hippocampus and default network activity during associative memory retrieval. (In review).

Hales, J. B., & Brewer, J. B. (2011). The timing of associative memory formation: Frontal lobe and anterior medial temporal lobe activity at associative binding predicts memory. *Journal of Neurophysiology, 105(4),* 1454-1463.

Hales, J. B., & Brewer, J. B. (2010). Activity in the hippocampus and neocortical working memory regions predicts successful associative memory for temporally discontiguous events. *Neuropsychologia, 48*(*11*), 3351-3359.

Hales, J. B., Israel, S. L., Swann, N. C., & Brewer, J. B. (2009). Dissociation of frontal and medial temporal lobe activity in maintenance and binding of sequentially presented paired associates. *Journal of Cognitive Neuroscience, 21*(*7*), 1244-1254.

Ramus, S. J, **Davis, J. B.,** Donahue, R. J., Discenza, C. B., & Waite, A. A. (2007). Interactions between the orbitofrontal cortex and the hippocampal memory system during the storage of long-term memory. *Annals of the New York Academy of Sciences, 1121,* 216-231.

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ABSTRACT OF THE DISSERTATION

Associative Encoding in Episodic Memory: Binding Items Across Time

by

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Doctor of Philosophy in Neurosciences

University of California, San Diego, 2011

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As individuals navigate the world, they encounter a constant stream of stimuli, some of which are important to attend to, encode, and associate with other stimuli separated in time. How does the brain attempt to form and succeed in forming associative memories for temporally-discontiguous stimuli? Does using different associative strategies influence which brain regions are engaged in encoding, and could this have clinical implications for potential treatment approaches in patients with neurological damage and disease? The studies described in this dissertation were

designed to address these questions using functional magnetic resonance imaging and behavioral memory testing.

Using a novel memory paradigm, in which subjects encoded and formed associations between temporally-discontiguous sequentially-presented stimuli, the established involvement of prefrontal and medial temporal regions in associative encoding was disentangled, as these regions were found to subserve different functions in maintaining and binding visual stimuli. Successful associative encoding of object pairs involved coordination of frontoparietal working memory regions and the hippocampus. Frontoparietal regions were also engaged in visuospatial encoding, where the spatial cue preceded the centrally-presented object; however, parietal regions were modulated by attempted visuospatial binding while frontal responses predicted successful binding. Additionally, when examining the timing of associative memory formation with a temporal delay between visual objects, positive modulation of frontal, lateral occipital, and anterior medial temporal regions were found to predict success at binding and not during maintenance.

Besides exploring the natural processes involved in associating and encoding temporally-discontiguous stimuli, another primary goal of this dissertation was to examine the influence of encoding strategy on regional memory effects. Encoding object pairs using a visual versus verbal strategy engaged similar regions as those reported in prior studies of visual- versus verbal-stimulus encoding. Such findings suggest a driving effect of strategy, not stimulus-type, on regional involvement in associative memory formation, which has implications for future development both in

basic memory research and for potential clinical treatments. Together, the studies that comprise this dissertation addressed existing unknowns in the field of human memory formation and contributed to the understanding of how individuals with intact and impaired cognitive function form associative memories.

CHAPTER 1:

INTRODUCTION

Remembering facts and events allows people to learn from their past experiences and make informed future decisions. This ability aids people in effectively navigating a complex world; however, losing this ability, through injury or neurodegeneration, is emotionally, physically, and financially devastating. Gaining a better understanding of the networks involved in the successful formation of memories is an important step towards preventing such a loss.

The goal of the work described in this dissertation was to examine the coordination of different brain regions and their contributions to successful associative memory formation. The studies were specifically designed to elucidate the processes involved in associative encoding of temporally discontiguous stimuli and the effects that associative strategy has on successful encoding. Functional magnetic resonance imaging (fMRI) was used in these studies to measure regional responses to the encoding events.

Long-term memory encoding

The processes and brain structures involved in the formation of memories remain a topic of broad interest in science, from the level of individual synapses to

systems level processing and interactions between brain regions. Long-term memory is made up of declarative memory, which requires the function of medial temporal lobe (MTL) regions, and nondeclarative memory, e.g., skill and habit learning, which is independent of these regions (Squire, 1992; Squire & Zola-Morgan, 1991). Declarative memory is further subdivided into memory for facts, i.e., semantic memory, and memory for events, i.e., episodic memory. The studies presented in this dissertation mainly involved episodic encoding. Furthermore, these studies focused on a specific type of episodic encoding, associative encoding, which involves associating items together and forming memory for these items and the association.

Functional Magnetic Resonance Imaging and Memory

The studies discussed in this dissertation examined the formation of associative memory using behavioral testing and fMRI. In order to examine how the brain forms associative memories, these studies involved subjects learning arbitrary stimulus associations while undergoing fMRI scanning. Following the scans, subjects performed tasks to assess their memory for what they learned during the scan, i.e., subsequent memory tests. The results of the subsequent memory tests could then be used to examine which encoding trials were subsequently remembered versus forgotten and which brain regions had response changes predictive of subsequent memory success, known as the subsequent memory effect (Brewer, Zhao, Desmond,

Glover, & Gabrieli, 1998; Wagner, Schacter, et al., 1998). This was the main type of analysis used in the studies described in this dissertation.

Functional MRI is a valuable technique for studying regional subsequent memory effects in the brain. Although the temporal resolution of fMRI is low, on the order of seconds, the spatial resolution is on the order of millimeters allowing for the attribution of responses to specific brain regions, both at the cortical surface and in deeper structures, such as the medial temporal regions, i.e., the parahippocampal gyrus, which is made up of perirhinal, entorhinal, and parahippocampal cortices, and the hippocampus. While fMRI gives researchers powerful insight into the function and contribution of particular brain regions to successful memory formation, it is also essential to remain connected to the findings from lesion and electrophysiological studies in both humans and animals. The studies presented in this dissertation were all designed and discussed in light of the established human lesion and animal literature.

Associative Encoding

The successful formation of associative memories is a fundamental ability; however, despite the abundance of events and stimuli that one encounters and attends to each day, some information will be later remembered and some will not. Which brain regions are involved in successful associative encoding is a critical area of research. Human and animal lesion studies have found MTL involvement to be critical for long-term memory encoding (Cohen & Squire, 1980; Mishkin, 1978; Scoville &

Milner, 1957). Functional imaging studies of long-term associative memory encoding have commonly reported activation in the subregions of the MTL (Achim & Lepage, 2005; Brewer, et al., 1998; Chua, Schacter, Rand-Giovannetti, & Sperling, 2007; Davachi, Mitchell, & Wagner, 2003; Davachi & Wagner, 2002; Eichenbaum, Yonelinas, & Ranganath, 2007; Gold, et al., 2006; Jackson & Schacter, 2004; Kirwan & Stark, 2004; L. J. Murray & Ranganath, 2007; Pihlajamaki, et al., 2003; Qin, et al., 2007; Qin, et al., 2009; Ranganath, Cohen, Dam, & D'Esposito, 2004; R. Sperling, et al., 2003; Staresina & Davachi, 2006; Wagner, Poldrack, et al., 1998). Neuroimaging and neuropsychological studies also suggest prefrontal cortex (PFC) contribution to associative memory encoding (Achim & Lepage, 2005; Blumenfeld, Parks, Yonelinas, & Ranganath, 2010; Blumenfeld & Ranganath, 2006, 2007; Chua, et al., 2007; Davachi & Wagner, 2002; Dolan & Fletcher, 1997; Fletcher, Shallice, & Dolan, 2000; Geuze, Vermetten, Ruf, de Kloet, & Westenberg, 2008; Haskins, Yonelinas, Quamme, & Ranganath, 2008; Jackson & Schacter, 2004; Kapur, et al., 1996; Montaldi, et al., 1998; L. J. Murray & Ranganath, 2007; Park & Rugg, 2008; Peters, Daum, Gizewski, Forsting, & Suchan, 2009; Pihlajamaki, et al., 2003; Prince, Daselaar, & Cabeza, 2005; Ranganath, et al., 2004; Ranganath, et al., 2003; Rauchs, et al., 2008; R. Sperling, et al., 2003; Staresina & Davachi, 2006; Tendolkar, et al., 2007; Uncapher, Otten, & Rugg, 2006; Wagner, Schacter, et al., 1998; Weyerts, Tendolkar, Smid, & Heinze, 1997). However, the specific role of MTL and PFC substructures remains a topic of debate.

The finding of MTL and PFC involvement in human imaging studies of associative encoding agrees with the known anatomical connections between these two regions. Anterograde and retrograde tracing studies in monkeys have shown bidirectional direct and indirect connections between specific regions of the MTL and PFC (Arikuni, Sako, & Murata, 1994; Carmichael & Price, 1995; Goldman-Rakic, Selemon, & Schwartz, 1984; Kondo, Saleem, & Price, 2005; Petrides & Pandya, 2002; Price, 2007). In humans, connections between dorsolateral (DLPFC) and ventrolateral (VLPFC) regions of PFC and the hippocampus / parahippocampal region have also been shown using fMRI and diffusion tensor imaging (Takahashi, Ohki, & Kim, 2007). Using a multimodal approach with data collected using fMRI, electroencephalography (EEG), and repetitive transcranial magnetic stimulation (rTMS), Gazzaley & D'Esposito (2007) were able to build on the known anatomical connections to show an interaction in which PFC had a top-down modulatory effect on visual association cortex and parahippocampal cortex during scene-selective processing. Based on these findings of connectivity and interaction between PFC and MTL regions, the involvement of both regions in associative encoding has a structural and functional foundation.

Most prior studies investigating relational or associative memory encoding have used temporally concurrent stimulus pairs. Such studies have reported robust PFC and MTL activity for encoding concurrent pairs of visual photographs (Henke, Buck, Weber, & Wieser, 1997), complex scenes (Montaldi, et al., 1998), pictures (Pihlajamaki, et al., 2003), face-names (Chua, et al., 2007; R. Sperling, et al., 2003; R.

A. Sperling, et al., 2001), words (Haskins, et al., 2008; Jackson & Schacter, 2004; Park & Rugg, 2008), and object-locations (Sommer, Rose, Glascher, Wolbers, & Buchel, 2005; Sommer, Rose, Weiller, & Buchel, 2005). There are limitations, however, to using concurrently presented stimuli. Comparing associative encoding of two stimuli to single item encoding is confounded by differences in the amount of material being presented and encoded. Additionally, when the two stimuli are presented concurrently, multiple processes are occurring at once: encoding of one stimulus, encoding of the other stimulus, associating the stimuli, and encoding this association. It is, therefore, difficult to parse the relative contributions of different brain regions or neurological responses to each process.

Associative Encoding Across a Temporal Delay

In the real world, stimuli that need to be associated and remembered together are not always experienced simultaneously, but instead are often encountered across time. Therefore, it is essential for people to be able to associate or bind items across a temporal delay. Up until recently, this process of forming associative memories for temporally discontiguous items had been largely ignored. A study by Murray & Ranganath (2007) had subjects encode two sequentially presented words with a relational or item-specific question accompanying the second word. This paradigm separated the encoding of the first word from the encoding of the second word; however, the relational question was presented concurrently with the second word,

and, consequently, regional activity in response to associative instruction could not be separated from regional activity in response to associative binding. Although the authors reported PFC and MTL involvement in associative encoding, they were unable to dissociate the involvement of each region to different aspects of the processing, i.e., response to associative instruction versus binding. This unknown drove the general goal of this dissertation, which was to examine, in humans, the successful and attempted formation of associative memory for items separated in time.

The first study of this dissertation, presented in Chapter 2, examined the separable contributions of the MTL and PFC in associative encoding of temporally separated items. The associative components that have been entangled in previous studies, i.e., the associative cue and the binding event, were temporally separated in this novel paradigm using sequential presentation of single items with or without intervening associative instruction. By separating these processes, it was discovered that PFC and MTL regions subserve different functions in maintenance and binding of visual stimuli into long-term associative memory, where frontal regions were modulated by the presence of associative instructions and the MTL was modulated only during binding. However, questions remained regarding whether such differences in activity are predictive of successful encoding.

The second study of this dissertation, presented in Chapter 3, was designed to address these questions by examining MTL and cortical activity in relation to successful or unsuccessful associative encoding of temporally separated items. In

order to form lasting associative memories for items presented over time, there must be some degree of cooperation between brain regions involved in working memory and long-term memory processing. Nevertheless, how regions involved in working memory processing contribute to bridging the temporal gap between to-be-associated items had not been thoroughly explored. Using the same task as the first study (described in Chapter 2), encoding of an item under associative instruction was examined with respect to subsequent associative- and item-memory performance. Successful item encoding, in the absence of remembered associative information, involved posterior cortical regions, whereas successful associative encoding involved the coordination of frontoparietal working memory regions and the hippocampus. Additionally, a model for how these structures work together to successfully form long-term associative memories for temporally discontiguous items was proposed.

The first two studies (described in Chapters 2 and 3) addressed existing questions in the field of episodic memory concerning the involvement of working memory and long-term memory structures in associatively encoding items separated in time. However, uncertainties regarding the temporal contribution of these structures remained. The first study described PFC involvement in the maintenance period following associative instruction with added involvement during binding. The second study added information regarding the importance of frontoparietal working memory activity for successful associative encoding. What remained unknown was at what time points, across the entire encoding event, regional activity was predictive of subsequent item and associative memory. The goal of the third study of this

dissertation, presented in Chapter 4, was to address this question regarding the timing of regional involvement in associative memory formation.

Human studies examining the MTL have reported a functional dissociation and separable contribution of particular MTL substructures, where anterior regions are involved in forming associative memories (Aminoff, Gronau, & Bar, 2007; Chua, et al., 2007; Jackson & Schacter, 2004; Mayes, Montaldi, & Migo, 2007; Peters, Suchan, Koster, & Daum, 2007; Pihlajamaki, et al., 2003; Rauchs, et al., 2008; R. Sperling, et al., 2003; Staresina & Davachi, 2006, 2009, 2010; Taylor, Moss, Stamatakis, & Tyler, 2006) and posterior regions are involved in forming visual item memories (Kirchhoff, Wagner, Maril, & Stern, 2000; Peters, et al., 2007; Rauchs, et al., 2008). However, there is debate on this issue as other studies have argued that the associative versus item encoding distinction instead lies between hippocampal and perirhinal structures, respectively (Chua, et al., 2007; Staresina & Davachi, 2008). Nevertheless, animal studies have also reported electrophysiological and anatomical dissociations of MTL substructures (Furtak, Wei, Agster, & Burwell, 2007; Higuchi & Miyashita, 1996; Sakai & Miyashita, 1991; Suzuki & Amaral, 1994b).

Chapter 4 presents the third study of this dissertation, which examines, across the entire encoding event, medial temporal and prefrontal regions involved in associative encoding of temporally separated items with attention to delay period activity and subsequent associative memory effects. By using a fixed delay period length within pairs, the complete encoding event, beginning with the onset of the first

item through the offset of the second item, could be explored. Left frontal and lateral occipital activity was predictive of successful associative binding once the second stimulus of the pair was presented and the items could be associated. This same pattern of activity was also seen in anterior MTL regions of left perirhinal and entorhinal cortices. In all four of these structures with activity predictive of associative encoding, when item memory strength was held constant, activity increased during associative binding, and not during maintenance. These findings addressed unanswered questions regarding the time course of regional involvement in associative encoding of temporally discontiguous visual object pairs. Additionally, this study showed the selective role of perirhinal and entorhinal cortex in associative binding, and not in maintenance.

Associative Encoding Strategy

The studies discussed in Chapters 2-4 examined the different processes involved in forming associative memories for visual objects presented across a temporal delay. In these studies, subjects were permitted to use any associative strategy that came most naturally to them, allowing examination of general robust group effects that dominate over any individual differences. However, it became clear, anecdotally, that subjects were using different strategies, often either in the more visual or more verbal domain, which led to questions regarding the effects of using visual versus verbal strategies. Although associative encoding studies often use visual

and/or verbal stimulus-types, few studies have directly manipulated the use of different associative strategies to examine how brain regions are differently engaged in and related to successful encoding. The use of different stimulus-types has been shown to influence subsequent memory effects, where visual or picture-based encoding involves regions including right prefrontal, superior parietal, lateral occipital, and fusiform cortices (Achim, Bertrand, Montoya, Malla, & Lepage, 2007; Bernstein, Beig, Siegenthaler, & Grady, 2002; Brewer, et al., 1998; Cansino, Maquet, Dolan, & Rugg, 2002; Deshpande, Hu, Lacey, Stilla, & Sathian, 2010; Ferber, Humphrey, & Vilis, 2005; Fletcher, et al., 2002; Gottlieb, Uncapher, & Rugg, 2010; Grill-Spector, Kourtzi, & Kanwisher, 2001; Harrison & Tong, 2009; Hocking & Price, 2009; Kohler, Moscovitch, Winocur, & McIntosh, 2000; Lacey, Flueckiger, Stilla, Lava, & Sathian, 2010; Lee, Robbins, Pickard, & Owen, 2000; Rama, Sala, Gillen, Pekar, & Courtney, 2001; Rugg, Otten, & Henson, 2002; Uncapher & Wagner, 2009; Wagner, Poldrack, et al., 1998), while verbal, word-based encoding often involves regions including left inferior frontal, parietal, superior temporal, lingual, and medial frontal cortices (Baker, Sanders, Maccotta, & Buckner, 2001; Demb, et al., 1995; Fletcher, Stephenson, Carpenter, Donovan, & Bullmorel, 2003; Grady, McIntosh, Rajah, & Craik, 1998; Heun, et al., 1999; Hocking & Price, 2009; Iidaka, Sadato, Yamada, & Yonekura, 2000; Kapur, et al., 1994; Kapur, et al., 1996; Kirwan, Wixted, & Squire, 2008; Kohler, et al., 2000; Park & Rugg, 2008; Prabhakaran, Narayanan, Zhao, & Gabrieli, 2000; Rama, et al., 2001; Rugg, et al., 2002; Uncapher & Wagner, 2009; Wagner, Poldrack, et al., 1998). Nevertheless, it remained unclear whether visual and verbal

strategies might similarly influence regional subsequent memory effects when stimulus-type is held constant.

The fourth study described in this dissertation, presented in Chapter 5, directly examined this question regarding the effect of associative encoding strategy. While encoding visual, nameable object pairs, subjects utilized either a visual or verbal associative strategy. Brain regions involved in encoding using a visual versus verbal strategy were very similar to those that have been reported to be engaged during the encoding of visual versus verbal stimuli, respectively. This finding suggests that the regional effects are not fixed to the stimuli encountered, but are driven by the strategy being employed. The discovered flexibility of this system has potential clinical relevance in its implications for rehabilitation strategies for patients with regional brain damage or neurodegenerative disease. This possibility was probed in two patients with focal lesions localized to left inferior frontal lobe due to a very recent stroke. Behavioral results indicated that while using the verbal strategy further impaired performance, using the visual strategy improved one patient's performance beyond that when using her own natural associative encoding strategy. This outcome illustrates a potential clinical approach for treatment of domain-related cognitive impairment and associated memory impairment in patients with focal brain damage due to trauma, stroke, or neurodegenerative disease, in that memory might be improved through an adaptive strategy designed to avoid damaged brain regions and engage spared regions.

Bringing Space into Associative Visual Object Memory Formation

The first three studies described in this dissertation, in Chapters 2-4, thoroughly examine attempted and successful formation of associative memories for temporally discontiguous visual objects. The fourth study, in Chapter 5, addressed how the use of different associative strategies affects regional involvement in visual stimulus processing and subsequent associative memory effects. What happens, however, when associative encoding of visual objects involves the spatial domain?

Human imaging studies examining working and long-term memory encoding of visuospatial associations have reported frontoparietal involvement (Bledowski, Kaiser, & Rahm, 2010; Cansino, et al., 2002; Diwadkar, Carpenter, & Just, 2000; Gould, et al., 2005; Gould, Brown, Owen, ffytche, & Howard, 2003; Hannula & Ranganath, 2008; Haxby, et al., 1991; Haxby, Petit, Ungerleider, & Courtney, 2000; Piekema, Rijpkema, Fernandez, & Kessels, 2010; Sala, Rama, & Courtney, 2003; Schon, Tinaz, Somers, & Stern, 2008; Sommer, Rose, Glascher, et al., 2005; Sommer, Rose, Weiller, et al., 2005). Such findings have been supported by reviews of spatial encoding in the human (Postma, Kessels, & van Asselen, 2008), monkey (Ungerleider, Courtney, & Haxby, 1998), and rat (Kesner, 2009). A dorsal frontoparietal network has additionally been implicated in controlling top-down, goal-directed attention during visuospatial encoding (Cabeza, Ciaramelli, Olson, & Moscovitch, 2008; Corbetta & Shulman, 2002; Uncapher & Wagner, 2009). What remained unanswered

was how dorsal frontal and parietal regions each contribute to forming visuospatial associative memories. The fifth and final study of this dissertation, described in Chapter 6, was designed to address this question.

A task design, similar to that used in the first three studies, was used to temporally separate the spatial cue from the object. This time, instead of using two visual objects, the first item was a spatial cue, and the second item was a visual object. The encoding of the object could be isolated with respect to whether the spatial cue had location information present or absent, and if present, whether that location was successfully or unsuccessfully associated with the remembered object. When the object was remembered with high confidence, superior parietal regions were modulated by the attempt to associate spatial information, regardless of binding success. In contrast, greater involvement of frontal regions was predictive of successful object-location binding. By temporally separating the location cue from the object being encoded allowed the relative contributions of frontal and parietal regions to visuospatial encoding to be disentangled.

Summary

Although examining associative memory encoding in humans using fMRI is currently a popular area of research, many questions remain unanswered. The studies that comprise this dissertation were carefully designed to address many of these questions. Together, these studies have teased apart the regional involvement of MTL

and other cortical structures in the attempted and successful formation of associative memory for temporally discontiguous visual objects and object-location stimuli. The findings suggest cooperation of brain regions involved in working memory processing and long-term memory encoding during the binding of items separated in time and have shed some light on the timing of associative memory formation. Additionally, the findings have elucidated the driving effects that strategy has on the brain regions recruited for encoding, which exposes potential avenues for clinical treatment development for patients who suffer from memory and other cognitive impairments due to neurological damage and disease.

CHAPTER 2:

DISSOCIATION OF FRONTAL AND MEDIAL TEMPORAL LOBE ACTIVITY IN MAINTENANCE AND BINDING OF SEQUENTIALLY PRESENTED PAIRED ASSOCIATES

Abstract

Substructures of prefrontal cortex (PFC) and medial temporal lobe are critical for associating objects presented over time. Previous studies showing frontal and medial temporal involvement in associative encoding have not addressed the response specificity of these regions to different aspects of the task, which include instructions to associate and binding of stimuli. This study used a novel paradigm to temporally separate these two components of the task by sequential presentation of individual images with or without associative instruction; fMRI was used to investigate the temporal involvement of PFC and parahippocampal cortex (PHC) in encoding each component. While both regions showed an enhanced response to the second stimulus of a pair, only PFC had increased activation during the delay preceding a stimulus when associative instruction was given. These findings present new evidence that prefrontal and medial temporal regions provide distinct temporal contributions during associative memory formation.

Introduction

Animal-lesion models and studies involving patients with selective damage to structures of the medial temporal lobe (MTL) have demonstrated critical involvement of this brain region in the encoding and retrieval of long-term declarative memory, the memory for facts and events (Squire, 1992). Multiple studies have demonstrated particular involvement of the parahippocampal cortex (PHC) in successful memory formation (Brewer, et al., 1998; Davachi, et al., 2003; Davachi & Wagner, 2002; Eichenbaum, et al., 2007; Gold, et al., 2006; Henke, et al., 1997; Kirwan & Stark, 2004; L. J. Murray & Ranganath, 2007). Neuroimaging and neuropsychological studies of patients with damage to the prefrontal cortex (PFC) have also suggested the contribution of PFC to the encoding of long-term memory (LTM) (Blumenfeld & Ranganath, 2007; Brewer, et al., 1998; L. J. Murray & Ranganath, 2007; R. Sperling, et al., 2003; Wagner, Schacter, et al., 1998). While imaging studies have commonly reported PFC and PHC activity in lockstep during associative encoding, the hypothesis of the present study was that activity in these two regions is dissociable, with PFC activity preceding PHC activity, supporting a mechanism for top-down modulation of MTL structures involved in associative encoding.

Anatomical studies using anterograde and retrograde tracing techniques in monkeys (Goldman-Rakic, et al., 1984) and imaging methods combining functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) in humans (Takahashi, et al., 2007) examined the connectivity between PFC and PHC. Both studies reported direct and indirect anatomical connections between subregions of

PFC and PHC. Recently, Gazzaley and D'Esposito (2007) examined the process of top-down modulation from PFC to visual association cortex and PHC during scene-selective processing. The top-down influence of prefrontal activity upon parahippocampal activity is consistent with the anatomical connectivity between these brain regions.

A recent fMRI study examined PFC activity using an associative memory paradigm in which two sequentially presented words were associated when the presentation of the second word was accompanied by a relational question and not associated when accompanied by an item-specific question (L. J. Murray & Ranganath, 2007). Greater activation of left PHC, dorsolateral-prefrontal cortex (DLPFC), and ventrolateral-prefrontal cortex (VLPFC) was observed during the encoding of the second presented word in relational trials compared to item-specific trials. As associative instructions were presented concurrently with the second word, increased activation could only be examined at that time point, and functional specificity of PFC and MTL activity could not be addressed. The present study, however, was designed to pursue this question of the particular involvement of these two brain regions in processes recruited for associative encoding.

In nonhuman primates, multiunit recording data suggest that PFC neurons play a role in associating temporally separate stimuli and show delay-period increases in activity (Deco, Ledberg, Almeida, & Fuster, 2005; Fuster, Bodner, & Kroger, 2000). Fuster et al. (2000) conducted extracellular recordings from bilateral regions of dorsolateral frontal cortex while monkeys performed an audio-visual memory task. As

monkeys learned the low tone-green and high tone-red associations, cells in this region showed the same relationship of firing to low and high tones as to green and red colors, respectively, with maintained activity during the delay between tones and associated colors. The presence of delay-period activity in medial temporal regions, however, has been more controversial. Some studies report rarely seen increases in delay-period activity in medial temporal regions such as the parahippocampal cortex in monkeys (Vidyasagar, Salzmann, & Creutzfeldt, 1991) or hippocampus in rats early in the delay-period (Hampson & Deadwyler, 2003), while other studies in monkeys report the presence of delay-period activity in medial temporal regions (Cahusac, Miyashita, & Rolls, 1989; Watanabe & Niki, 1985; Young, Otto, Fox, & Eichenbaum, 1997). Despite the disagreement in the literature regarding MTL activity during the delay-period in associative tasks, there is strong electrophysiological evidence for PFC activity during the delay-period in rats and monkeys.

The present study further examines the involvement of PFC and PHC in the encoding of associative memory compared to single-item memory. Rapid-event-related fMRI was used to identify the temporal involvement of PFC and PHC in encoding sequentially presented images with varying interstimulus intervals (ISIs). A plus-sign presented during some ISIs instructed participants to associate the image preceding and following the plus-sign as a pair. The timing separation between the plus-sign (instructing the subject to pair the previous image with the upcoming image) and the presentation of the second image (at which point the images can be associated) allowed temporal investigation of PFC and PHC involvement in associative memory

encoding. After the scan, participants completed a recognition test examining associative and single-item memory. Based on previous findings, the hypotheses were that PFC and PHC would show greater activation during the encoding of paired versus unpaired images. Prefrontal activity was expected to precede parahippocampal activity supporting top-down influence on PHC.

Materials and Methods

Participants

Thirteen healthy volunteers (mean age = 23.69, 3 men) recruited from the University of California- San Diego (UCSD) community and the surrounding area were enrolled in this study. Participants gave informed consent approved by the UCSD Institutional Review Board and had normal or corrected vision. Twelve additional volunteers (mean age = 25.08, 6 men) were recruited for a behavioral pilot task.

Stimuli

Stimuli included 256 color images of common objects which were presented individually while the participant was in the scanner. A plus-sign appeared between some of the stimuli. An additional 40 novel stimuli were used during the recognition test following the scan. Images were acquired from Rossion and Pourtois color

Snodgrass images (Rossion & Pourtois, 2004) and Hemera object library (Hemera Technologies; Quebec, Canada).

Experimental Procedure

While in the scanner, participants were presented with individual images (each remaining on the screen for 2.5 sec) followed by jittered ISIs ranging from 0.5-11 sec (Figure 1A). Jitter was calculated to optimize the design (Dale, 1999; Dale & Buckner, 1997). Immediately following some of the images, a plus-sign appeared in the center of the screen for 0.5 sec. Participants were asked to remember the presented images and, if an image was followed by a plus-sign, to associate the image with the subsequent image as a pair. Participants were given a button box and were asked to press one button if the image represented a living object and the other button if the image represented a non-living object. Image stimuli were presented in a series of four runs, each lasting 362 sec and containing 64 images. Over all four runs, 130 images were included in associated pairs and 126 images were unpaired. The presentation of stimuli varied pseudorandomly between paired and unpaired stimuli. For analysis purposes, but unannounced to the participants, paired and unpaired items were presented sequentially in multiples of two. For simplicity, stimuli preceding a plus-sign will be denoted as “1P,” and the stimuli following the plus-sign as “2P.” After a “2P” stimulus, the next image could be a “1P” (which would then be followed by a plus-sign and a “2P”), or the next image could be an individual unpaired stimulus,

denoted “1U” for unpaired. “1U”s were always followed by “2U”s. This terminology is used in Figure 1 and throughout the analysis.

Following the scan, participants completed a recognition test (Figure 1B). Participants were shown an image and were asked to rate how well they remembered seeing that image during the scanner presentation, 1 being “poorly” and 5 being “very well.” This question was asked for each of the 256 images that the participant was shown while in the scanner plus 40 additional novel images. After rating each image, participants were shown two additional images, labeled “1” and “2,” and were instructed to identify the pair of the originally presented image or to identify the original image as unpaired (option labeled “3”). If the original image was novel, this question was skipped all-together and the next recognition image was presented. The post-scan recognition test lasted approximately 30 min.

Functional MRI Parameters

Participants were scanned using a 3-T GE scanner at the Keck Center for Functional MRI at the University of California, San Diego. Functional images were acquired using a gradient-echo, echo-planar, T2*-weighted pulse sequence (repetition time = 1.5 sec; one shot per repetition; echo time = 30; flip angle = 90°; bandwidth = 31.25 MHz). Twenty-two slices covering the brain were obtained perpendicular to the long axis of the hippocampus with 4 x 4 x 7 mm voxels. T1-weighted structural scans were acquired in the same plane as the functional scans and of the same voxel size.

Structural images were also acquired using high resolution T1-weighted (1 x 1 x 1 mm) magnetization-prepared rapid gradient echo sequence.

Data Analysis

Data from each run were reconstructed using the AFNI (Cox, 1996) suite of programs. Slices were aligned temporally and then co-registered using a three-dimensional image alignment algorithm. A threshold mask of the functional data was used to eliminate voxels outside the brain. Series of functional images from separate runs were corrected for motion and concatenated. Two general linear models were constructed using multiple regression analysis. Each model included six motion regressors obtained from the registration process and additional task related regressors in which impulse responses were modeled from the data for each of the stimulus conditions. The first general linear model included regressors for 1P, 2P, 1U, 2U condition correct and incorrect responses. The second general linear model included regressors for paired trials (1P and 2P with an ISI of 3.5 sec) and unpaired trials (1U and 2U with an ISI of 3.5 sec) (Daselaar, et al., 2008; Schluppeck, Curtis, Glimcher, & Heeger, 2006). An ISI of 3.5 sec was selected because it was the most frequent jitter interval and allowed sufficient measurements for analysis. In addition, parameter estimates for all delay periods between two paired images with remembered associative properties were analyzed relative to all delay periods between two unpaired images using repeated measures ANOVA.

Only paired and individual unpaired images correctly identified during the post-scan recognition test were included in the analysis of fMRI data. The hemodynamic response function was derived from the fMRI data using signal deconvolution and a defined time window following stimulus onset (Cox, 1996). This time window was from 0 to 15 sec for single stimulus events, and 0 to 21 sec for two-stimulus trials with 3.5-sec ISIs. Standard landmarks were defined manually on the anatomical scans. Data from the anatomical and functional scans were then transformed into Talairach space (Talairach & Tournoux, 1998) by AFNI using nearest-neighbor interpolation. No spatial smoothing was performed. The areas under the hemodynamic response function for the following conditions were examined using voxelwise *t* tests (two-tailed) carried out across all 13 participants: (1) 2P versus 2U, (2) trials with two paired images with an ISI of 3.5 sec (with a plus-sign present for the first 0.5 sec of the ISI) versus trials with two unpaired images with an ISI of 3.5 sec. Given the reduced number of trials with an ISI of 3.5 sec, all trials were included in this analysis. A voxelwise threshold of $p < .01$ was used to identify significant regional activity. Analyses were restricted to clusters containing at least 4 voxels connected by face surfaces, yielding a significance value of $p < .01$ when corrected for multiple comparisons across the whole brain. These clusters were used to create impulse-response plots displaying the temporal characteristics of the activation.

Results

Behavioral Pilot Task

A behavioral pilot task was conducted to evaluate whether an instructional cue can effectively manipulate episodic associative memory for items presented sequentially and to ensure that incidental associations are not being made between proximally presented unpaired images. Following the encoding task, which was the same as was used for the imaging study, participants completed a postscan recognition task similar to that used in the current experiment, except for that they were asked which of two images was presented closest in time to the image they just saw during the previous item memory question. Participants identified the item presented adjacent in time when no associative cue had been presented at a low rate (60 ± 4%), significantly below their performance in identifying the item presented adjacent in time when an associative cue had been presented (81 ± 6%; $p < .001$, $t = 6.623$).

Behavioral Analysis

Eighty-two percent (± 3%) of paired stimuli were recognized with a high degree of confidence (subject response of 4 or 5), and for those recognized items, the correct associated pair was identified at a rate of 71% (± 4%). Unpaired items were recognized with a high degree of confidence at a rate of 73% (± 4%). Data for

correctly identified paired and unpaired items were included in the fMRI analysis. Subjects incorrectly identified novel images as recognized at a rate of 11% (± 3%).

fMRI Analysis

Based on previous studies that have found activation in the MTL structures as well as in regions of PFC during the encoding of associated items (Dickerson, et al., 2007; Dolan & Fletcher, 1997; Gold, et al., 2006; Henke, et al., 1997; Law, et al., 2005; Meltzer & Constable, 2005; L. J. Murray & Ranganath, 2007; Pihlajamaki, et al., 2003; Prince, et al., 2005; Rombouts, et al., 1997; R. Sperling, et al., 2003; Staresina & Davachi, 2006; Tendolkar, et al., 2007; Yonelinas, Hopfinger, Buonocore, Kroll, & Baynes, 2001), analysis was focused on these brain regions. For the present study, parahippocampal regions were predicted to show greater activation during the encoding of the 2P stimuli (items paired with the preceding stimulus) than during the encoding of 2U stimuli (items not paired with the preceding stimulus and which only follow unpaired stimuli). Prefrontal regions, specifically the DLPFC and the VLPFC, were also predicted to show increased activation during the encoding of 2P stimuli.

Activation during the viewing of 2P stimuli was compared to activation during the viewing of 2U stimuli. This contrast between processing 2P versus 2U stimuli revealed left PHC activation ($p < .01$; Figure 2A, B). The impulse response curve for 2U indicated PHC activity during single item encoding as well as during associative

encoding; however, the activity in this region was greater during the encoding of 2P stimuli (Figure 2C).

Previous studies reported that DLPFC (Brodmann's area 9, 46) is active during encoding of individual items (Brewer, et al., 1998; Staresina & Davachi, 2006), and such activity is further increased by associative memory conditions (L. J. Murray & Ranganath, 2007). Consistent with these findings, greater activation of DLPFC during encoding of 2P stimuli relative to the encoding of 2U stimuli was observed ($p < .01$; Figure 3A, B). Similar to PHC involvement, DLPFC was active during the encoding of all remembered images; however, the activation was greatly enhanced during associative encoding of 2P (Figure 3C). Activity in VLPFC was also analyzed for this contrast between the encoding of 2P stimuli and 2U stimuli. Similar to activity in DLPFC, there was an increase in activation in VLPFC (Brodmann's area 44, 45, 47) during the encoding of 2P stimuli ($p < .01$; Figure 3A, B). However, VLPFC did not show significant activity for 2U stimuli ($p > .05$). Examination of the time-course of activity in VLPFC also showed a small response for 2U stimuli that did not reach significance (Figure 3D). A complete list of regions of activation for this contrast is listed in Table 1.

Analyses were also performed comparing activity during the encoding of trials with two paired images versus trials with two unpaired images, allowing for the examination of activity differences during the ISI. The time-course of activity was examined beginning with the presentation of the first paired (1P) or unpaired (1U)

image followed by a 3.5-sec ISI and the presentation of the second image (i.e., 2P or 2U, respectively). Although ISIs varied between 0.5 and 11 sec due to jitter, trials with 3.5-sec ISIs were used for this comparison. The same functional regions of interest as were previously discussed were also predicted to be important in this contrast.

The comparison between the encoding of two paired stimuli and two unpaired stimuli showed increased activity in two frontal regions, left DLPFC (Figure 4A, B) and left medial frontal cortex (Figure 4E, F) during the paired trials ($p < .01$). The time course of activity in left DLPFC showed a similar response for 1P and 1U (4.5-7.5 sec). In the unpaired trial, the activation decreased during the ISI and then increased during the presentation of 2U with a time-course similar to that of 1U. In contrast, the paired trial showed sustained DLPFC activity throughout the ISI and rising further with the onset of 2P (Figure 4C). The time-course of activity during paired and unpaired trials diverged at 7.5 sec, corresponding to the instruction to associate the 1P stimulus with the following stimulus. The larger activation during the encoding of 2P relative to that of 2U, seen in Figure 4C, was the result of increased size of response in addition to the increase in baseline (revealed when all jittered ISI trials are analyzed with separate covariates for paired and unpaired ISIs modeled as sustained responses; Figure 4D).

Left medial frontal cortex showed a similar increase in activity following the plus-sign in the paired trials (Figure 4E, F). Much like left DLPFC, the response curve for left medial frontal cortex showed a matched response for 1P and 1U, with

divergence occurring at the instruction to associate and a further increase in response during the presentation of 2P (Figure 4G). Figure 4H illustrates the larger left medial frontal response during the encoding of 2P than during 2U. For a complete list of regions of activation for this contrast, see Table 2.

No significant clusters were identified in PHC using the comparison of the above subset of trials containing two paired or two unpaired stimuli with 3.5-sec ISIs ($p > .05$). In addition, when ISIs spanning all delay periods were analyzed, left DLPFC showed a significant increase in activity during the delay period between two paired images ($p < .05$, $t = 2.195$). However, there was no significant difference in activity during the delay periods between paired images and between unpaired images in left PHC ($p = .51$, $t = 0.673$). An interaction analysis between these two delay period conditions for each brain region showed a significant region by condition interaction ($p < .05$).

Discussion

The present study is the first to examine temporal contributions of PFC and PHC in associative memory encoding by separating the associative instruction from the time at which binding may occur. Activity in PFC and PHC was analyzed while subjects were instructed to encode sequentially presented stimuli as paired or as separate items. Contrasts between the encoding of 2P and 2U stimuli and the encoding of paired and unpaired trials with a 3.5-sec ISI were examined. Left PHC and DLPFC

were active for all correctly encoded stimuli, with increased activity during 2P encoding versus 2U encoding. In contrast, left VLPFC was significantly active during 2P, but not during 2U encoding.

Declarative memory encoding with associative instruction

In the present study, participants were instructed only to associate two stimuli when a plus-sign intervened; all other stimuli were to be remembered as single items. Although it is possible that associations can develop between sequentially presented images with or without associative instruction, episodic associative memory was improved by the presence of the cue. In addition, subsequent recognition of individual stimuli was improved by the presence of the cue (paired items recognized at a rate of 82%, and unpaired items recognized at a rate of 73%, $p < .01$). Thus, the instruction to associate modulates episodic memory performance along with its enhancement of brain activity.

Using sequential presentation of single images, semantic information was balanced across stimuli. However, the instruction to associate may engage verbal processes when nameable stimuli are used. It is possible that using nonverbal stimuli could result in different patterns or degrees of left frontal lobe activation. The left lateralization reported in the present study with namable stimuli is, on one hand, similar to that reported in other encoding studies using verbal stimuli (Blumenfeld & Ranganath, 2007; L. J. Murray & Ranganath, 2007; R. Sperling, et al., 2003; Wagner,

Schacter, et al., 1998). On the other hand, the data are also in agreement with the revised Hemispheric Encoding/Retrieval Asymmetry model (Habib, Nyberg, & Tulving, 2003), which would predict left-sided activation for encoding regardless of stimulus type. The paradigm presented here could be adapted to address such questions through the use of nonverbal stimuli.

Increased PHC activity during associative encoding

The involvement of particular MTL substructures in various aspects of LTM is debated in the literature (Eichenbaum, et al., 2007). The present study showed PHC activity during encoding of individual images and pairs of associated images; however, this region showed selectivity through an increased response during associative encoding relative to individual-item encoding. These results complement other studies demonstrating PHC involvement in item encoding with enhanced activity during associative encoding (Kirwan & Stark, 2004; L. J. Murray & Ranganath, 2007). Using a different paradigm where three words were presented concurrently under instructions to repeat the words throughout the trial or to order the words according to their desirability, different patterns of brain activity were reported (Davachi & Wagner, 2002). Bilateral hippocampus was active for both encoding tasks, whereas right entorhinal and bilateral parahippocampal gyri were more active during the repetition task. While only the reordering task is described as using relational processing, both tasks could involve associative encoding. The cognitive strategies

adopted to perform each type of task, however, will differ. The current study, which requires the association of two namable visual stimuli, involves a cognitive strategy that is perhaps more similar to the repetition condition than to the reorder condition of the previous study (Davachi & Wagner, 2002). Therefore, the presence of parahippocampal activity in both the present study and in the repetition task in the previous study could reflect a common strategy.

PFC activity and dissociation of substructures

Results from the current study showed increased DLPFC and VLPFC activity during the encoding of stimuli under associative conditions and revealed that enhancement of DLPFC activity begins at associative memory instruction. The noted further increase in DLPFC and VLPFC activity during 2P stimuli agrees with the present literature. DLPFC is also active during the encoding of unpaired stimuli, whereas VLPFC does not significantly respond to unpaired stimuli. This dissociation differs from previous results examining regional specificity within PFC.

Previous studies have examined dissociations between regions of PFC in relational and item-specific memory encoding (Blumenfeld & Ranganath, 2006; L. J. Murray & Ranganath, 2007). In an fMRI study using pairs of sequentially presented words, the second word was accompanied by a question prompting the participant to (1) relate the two words together (‘relational trial’) or (2) semantically evaluate the second word (‘item-specific trial’) (L. J. Murray & Ranganath, 2007). A dorsal-ventral

dissociation was reported in lateral PFC activation. Both regions showed increased activation for encoding relational words versus item-specific words. VLPFC activity also predicted both successful relational and item-specific encoding, whereas DLPFC activity only predicted successful relational encoding. An earlier study examined the function of DLPFC in LTM formation using a paradigm where three words were presented with the instruction either to rehearse the words or to reorder them according to the weight of the object (Blumenfeld & Ranganath, 2006). Based on results showing increased DLPFC activity during the encoding of reorder trials relative to rehearse trials and for the encoding of reorder trials where words were subsequently remembered, this study concluded that DLPFC is involved in encoding organizational information. There are, however, several key differences between the current study and previous studies examining sub-regional contributions of PFC to LTM.

The purpose of the present study was to examine the contributions of PFC and PHC in the encoding of pairs of associated images versus the encoding of unpaired images. Differences in activation between remembered compared to forgotten images was not the focus of the current study, and will be a topic of future investigation. Only correctly encoded images, as determined by the recognition task, were included in the analysis. A design optimized to examine subsequent memory-related activity might reveal different results. For example, activity seen in DLPFC for the encoding of unpaired images might not differ based upon subsequent memory performance. Such

results would then support previous findings of DLPFC activity predicting successful associative, and not individual-item, encoding.

Results from the current study show that VLPFC does not significantly respond to the encoding of subsequently remembered unpaired images. These observations appear to differ from those of previous studies, which report VLPFC involvement in successful encoding of relational and item-specific memory (L. J. Murray & Ranganath, 2007) and memory for word rehearsal and reordered words (Blumenfeld & Ranganath, 2006). However, small differences in VLPFC-cluster location may be relevant. The location of DLPFC activity (BA 46, 9) in the present study is very similar to the location of DLPFC activity in the previous studies, but the peak location of VLPFC activity (BA 45) is more anterior in the present study. One study separated VLPFC into two different clusters, anterior VLPFC (BA 47, 45), with a location similar to the current study, and posterior VLPFC (6, 44), and while both clusters were predictive of subsequent memory for reorder trials, only the posterior cluster was predictive of subsequent memory for rehearse trials (Blumenfeld & Ranganath, 2006). Another study that also reports VLPFC activation predictive of subsequent memory for item-specific trials also describes a VLPFC cluster that appears more posterior than the VLPFC cluster in the present study (L. J. Murray & Ranganath, 2007).

The points discussed earlier in the discussion concerning the differences between three-word-reordering/rehearsal paradigms and the present paradigm

regarding activation in PHC, are also relevant when discussing dissociations in PFC activity. Rehearsing and reordering words may each involve associative memory, with reordering implementing additional working memory components. Rehearsal could establish a phonological association, while reordering may create visual and spatial associations. While both types of trials may involve associative memory formation, each may utilize different organizational strategies resulting in differential VLPFC activity. In contrast, DLPFC has been shown to be involved in task-switching (Loose, Kaufmann, Tucha, Auer, & Lange, 2006; Smith, Taylor, Brammer, & Rubia, 2004; Sylvester, et al., 2003; Vanderhasselt, De Raedt, Baeken, Leyman, & D'Haenen, 2006). The above studies examining associative memory formation, as well as the present study, require a switch in task as instructed by a cue, which may contribute to the overlapping activity of DLPFC despite the differences in study design.

Top-down influence of PFC on PHC activity

The sequential presentation of stimuli and an intervening plus-sign allowed for temporal separation of the neural activity related to (1) instructions to associate and (2) presentation of the second stimulus required to form the association. Following the plus-sign, left DLPFC and medial frontal cortex showed a sustained increase in activation relative to ISIs without a plus-sign (during which, activity in these regions returned to baseline; Figure 4C, G). Left PHC activity was not significantly different during the ISIs in paired and unpaired conditions ($p = .51$). These results suggest that

left DLPFC and left medial frontal cortex are involved in maintaining 1P in working memory to create the association once 2P is presented.

When 2P is presented, increased activity is observed in left DLPFC, medial frontal cortex, and PHC compared to the response to 2U. Left VLPFC is also active during the encoding of 2P, but does not show a significant response to 2U (Figure 3D). These results suggest that left DLPFC, VLPFC, medial frontal cortex, and PHC are involved in associating the two paired stimuli. Left DLPFC and medial frontal cortex also show increased activity in the paired trials starting at the plus-sign and continuing through the ISI (blank screen) and 2P, whereas left PHC and VLPFC show increased activity beginning at the presentation of 2P. The dynamics of encoding activation across DLPFC/medial frontal cortex and PHC/VLPFC demonstrate the temporal characteristics of functional interaction between these regions in associative encoding.

Increases in PFC activity during the delay-period under associative instruction support results from electrophysiology studies using nonhuman primates (Deco, et al., 2005; Fuster, et al., 2000). Fuster et al. (2000) reported PFC neuronal activity in the delay-period during the association of tones and colors. Similarly, the present study shows increased PFC activity in the delay-period during the association of two visual stimuli using human functional imaging (Figure 4). Electrophysiological evidence of MTL activity in rats and nonhuman primates during the delay-period is less consistent, with some studies reporting the presence of MTL activity (Cahusac, et al., 1989;

Watanabe & Niki, 1985; Young, et al., 1997) and others reporting very rare MTL activity (Hampson & Deadwyler, 2003; Vidyasagar, et al., 1991). Such discrepancies in MTL delay-period activity may be the result of subtle differences in tasks. Nevertheless, two of the studies using delayed nonmatch-to-sample in rats also reported divergent results. Further study is required to examine the circumstances in which sustained MTL delay period activity may be present in rats, monkeys, and humans. In the current study, no significant increase in MTL activity was observed during the delay-period between paired stimuli.

Previous studies have shown direct and indirect anatomical connections between PFC and PHC using anterograde and retrograde tracing techniques in rhesus monkeys (Goldman-Rakic, et al., 1984) and using DTI and fMRI in humans (Takahashi, et al., 2007). Furthermore, top-down modulation from PFC to PHC has been examined using human imaging techniques, including fMRI, electroencephalography (EEG), and transcranial magnetic stimulation (TMS). Gazzaley and D'Esposito (2007) employed a visual working memory task for scenes with constant sensory input for all conditions to control bottom-up processing and isolate top-down mechanisms of enhancement and suppression. Event-related fMRI and EEG measured enhanced activity relative to passive baseline in scene-specific visual association areas (parahippocampal/lingual gyrus) when subjects were told to remember scenes and to ignore faces. When opposite instructions were given, these regions showed suppressed activity. This effect demonstrated top-down modulation of PHC. Further research is examining whether PFC is critical for modulating PHC

activity; preliminary results using repetitive-TMS to disrupt PFC activity and studies using working memory tasks that challenge PFC function suggest that disrupted PFC activity results in deficits in top-down suppression (Gazzaley & D'Esposito, 2007).

The current study shows that the PFC and PHC responses to a visual stimulus change depending upon the presence or absence of preceding associative instruction. Enhanced prefrontal activity at the presentation of associative instruction and the resulting enhancement of PFC and PHC activity during the following stimulus correspond to improved subsequent memory for that item as well as for the association. These findings reveal that frontal and medial temporal regions subserve different functions in maintaining and binding visual stimuli into long-term associative memory.

Acknowledgments

Chapter 2, in full, is a reprint of the material as it appears in Journal of Cognitive Neuroscience, 2009. Hales, Jena B.; Israel, Sarah L.; Swann, Nicole C.; Brewer, James B. The dissertation author was the primary investigator and author of this paper.

CHAPTER 3:

ACTIVITY IN THE HIPPOCAMPUS AND NEOCORTICAL WORKING MEMORY REGIONS PREDICTS SUCCESSFUL ASSOCIATIVE MEMORY FOR TEMPORALLY DISCONTIGUOUS EVENTS

Abstract

Models of mnemonic function suggest that the hippocampus binds temporally discontiguous events in memory (Wallenstein, Eichenbaum, & Hasselmo, 1998), which has been supported by recent studies in humans. Less is known, however, about the involvement of working memory in bridging the temporal gap between to-be-associated events. In this study, subsequent memory for associations between temporally discontiguous stimuli was examined using functional magnetic resonance imaging. In the scanner, subjects were instructed to remember sequentially presented images. Occasionally, a plus-sign was presented during the interstimulus interval between two images, instructing subjects to associate the two images as a pair. Following the scan, subjects identified remembered images and their pairs. Images following the plus-sign were separated into trials in which items were later recognized and the pair remembered, recognized and the pair forgotten, or not recognized. Blood-oxygen-level-dependent responses were measured to identify regions where response amplitude predicted subsequent associative or item memory. Distinct neocortical regions were involved in each memory condition, where activity in bilateral frontal and parietal regions predicted memory for associative information and bilateral

occipital and medial frontal regions for item information. While activity in posterior regions of the medial temporal lobe showed an intermediate response predicting memory for both conditions, bilateral hippocampal activity only predicted associative memory.

Introduction

The human brain has remarkable capacity for forming associations between items, yet given the constant stream of stimuli that one encounters and attends to each day, some experiences will be later remembered and some will not. Even if elements of an experience are remembered, particular associations between those elements may be forgotten. While many studies have examined the formation of associative memory for concurrently presented items, few have considered the more natural experience of encoding stimuli across time (Hales, Israel, Swann, & Brewer, 2009; Konkel, Warren, Duff, Tranel, & Cohen, 2008; L. J. Murray & Ranganath, 2007; Qin, et al., 2007; Qin, et al., 2009; Sommer, Rose, Glascher, et al., 2005; Sommer, Rose, Weiller, et al., 2005; Staresina & Davachi, 2009; Takeda, Naya, Fujimichi, Takeuchi, & Miyashita, 2005).

Forming lasting associative memories for items presented over time involves cooperation of working memory and long-term memory (LTM). Information pertaining to an initial item must be held in mind until information regarding a subsequent item can be added to the memory. Cortical regions, including prefrontal cortex (PFC) and parietal cortex, are commonly activated during working memory tasks where active maintenance of information over time is needed (Cabeza & Nyberg, 2000; D'Esposito, 2007; D. I. Kim, et al., 2009; Mottaghy, 2006; Passingham & Sakai, 2004). In order for the association to be formed and stored into memory, additional brain regions important for LTM encoding must be recruited. This cooperation

between brain systems might allow for more flexibility in encoding wide-ranging experiences into LTM. Encoding of experiences across time is fundamental to episodic memory, and so it is important to explore the involvement and coordination between brain regions involved in working memory and LTM during the formation of associative memories for temporally-discontiguous stimuli. Such research may provide wider understanding of episodic memory and whether encoding relies on distributed brain regions whose participation depends on task demands.

Although associative memory research has focused primarily on activity in the MTL, involvement of certain neocortical regions in associative and/or item encoding has been reported for concurrently presented stimuli or associations made without temporal discontiguity. PFC involvement in item and associative memory formation has been described in several neuroimaging, neuropsychological, and electrophysiological studies (Achim & Lepage, 2005; Blumenfeld, et al., 2010; Blumenfeld & Ranganath, 2006, 2007; Chua, et al., 2007; Davachi & Wagner, 2002; Dolan & Fletcher, 1997; Fletcher, et al., 2000; Geuze, et al., 2008; Haskins, et al., 2008; Jackson & Schacter, 2004; Kapur, et al., 1996; Montaldi, et al., 1998; Park & Rugg, 2008; Peters, et al., 2009; Pihlajamaki, et al., 2003; Prince, et al., 2005; Ranganath, et al., 2004; Ranganath, et al., 2003; Rauchs, et al., 2008; R. Sperling, et al., 2003; Staresina & Davachi, 2006; Tendolkar, et al., 2007; Uncapher, et al., 2006; Wagner, Schacter, et al., 1998; Weyerts, et al., 1997). These studies commonly report greater activity in frontal regions during the encoding of subsequently remembered associations. Additional cortical regions have also been identified as engaged in

associative encoding, including parietal (Achim & Lepage, 2005; Chua, et al., 2007; Fletcher, et al., 2000; Park & Rugg, 2008; Peters, et al., 2009; Pihlajamaki, et al., 2003; Rauchs, et al., 2008; Tendolkar, et al., 2007; Uncapher, et al., 2006; Uncapher & Wagner, 2009), temporal (Qin, et al., 2007; Rauchs, et al., 2008; Uncapher, et al., 2006), and occipital (Fletcher, et al., 2000; Ranganath, et al., 2004; Tendolkar, et al., 2007) regions.

Animal studies, primarily using lesions or electrophysiological recordings, have also examined MTL and cortical contributions to associative memory formation. Lesions of the hippocampus result in associative learning impairments in monkeys performing a spatial relational learning task (Lavenex, Amaral, & Lavenex, 2006) and a concurrent discrimination task (Mahut, Zola-Morgan, & Moss, 1982). Electrophysiological studies have also shown hippocampal involvement in forming associative memories (Cahusac, Rolls, Miyashita, & Niki, 1993; Wirth, et al., 2009; Wirth, et al., 2003). Cortical involvement in associative learning has also been assigned to prefrontal (Asaad, Rainer, & Miller, 1998; Friedman & Goldman-Rakic, 1994; Inase, Li, Takashima, & Iijima, 2006), parietal (Friedman & Goldman-Rakic, 1994), and temporal (Takeda, et al., 2005) regions in monkeys, and in parietal and temporal regions in rats (Davis & McDaniel, 1993).

How are items that are separated by time or space associated into LTM? In addition to the engagement of brain regions involved in working memory, areas involved in LTM encoding, such as the medial temporal lobe (MTL; Squire, 1992),

play an important role in the formation of associative memories. A recent study has examined how the hippocampus is specifically involved in associative encoding when relational gaps, either spatial or spatiotemporal, are present (Staresina & Davachi, 2009). Items and colors were presented ‘combined’ (e.g., a blue shirt), ‘spatially discontiguous’ (e.g., grey-scale grapes, with a green boarder around the image), or ‘spatiotemporally discontiguous’ (e.g., a red border followed by a grey-scale cup). With increasing relational separation (‘combined’ to ‘spatial’ to ‘spatiotemporal’), they found increased hippocampal activity. The researchers concluded that the hippocampus is uniquely involved in forming associations across relational gaps (spatial and temporal). Although they found increased hippocampal activity in the spatiotemporal condition relative to the purely spatial condition, both types of trials included a spatial transformation; no trials examined purely temporal discontinuity. Also, the study examined intra-item associations, which were established between an item and its color. What remains unclear is whether the hippocampus is similarly recruited when spatial components are held constant and only temporal discontinuity exists between items to be associated. Further, their study focused primarily on hippocampal participation in encoding discontiguous events, and the involvement of wider cortical regions during such encoding requires further exploration.

Another recent study used sequential presentation of two visual items in a pair to examine regional brain responses for successful individual item encoding and successful associative item-item encoding (Qin, et al., 2009). Every item was included in a pair and a delay period separated the two paired items. A functional dissociation

was measured in the MTL and adjacent cortical regions, where posterior parahippocampal, perirhinal, and inferior temporal cortices were more active for remembered items regardless of subsequent associative memory, whereas the hippocampus and inferior prefrontal cortex were more active only when associative information was remembered. While this study shed light on the differential involvement of hippocampal and MTL cortical regions during encoding of temporally-discontiguous events, wider examination of frontal and parietal working memory circuitry was not presented. In addition, the study explored activation differences between the first and second presented stimulus of associated pairs rather than holding stimulus order constant. Thus, no study that we know of has yet isolated neural activity in humans that predicts successful memory for associations across time.

The present study examines brain activity related to successful item- and association-based encoding of discrete events, allowing the BOLD response amplitude to be examined for items based on the success of subsequent memory for the item and association. Items were presented sequentially to assure that each item was individually processed and to examine regions involved in the associative encoding of discrete events presented across time. Rapid-event-related functional magnetic resonance imaging (fMRI) was used to examine MTL and cortical activity during an associative encoding task, and a post-scan recognition test was used to determine the subsequent associative- and item-memory for each visual stimulus. Activity in these regions was then examined relative to the subsequent memory for items and their associative properties. Given previous findings, the hypotheses were that frontal and

medial temporal regions, particularly dorsolateral prefrontal cortex (DLPFC) and hippocampus, would show subsequent memory effects in regards to association-based encoding for temporally-discrete events. Posterior cortical and medial temporal regions were predicted to show subsequent memory effects for the individual items.

Materials and methods

Subjects

Twenty-six healthy volunteers (mean age = 23.23 ± 1 years, seven males) were recruited from the University of California, San Diego (UCSD) community and the surrounding area. All subjects had normal or corrected vision and gave informed consent approved by the UCSD Institutional Review Board.

Stimuli

Stimuli in this experiment consisted of 296 color images of everyday objects. Two-hundred, fifty-six of the images were presented sequentially while the subject was in the scanner, and a plus-sign appeared between some of the stimuli. An additional forty novel stimuli were included in the post-scan recognition test as foils for the item memory test. Images were acquired from Rossion and Pourtois color

Snodgrass images (Rossion & Pourtois, 2004) and Hemera object library (Hemera Technologies Inc).

Experimental procedure

During the scan, subjects were shown individual images, each presented for 2.5 seconds with jittered interstimulus intervals (ISIs) ranging between 0.5 and 11 seconds (Figure 5A). The ISIs were calculated to optimize the study design for modeling the hemodynamic response to trials (Dale, 1999; Dale & Buckner, 1997). Subjects were told to remember all individual images. A plus-sign was presented in the center of the screen for 0.5 seconds immediately following some of the images; during these trials, subjects were instructed to associate the image that preceded the plus-sign (1P) with the image that followed the plus-sign (2P) and to remember the items as a pair. To ensure that the 'plus-sign' contained meaningful information to subjects as an instruction to associate items, unpaired items were also presented (1U and 2U). These items were also presented as pairs, but without an intervening 'plus-sign.' This design allowed assessment of the effects of explicit instruction to associate on associative memory performance and brain activity (Hales, et al., 2009). Unpaired stimuli are not considered further in the present study. To ensure that subjects saw each image, they were given a button box and asked to press a left or right button if the image represented a living or non-living object, respectively. Two hundred and fifty-six images were presented over four 362 second runs. Each image was presented

once; 130 images were included in associated pairs, and 126 were unpaired. Image presentation pseudorandomly varied between paired and unpaired stimuli. Objects in each pair were unrelated. Inclusion of unpaired items prevented subjects from predicting before the time of the plus-sign which items would be associated.

Subjects completed a self-paced post-scan recognition test in which they were shown all stimuli previously viewed during the encoding task as well as novel stimuli used as foils for the item-memory question. When each stimulus was presented, subjects were asked to rate how well they remembered that image from the scanner presentation, from "1, Poorly," meaning they believe the item is new, to "5, Very Well," meaning they believe the item is old (Figure 5B). For trials in which the object was previously viewed during encoding, subjects were given an immediate follow up question in which they were shown two choice images (both of which were previously shown during encoding) and were told to identify which of the two images was the pair of the original image or to respond that the original image was unpaired. For analyses, scores of 4 and 5 were considered to be "remembered." All 256 images were judged in this manner; the 40 novel items were also judged in the same manner, but without a follow-up question. This recognition test lasted approximately 30 minutes.

Functional MRI parameters

Subjects were scanned at the Keck Center for Functional MRI at the University of California, San Diego using a 3T GE scanner. Functional images were acquired

using gradient-echo, echo-planar, T2*-weighted pulse sequence (repetition time = 1.5 s; one shot per repetition; echo time = 30; flip angle = 90°; bandwidth = 31.25 MHz). The brain was covered using 22 slices obtained perpendicular to the long axis of the hippocampus with 4 mm x 4 mm x 7 mm voxels. The largest dimension of the functional voxels was along the length of the hippocampus allowing for the inclusion of more tissue within each voxel and smoothing within the direction of the hippocampus. This technique also takes advantage of the linear structure of the hippocampus and parahippocampal gyrus to maximize signal. Field maps were acquired to measure and correct for static field inhomogeneities (S. M. Smith, et al., 2004). A T1-weighted structural scan was acquired in the same plane and with the same voxel size as the functional scans. A high resolution structural scan was also acquired sagittally using a T1-weighted (1 mm x 1 mm x 1 mm) magnetization-prepared rapid gradient echo sequence or an inversion recovery prepared fast spoiled gradient recalled sequence.

Data analysis

Functional data from each run were field-map corrected (S. M. Smith, et al., 2004). Using the AFNI suite of programs (Cox, 1996), slices were temporally aligned and co-registered using a three-dimensional image alignment algorithm, voxels outside the brain were eliminated using a threshold mask of the functional data, and functional runs were corrected for motion and concatenated. A general linear model

was constructed using multiple regression analysis; six motion regressors obtained from the registration process were included along with regressors for correctly and incorrectly encoded paired and unpaired images.

Standard landmarks, including the anterior and posterior commissures, were defined manually on the anatomical scans and used to transform the structural and functional data into Talairach space (Talairach & Tournoux, 1998) by AFNI using nearest-neighbor interpolation (Cox, 1996). No spatial smoothing was performed because our functional voxel size allowed for smoothing while maintaining anatomical specificity. For all conditions, hemodynamic response functions were derived from the fMRI data using signal deconvolution with delta basis functions and a defined time window of 15 seconds following the onset of each stimulus (Cox, 1996). Multiple linear regression analyses were used to examine relative activity during the encoding of items that followed a plus-sign (2P items) when they were later recognized and associative properties were remembered ("associative"), when they were later recognized and associative properties were forgotten ("item-only"), or when they were not later recognized ("forgotten"). Whole brain voxel-wise *t*-tests (two-tailed) carried out across all 26 subjects were conducted to examine which brain regions showed more activity under the following contrasts: (1) associative minus item-only, (2) item-only minus forgotten. Associative and item-only trials were performed under the same instructions allowing for better isolation of associative subsequent memory effects. Comparing associative trials to unpaired trials would result in higher trial numbers, but the contrast would be less controlled given the difference in instructions for paired and

unpaired trials. In order to correct for multiple comparisons and yield a whole brain significance value of $p < 0.05$ corrected for all comparisons (based on Monte Carlo simulations), functional clusters of least 5 contiguous voxels were identified in conditions (1) and (2). Statistical activation maps were displayed using SUMA- AFNI Surface Mapper (Saad, Reynolds, Argall, Japee, & Cox, 2004) on the smooth white matter surface of the Talairach and Tournoux N27 average brain (from Freesurfer). The average hemodynamic response function was extracted for each cluster of interest.

In order to improve MTL alignment between subjects, the region of interest large deformation diffeomorphic metric mapping (ROI-LDDMM) alignment technique (Miller, Beg, Ceritoglu, & Stark, 2005) was applied. Bilateral hippocampus and subregions of parahippocampal gyrus (PHG), including perirhinal (PRC), entorhinal (ERC), and parahippocampal (PHC) cortices, were defined for each subject on Talairach transformed images. Previously described landmarks were used to define PRC and ERC (Insausti, et al., 1998) and PHC (Stark & Okado, 2003). These defined anatomical regions of interest for each subject were normalized using ROI-LDDMM to a modified model of a previously created template segmentation (Kirwan, Jones, Miller, & Stark, 2007). Functional imaging data, after being corrected for spatial distortions using field maps acquired during each subject's scanning session (S. M. Smith, et al., 2004) underwent the same ROI-LDDMM transformation as was applied to the anatomical data. Hippocampal voxels active in the associative minus item-only condition, the item-only minus forgotten condition, or both were identified using a

conjunction analysis of these two conditions masked by the anatomically defined left and right hippocampus.

Results

Behavioral analysis

Analyses were focused on responses to 2P stimuli, those that followed the associative instruction (plus-sign). Seventy-seven percent (± 2% SEM; range of 49-94%) of 2P stimuli were subsequently recognized with confidence level 4 or 5 out of the 5-point scale (chance level of 40%). Following the recognition of a stimulus, subjects were presented with three options: (1) the stimulus was paired with item 'A,' (2) the stimulus was paired with item 'B,' or (3) the stimulus was 'unpaired.' Of the recognized 2P stimuli, the correct associative pair was identified at a rate of 63% (± 3% SEM; range of 21-90%). Of these stimuli, 25% were not included in the analyzed group of "associative" trials because the correct pair (2P) was not identified when the 1P item was the cue. The exclusion of trials in which associative information was remembered in only one direction resulted in lower trial numbers in each condition, but allowed for purer samples of associative and item-only conditions. Each subject's performance yielded a bin size for each trial category that was within two standard deviations from the category's mean bin size, and, therefore, all subjects were included in the analysis. Subjects had an average of 24.8 associative memory trials,

14.0 item-only memory trials, and 15.3 forgotten trials with no significant pattern of distribution across ISI length.

fMRI Analysis

"Associative memory" (i.e., 2P associative relative to 2P item-only) brain regions were identified where the size of the BOLD response predicted memory for associative information. Regions identified by this contrast with an alpha value of 0.05, corrected, are listed in Table 3. Bilateral frontal and parietal neocortical regions as well as posterior regions of the MTL showed increased activity during the encoding of associative trials relative to item-only trials ($p < 0.05$). Specific regions responding in an "associative memory" fashion include bilateral prefrontal cortex, left lateral parietal cortex, occipital cortex, and right precuneus (Figure 6A-D). Although these regions showed a response to both item-only and forgotten trials, the activation did not differ between them, and the responses were significantly smaller than the response to associative trials. Increased activity during associative trials relative to item-only trials was also seen in bilateral posterior regions of the MTL, including posterior PHC, fusiform, and ventral occipital regions (Figure 6E, F). These regions, however, exhibited a graded effect, where the response during associative trials was greater than during item-only trials, and the response during item-only trials appeared greater than during forgotten trials. Whole-brain analysis of item-only trials relative to forgotten trials, however, was used to confirm an "item memory" effect in these regions.

"Item memory" (i.e., 2P item-only relative to 2P forgotten) brain regions were identified where the size of the BOLD response predicted memory for items without memory for the pair. Regions identified by this contrast with an alpha value of 0.05, corrected, are listed in Table 4. Bilateral occipital and right medial frontal neocortical regions as well as posterior regions of the MTL, including posterior PHC and fusiform, showed increased activity during the encoding of item-only trials relative to forgotten trials ($p < 0.05$; Figure 7A-D). In these regions, the response to forgotten trials was significantly smaller than the responses to associative and item-only trials. These regions were not identified in the above analysis of regions important for associative memory. Posterior MTL regions functionally defined in this contrast were near those defined in the previous contrast (Figure 6E, F). The only region of overlap, however, between the "associative memory" and "item memory" contrasts was in left fusiform (Figure 8). Accordingly, activity in this region showed a step-wise activation increase over the three trial types, as these voxels satisfied the statistical threshold for significant activation when associative trials were compared to item-only trials and also when item-only trials were compared to forgotten trials.

The functionally defined posterior MTL regions identified in both contrasts included voxels extending into different anatomical regions, including hippocampus, parahippocampus, fusiform, and occipital lobe. In order to examine the specific contribution of the hippocampus to associative and item memory formation, active voxels for both conditions overlapping with the anatomically defined hippocampus were isolated (peak locations: -26, -28, -8; 31, -29, -4), and impulse response curves in

these overlapping voxels were analyzed. Despite wider posterior MTL involvement in both “associative memory” and “item memory,” bilateral hippocampus showed an “associative memory” response, with increased activity only predicting memory for temporally-discontiguous associative pairs (Figure 9).

Discussion

The present study examined the successful formation of associative and item memory for sequentially presented visual stimuli. Distinct neocortical regions were involved in binding temporally-discontiguous items into memory (bilateral frontal and parietal regions) and item encoding (bilateral occipital and medial frontal regions). Overlapping effects were seen in posterior regions of the MTL and adjacent cortex, including fusiform cortex, while bilateral hippocampal activity predicted associative memory for temporally-discontiguous stimuli.

Working memory regions involved in long-term memory associative encoding

Increased response in bilateral frontal and parietal cortex was found in the present study for the successful encoding of item and associative information relative to item-only information. These regions have often been described as playing a role in working memory maintenance in human imaging studies, using techniques such as positron emission tomography, fMRI, electroencephalography, and transcranial

magnetic stimulation, as well as animal electrophysiological studies (see Cabeza & Nyberg, 2000; D'Esposito, 2007; D. I. Kim, et al., 2009; Mottaghy, 2006; Passingham & Sakai, 2004 for review).

The current results extend these findings to include the involvement of frontal and parietal regions in the formation of associative memory across discrete events. In order to succeed in this task that involves encoding the association between items across time, working memory structures might maintain the first item in mind through the delay in order for it to be bound with the second item into a long-term associative memory. During the binding of the two items, coordinated involvement of working memory and LTM structures would be expected. The results of the present study support this model, as successful associative encoding engaged regions involved in working memory (bilateral frontal and parietal regions) as well as LTM (bilateral hippocampus and posterior PHC). Blumenfeld and Ranganath (2006) examined working memory and LTM interactions focusing on the contribution of DLPFC. In their study, subjects performed two working memory tasks, i.e., three noun rehearsal and three noun reordering based on the weights of the objects described by each noun, followed by a post-scan LTM test in which they reported the strength of their memory for each word. Activity in DLPFC was correlated with subsequent memory performance for words encoded in the reorder condition but not in the rehearsal condition. Their results support DLPFC involvement in both working memory, through the organization of information, and in associative LTM encoding.

Additional support for this model of working memory and LTM coordination comes from a previous study that found increased delay period activity in PFC between associated relative to non-associated discontiguous items, whereas increased MTL activity was not seen until the two events could be bound into memory (Hales, et al., 2009). However, delay period subsequent memory effects for different trial types (associative, item-only, and forgotten) have not been examined, which might further explain how these different memory processes cooperate to associate events across time. The current findings also support a model discussed by D'Esposito (2007) in which multimodal cortical areas, such as lateral PFC and parietal cortex, are involved in working memory processing, and via their connections to primary, unimodal sensory areas, together work to maintain representations over a delay. Given this model, DLPFC and parietal activity would be expected to be accompanied by an increased response in occipital and left lateral inferior frontal regions for nameable, visual object stimuli, such as those used in the current study.

Posterior cortical involvement in visual item memory

Studies examining item-memory encoding in relation to associative-memory encoding usually focus on MTL substructure involvement and with less attention to neocortical contributions. A few studies have reported certain cortical regions showing an increased response during the encoding of subsequently remembered items, including ventrolateral prefrontal (Blumenfeld, et al., 2010; L. J. Murray &

Ranganath, 2007), posterior inferior temporal (Qin, et al., 2009; Uncapher, et al., 2006), retrosplenial (Chua, et al., 2007), and fusiform (R. Sperling, et al., 2003) cortices. In one of the earliest fMRI studies to report signal changes in the hippocampus, the authors reported an interaction between ventral cortical regions and MTL structures for novel picture encoding (Stern, et al., 1996). They found response changes for novel picture encoding in bilateral hippocampus as well as in lingual and fusiform areas, regions known to be important for visual object recognition and discrimination. A recent study demonstrated repetition effects in posterior regions of the inferior temporal lobe that were sensitive only to visual features of stimuli and not to conceptual features (Wig, Buckner, & Schacter, 2009). The present findings extend prior results by showing a network of posterior cortical areas, including bilateral occipital and fusiform cortex, that exhibit increased response for the successful encoding of items, but where the response is not enhanced by additional encoding of associative information.

Subsequent memory effects in the MTL and adjacent cortex

The established role of the MTL in successful memory encoding motivated the additional analysis of this region. With debate surrounding the specific involvement of MTL substructures, a number of studies and reviews have examined the specific involvement of the PHG versus the hippocampus proper in successful versus unsuccessful associative- and item-encoding (Cohen, Poldrack, & Eichenbaum, 1997;

Davachi, 2006; Diana, Yonelinas, & Ranganath, 2007; Mayes, et al., 2007; Ranganath & D'Esposito, 2001; Rauchs, et al., 2008; Staresina & Davachi, 2008; Tendolkar, et al., 2007).

The role of posterior PHC in memory formation is debated. Some studies have ascribed associative memory functions to posterior PHC for its involvement in encoding source (Davachi, et al., 2003), associative (Kirwan & Stark, 2004; Sommer, Rose, Glascher, et al., 2005), and contextual (Davachi, 2006) information. Kirwan and Stark (2004), for instance, reported increased activity in the hippocampus and PHC during successful associative encoding of face-name pairs. Meanwhile, other studies have emphasized the importance of posterior PHC in item encoding (Brewer, et al., 1998; Fernandez, et al., 1998; George, Horel, & Cirillo, 1989; Kirchhoff, et al., 2000; Rauchs, et al., 2008; Stern, et al., 1996; Wagner, Schacter, et al., 1998). One such study conducted a temporary lesion experiment in monkeys where cooling probes placed over PHG caused deficits in a visual memory task (George, et al., 1989). In the present study, posterior regions of PHC, and adjacent fusiform cortex, exhibited subsequent memory effects for both item and associative information, with maximal overlap between contrasts in left fusiform (Figure 8). Therefore, these findings do not distinguish between these two possibilities, but support a third possibility, that the PHG is involved in both item- and associative-encoding, and the graded response may represent simple memory strength. Gold, et al. (2006) reported a similar finding in posterior PHC / fusiform gyrus. Subjects learned a series of adjectives in the scanner and were asked to create a mental image of either an indoor or outdoor scene that fits

with the word they were shown. Following the scan, subjects were tested on their item and source memory. The researchers found that different MTL regions, including posterior PHC / fusiform gyrus, showed both a subsequent item-memory and source-memory effect. The current findings complement these results for this area of the MTL.

Hippocampal involvement in successful item and associative encoding has also been reported and debated. The hippocampus has a well-established critical role in declarative memory formation (see Squire, 2009 for review). Numerous lesion studies in humans and animals have supported the need for an intact functional hippocampus for encoding declarative information into LTM (Cohen & Squire, 1980; Manns & Eichenbaum, 2006; Mishkin, 1978; Scoville & Milner, 1957; Squire & Zola-Morgan, 1991). More recent human fMRI studies have examined the specific role of the hippocampus, relative to other subregions of the MTL, in the encoding of associated items. Functional MRI studies have found increased activity in the hippocampus during the encoding of associated names and faces for pairs that are later remembered compared to those later forgotten (Chua, et al., 2007; R. Sperling, et al., 2003). Studies examining other types of associative encoding, between pairs of visual pictures or words or between an object and a location, have reported similar results with greater hippocampal activity for subsequently remembered associations relative to forgotten associations (Achim & Lepage, 2005; Jackson & Schacter, 2004; Qin, et al., 2007; Qin, et al., 2009; Ranganath, et al., 2004; Staresina & Davachi, 2006).

Unlike previous associative encoding studies which have commonly presented two items concurrently, some recent studies have examined the formation of associations across spatial and/or temporal gaps (Hales, et al., 2009; Konkel, et al., 2008; L. J. Murray & Ranganath, 2007; Qin, et al., 2007; Qin, et al., 2009; Staresina & Davachi, 2009). As a strategy for examining temporal relational gaps, using sequential presentation of items forces subjects to create associations between the items across time (Hales, et al., 2009; Qin, et al., 2009). Hales et al. (2009) examined differential MTL and PFC responses for paired versus unpaired items and found distinct temporal contributions of these two regions towards associative encoding. While PFC was active in response to the cue to associate and during the delay between paired stimuli, the MTL did not increase in response until the presentation of the second item. Focusing on paired items and activity within and around the MTL, Qin et al. (2009) conducted a task to examine MTL subregional involvement in forming successful associative and item memories. In accordance with previous studies and those mentioned above, they found an increased response in the hippocampus, as well as inferior PFC, for successful associative encoding and in posterior PHC for successful item encoding. Working memory circuitry may have been less salient in their analysis because items following the temporal gap were not used for identifying item-memory regions and were not used as cues for testing associative memory. In the present study, associations were tested in each direction, which assures that the association was strong and less likely contaminated by guesses in a forced-choice recognition test.

Another recent study examined the formation of associations across spatial and temporal relational gaps (Staresina & Davachi, 2009). They reported increased hippocampal response for encoding spatially discontiguous associations relative to spatially contiguous associations with even greater response to the successful formation of spatiotemporally-discontiguous associations. Both types of discontiguous associations, however, involved spatial relational gaps. The present study extends these findings by addressing and supporting the selective involvement of the human hippocampus in forming associations across temporal gaps without the need for spatial manipulations. In addition, this study examines the involvement of cortical working memory regions, including frontal and parietal cortices, along with LTM regions in encoding temporally-discontiguous associations.

The current study provides evidence for a functional dissociation between frontoparietal and posterior cortical regions for associative encoding, where frontoparietal regions are more active for binding associative information across time and posterior cortical regions are more active for forming individual memories of visual objects. This study uniquely examines subsequent memory effects in both the MTL and neocortex for items associated across time and the process of linking new information to a previously encoded item. These findings support the following model for associating temporally-discontiguous events: neocortical working memory regions maintain neural representation of an item across a delay, allowing concurrence

between that active representation and later ones for hippocampal binding. Further investigation is needed regarding cortical and MTL regional activity during the time delay between stimuli being associatively encoded into LTM. The present findings suggest coordination between working memory and LTM structures in the fundamental ability of organisms to associate information across discrete events into memory and to form relational episodic memory for ongoing experience.

Acknowledgments

Chapter 3, in full, is a reprint of the material as it appears in Neuropsychologia, 2010. Hales, Jena B.; Brewer, James B. The dissertation author was the primary investigator and author of this paper.

CHAPTER 4:

THE TIMING OF ASSOCIATIVE MEMORY FORMATION: FRONTAL LOBE AND ANTERIOR MEDIAL TEMPORAL LOBE ACTIVITY AT ASSOCIATIVE BINDING PREDICTS MEMORY

Abstract

The process of associating items encountered over time and across variable time delays is fundamental for creating memories in daily life, such as for stories and episodes. Forming associative memory for temporally discontiguous items involves medial temporal lobe structures and additional neocortical processing regions, including prefrontal cortex, parietal lobe, and lateral occipital regions. However, most prior memory studies, using concurrently presented stimuli, have failed to examine the temporal aspect of successful associative memory formation to identify when activity in these brain regions is predictive of associative memory formation. In the current study, functional MRI data were acquired while subjects were shown pairs of sequentially presented visual images with a fixed inter-item delay within pairs. This design allowed the entire time course of the trial to be analyzed, starting from onset of the first item, across the 5.5-second delay period, and through offset of the second item. Subjects then completed a post-scan recognition test for the items and associations they encoded during the scan and their confidence for each. After controlling for item-memory strength, brain regions selectively involved in associative encoding were isolated. Consistent with prior findings, increased regional activity

predicting subsequent associative memory success was found in anterior medial temporal lobe regions of left perirhinal and entorhinal cortices and in left prefrontal cortex and lateral occipital regions. The temporal separation within each pair, however, allowed extension of these findings by isolating the timing of regional involvement, showing that increased response in these regions occurs during binding, but not during maintenance.

Introduction

When navigating through the world, people encounter a stream of information. Items that are deemed important will be attended to, and associations will be made between these related items to create more robust memory for the event. What factors predict which associated items will be later remembered? Prior studies using concurrently presented stimuli focused mainly on which regions are involved in forming associations. This approach, however, represents a very limited view of associative memory formation in the real world and misses an important aspect of encoding the stream of information one encounters. Thus, recent studies have delved deeper into associative memory formation to examine how items are linked and encoded across a delay (Hales & Brewer, 2010; Hales, et al., 2009; Konkel, et al., 2008; L. J. Murray & Ranganath, 2007; Qin, et al., 2007; Qin, et al., 2009; Sommer, Rose, Glascher, et al., 2005; Sommer, Rose, Weiller, et al., 2005; Staresina & Davachi, 2009; Takeda, et al., 2005). These studies have reported the involvement of medial temporal lobe (MTL) structures as well as additional neocortical regions, including prefrontal cortex (PFC), medial frontal cortex, parietal cortex, and lateral occipital / inferior temporal regions in forming associative memories for temporally discontiguous items. In order to address how regions cooperate in and contribute to forming these memories, investigation of the time course of activity across the entire encoding event is essential; in humans, however, examination of these temporal components has only recently gained attention.

Beyond these questions regarding the timing of regional contribution to memory formation, fundamental disagreement remains about the specific involvement of MTL substructures in associative memory formation. Although several neuropsychological and neuroimaging studies have reported the involvement of the parahippocampal gyrus (PHG) in associative memory encoding (Chua, et al., 2007; Davachi, et al., 2003; Davachi & Wagner, 2002; Eichenbaum, et al., 2007; Gold, et al., 2006; Hales & Brewer, 2010; Hales, et al., 2009; Kirwan & Stark, 2004; L. J. Murray & Ranganath, 2007; Pihlajamaki, et al., 2003; Qin, et al., 2007; Qin, et al., 2009; Staresina & Davachi, 2010; Taylor, et al., 2006; Tendolkar, et al., 2007), studies have suggested functional distinctions between PHG substructures based on associative versus item encoding (Achim & Lepage, 2005; Aminoff, et al., 2007; Davachi, 2006; Peters, et al., 2007; Sommer, Rose, Glascher, et al., 2005; Staresina & Davachi, 2008, 2009), novel object perception versus spatial processing (Pihlajamaki, et al., 2003), encoding versus retrieval process (Daselaar, Fleck, & Cabeza, 2006), and context-dependent learning versus explicit recognition memory (Preston & Gabrieli, 2008). These results support the separable contribution of particular MTL substructures to different aspects of memory encoding and retrieval.

Many neuroimaging studies have reported that anterior regions of the MTL, such as perirhinal cortex (PRC), entorhinal cortex (ERC), anterior parahippocampal cortex (PHC), and anterior hippocampus, are involved in the formation of associative memories (Aminoff, et al., 2007; Chua, et al., 2007; Jackson & Schacter, 2004; Mayes, et al., 2007; Peters, et al., 2007; Pihlajamaki, et al., 2003; Rauchs, et al., 2008;

R. Sperling, et al., 2003; Staresina & Davachi, 2006, 2009, 2010; Taylor, et al., 2006), whereas more posterior regions of the PHC and hippocampus are involved in visual item memory (Kirchhoff, et al., 2000; Peters, et al., 2007; Rauchs, et al., 2008). Such findings, however, are not universal. Some studies have suggested that the locus for associative memory formation is the hippocampus, while item memory formation preferentially involves PRC (Chua, et al., 2007; Diana, et al., 2007; Eichenbaum, et al., 2007; Staresina & Davachi, 2009).

Recently, studies have started addressing this discrepancy by looking closer at the specific types of associations being made. In a recent review, Mayes et al. (2007) provided support for PRC involvement in within-domain associative encoding and hippocampal involvement in between-domain associative encoding based on human psychological and functional imaging studies, as well as human and animal lesion studies. Additional studies have also supported this distinction in PRC and hippocampal contribution to associative encoding, where PRC is involved in forming associations that are unitized or regarding item-related details (such as item-color associations) and the hippocampus is involved in forming domain-general or item-context associations (Diana, et al., 2007; Staresina & Davachi, 2008, 2010).

Extensive anatomical research of the cortical projections to MTL substructures also supports a functional dissociation within PHG. Tracing studies in the macaque monkey have indicated that PRC receives cortical inputs that are distinct from inputs to PHC (Suzuki & Amaral, 1994a). ERC receives the majority of its inputs from PRC

and PHC, but also receives projections from additional neocortical regions, including superior temporal gyrus and orbitofrontal cortex. Similar results have been reported using retrograde tracing in the rat, where PRC and postrhinal cortex each receive distinct cortical and subcortical inputs (Furtak, et al., 2007). The anatomical evidence of distinct cortical inputs to PRC and PHC suggests and supports functional differences between anterior and posterior regions of the PHG.

Results from electrophysiological studies in monkeys provide further support for involvement of anterior parahippocampal regions, such as PRC and ERC, in associative memory. Neurons in inferotemporal cortex showed ‘associative’ responses while monkeys performed a visual paired-associates task (Higuchi & Miyashita, 1996; Sakai & Miyashita, 1991). In these studies, neurons were identified as ‘pair coding’ if, after training, they showed a preferential response to a stimulus and to its associated pair. Neurons were identified as ‘pair-recall’ if, having showed a strong response to a stimulus, the neuron also fired strongly in the period following the presentation of the pair of the stimulus. These responses were identified only in monkeys with an intact entorhinal and perirhinal region. Though anterior PHG lesions ablated the associative memory responses, they did not diminish neuronal responses to individual stimuli (Higuchi & Miyashita, 1996).

Electrophysiological studies in monkeys have also examined delay period activity in PFC and MTL regions during associative encoding of temporally discontiguous stimuli. Fuster et al. (2000) recorded extracellularly from dorsolateral

prefrontal cortex (DLPFC) while monkeys performed a sound-color associative encoding task. The authors reported that cells in DLPFC exhibited correlated firing for associated colors and tones and that some of these cells also showed increased firing during the delay between tones and their associated colors (Deco, et al., 2005; Fuster, et al., 2000). Electrophysiological results in rats and monkeys are inconsistent, however, regarding MTL activity during short-delay maintenance. Some studies have reported MTL activity during short-delay maintenance (Cahusac, et al., 1989; Watanabe & Niki, 1985; Young, et al., 1997), while others have reported very rare or no MTL activity during the delay period (Hampson & Deadwyler, 2003; Vidyasagar, et al., 1991). Human lesion and imaging studies looking at working memory also report mixed results of MTL involvement in delay period maintenance (Axmacher, et al., 2007; Cave & Squire, 1992; Ezzyat & Olson, 2008; Grady, McIntosh, Bookstein, et al., 1998; Habeck, et al., 2005; Hannula, Tranel, & Cohen, 2006; Hartley, et al., 2007; Kessler & Kiefer, 2005; Monk, et al., 2002; Nichols, Kao, Verfaellie, & Gabrieli, 2006; Olson, Moore, Stark, & Chatterjee, 2006; Petit, Courtney, Ungerleider, & Haxby, 1998; Picchioni, et al., 2007; Piekema, Kessels, Mars, Petersson, & Fernandez, 2006; Ranganath, et al., 2004; Ranganath & D'Esposito, 2001; Shrager, Levy, Hopkins, & Squire, 2008; Stern, Sherman, Kirchhoff, & Hasselmo, 2001). While delay period activity has been examined in fMRI studies of working memory, the few studies that have looked at associative encoding of temporally discontiguous stimuli have focused on subsequent memory effects during the encoding of the items (Hales & Brewer, 2010; Hales, et al., 2009; Konkel, et al., 2008; L. J. Murray &

Ranganath, 2007; Qin, et al., 2007; Qin, et al., 2009; Sommer, Rose, Glascher, et al., 2005; Sommer, Rose, Weiller, et al., 2005; Staresina & Davachi, 2009; Takeda, et al., 2005). One exception is a study that examined associative and item encoding of temporally discontiguous stimuli, which showed increased PFC activity during the delay between paired items relative to the delay between unpaired items (Hales, et al., 2009). This study, however, only examined successfully encoded paired and unpaired items; therefore, intra-pair delay period activity has yet to be explored in relation to subsequent associative memory.

The current study examines the time course of activity across the entire associative encoding event of two temporally discontiguous items. MTL and PFC activity during this associative encoding task was examined using rapid-event-related functional magnetic resonance imaging (fMRI), and the subsequent associative- and item-memory for the visual stimuli was determined using a post-scan recognition test. By presenting each item individually and controlling for item memory strength, brain activity in response to successful associative binding could be isolated. Based on previous findings, the prediction was that anterior MTL regions, such as PRC, ERC, and anterior hippocampus, and PFC regions would show increased activity for successful associative binding. Additionally, subsequent associative memory effects were predicted to occur in frontal regions during both maintenance (following the presentation of the first item of the pair) and binding (once the second item of the pair was presented); however, subsequent associative memory effects were predicted to

occur in anterior MTL regions only during binding with no difference during maintenance.

Materials and Methods

Subjects

Fifteen healthy volunteers (mean age = 26.6 ± 3 years, seven males) were recruited from the University of California, San Diego (UCSD) community and the surrounding area. All subjects gave informed consent approved by the UCSD Institutional Review Board and had normal or corrected vision.

Stimuli

Two-hundred and ninety color images of everyday objects were used as stimuli in this experiment. While subjects were in the scanner, 250 of the images were presented sequentially; a plus-sign was presented during the inter-item delay to link each set of two images and reduce cross-pair binding. During the post-scan recognition test for item memory, the remaining 40 stimuli were included as foils. Images were acquired from Rossion and Pourtois color Snodgrass images (Rossion & Pourtois, 2004) and Hemera object library (Hemera Technologies Inc).

Experimental Procedure

During the associative encoding task in the scanner, subjects were shown pairs of sequentially presented individual images, with each image presented for 2 seconds (Figure 10A). All items were paired pseudorandomly to remove obvious semantic relationships between pairs. Between the two images of a pair, a fixed inter-item delay of 5.5 seconds was used with a plus-sign presented in the center of the screen for the first 0.5 seconds of the delay and followed by a blank screen for the remaining 5 seconds. Between pairs were jittered intertrial intervals (ITIs) ranging between 0.5 and 10.5 seconds. The ITIs were calculated to optimize the study design for modeling the hemodynamic response to trials (Dale, 1999; Dale & Buckner, 1997). Subjects were told to remember all individual images. Subjects were also instructed to associate the image that preceded the plus-sign (1P) with the image that followed the plus-sign (2P) and to remember the items as a pair. By separating the 2P item from the instruction to associate (plus-sign), this design allowed for isolation of the response to associative binding. Subjects were given a button box and were asked to press a left or right button if the image represented a living or non-living object, respectively, to make sure that subjects were attending to each image. One hundred and twenty-five image pairs were presented to subjects in the scanner across five 383 second runs. Each image was presented once, and objects in each pair were unrelated.

Following the encoding task in the scanner, subjects completed a self-paced post-scan recognition test to examine subsequent item- and associative-memory.

Subjects were shown all stimuli previously viewed during the encoding task that followed the plus-sign (2Ps) as well as 40 novel stimuli that were used as foils for the item-memory question. For each of the 165 stimuli, subjects were asked to rate their confidence that the picture was new or that it was shown during the scan (old) on a "1- Definitely New" to "6 - Definitely Old" scale (Figure 10B). For trials in which the object was previously viewed during encoding, subjects were given an immediate follow-up question in which they were shown two choice images, A and B (both of which were previously shown during encoding) and were asked to rate their confidence that the picture was paired with image A or B on a "1- Definitely A" to "6 - Definitely B" scale (Figure 10B). All 125 2P images from the encoding task were judged in this manner; the 40 novel items were also judged in the same manner, but without a follow-up question. This recognition test lasted approximately 30 minutes.

Functional MRI Parameters

Subjects were scanned using a 3T GE scanner at the Keck Center for Functional MRI at the University of California, San Diego. Functional images were acquired using gradient-echo, echo-planar, T2*-weighted pulse sequence (repetition time = 2.5 s; one shot per repetition; echo time = 30; flip angle = 90°; bandwidth = 31.25 MHz). Forty slices covering the brain were obtained perpendicular to the long axis of the hippocampus with 4 x 4 x 4 mm voxels. Field maps were acquired to measure and correct for static field inhomogeneities (S. M. Smith, et al., 2004). A T1-

weighted structural scan was acquired in the same plane and with the same voxel size as the functional scans. A high resolution structural scan was also acquired sagittally using a T1-weighted (1 x 1 x 1 mm) inversion recovery prepared fast spoiled gradient recalled sequence.

Data Analysis

After functional data from each run were field-map corrected (S. M. Smith, et al., 2004), slices were temporally aligned and co-registered using a three-dimensional image alignment algorithm, voxels outside the brain were eliminated using a threshold mask of the functional data, and functional runs were corrected for motion and concatenated all using the AFNI suite of programs (Cox, 1996). A 4.0 mm FWHM Gaussian filter was also applied to smooth the functional data from each run. A general linear model was constructed using multiple regression analysis; six motion regressors obtained from the registration process were included along with eight behavioral regressors based on subsequent memory performance. Subjects' behavioral trials were sorted based on accuracy and subject ratings of item memory confidence and associative memory confidence. Based on item memory confidence, trials were divided into four outcomes: 'high,' 'medium,' and 'low' confidence hits ("Definitely," "Probably," or "Maybe Old", respectively) and misses ("Definitely," "Probably," or "Maybe New," together). Associative memory was defined as successful ('associative') or unsuccessful ('item-only') based on testing responses. 'Associative'

trials were those in which the subject indicated the correct pair with responses of "Definitely" or "Probably." 'Item-only' trials were those in which the subject indicated the incorrect pair with responses of "Definitely" or "Probably" or made any "Maybe" judgment. For each outcome, a hemodynamic response function was derived from the fMRI data using signal deconvolution with TENT basis functions and a defined time window of 22.5 seconds following the onset of each 1P stimulus (Cox, 1996). Multiple linear regression analyses were used to examine activity only during the encoding of items that were later remembered with high confidence, with separate measures for when targeted associative information was remembered ('associative') or forgotten ('item-only'). These were the only two conditions used for analysis; therefore, all discussions of associative and item-only trials are referring to trials with high-confidence item memory with associative memory or with high-confidence item memory without associative memory.

Structural and functional data were transformed into Talairach space (Talairach & Tournoux, 1998) by AFNI using nearest-neighbor interpolation (Cox, 1996) after standard landmarks, including the anterior and posterior commissures, were manually defined on the anatomical scans. Whole brain voxel-wise *t*-tests (two-tailed) carried out across all 15 subjects were conducted to examine which brain regions showed more activity for associative versus item-only memory encoding. Difference during each time period of the event (i.e., 1P, delay, 2P) was examined separately. In order to correct for multiple comparisons and yield a whole brain significance value of $p < 0.01$ corrected for all comparisons (based on Monte Carlo simulations), functional

clusters of least 5 contiguous voxels were identified in this condition. The average hemodynamic response function was extracted for each cluster of interest.

In order to improve MTL alignment between subjects, the region of interest large deformation diffeomorphic metric mapping (ROI-LDDMM) alignment technique (Miller, et al., 2005) was applied. Bilateral hippocampus and subregions of PHG, including PRC, ERC, and PHC, were defined for each subject on Talairach transformed images. Previously described landmarks were used to define PRC and ERC (Insausti, et al., 1998) and PHC (Stark & Okado, 2003). These defined anatomical regions of interest for each subject were normalized using ROI-LDDMM to a modified model of a previously created template segmentation (Kirwan, et al., 2007). Functional imaging data, after being corrected for spatial distortions using field maps acquired during each subject's scanning session (S. M. Smith, et al., 2004), underwent the same ROI-LDDMM transformation as was applied to the anatomical data. Active voxels in the associative minus item-only condition, $p < 0.05$, which were located in the MTL were identified using a mask of the anatomically defined MTL substructures.

Results

Behavioral Analysis

Analyses were focused on trials in which 2P stimuli were recognized with high confidence (61% ± 5% SEM of all trials). Of these strongly remembered stimuli, the correct associative pair was identified with medium to high confidence at a rate of 76% (± 5% SEM; 'associative' condition), and the correct associative pair was not identified or was identified with low confidence at a rate of 24% (± 5% SEM; 'item-only' condition). Subjects' memory performance was generally accurate, leading to a large number of "associative" trials, with a mean of 59.9 (± 7.3 SEM) trials per subject. There were fewer comparison trials in which the subject confidently remembered the item, but forgot the association; this "item-only" condition had a mean of 16.2 (± 3.0 SEM) trials per subject. Behavioral results are summarized in Table 5.

fMRI Analysis

By holding item memory strength constant, brain regions with selective involvement in the successful formation of associative memory could be isolated. These associative memory binding regions were identified where the size of the BOLD response was greater during the encoding of the 2P stimulus when the association was remembered than when it was forgotten (associative minus item-only trials). Regions identified by this contrast ($p < 0.01$, corrected) are listed in Table 6. Left frontal regions, including DLPFC, ventrolateral prefrontal cortex (VLPFC), middle frontal cortex, and medial frontal cortex, as well as left lateral occipital /

fusiform cortex showed increased activity during associative trials relative to item-only trials; this increase was not present during the encoding of the 1P stimulus or during the inter-item delay, but only once the 2P stimulus was presented and the two items could be associated (Figure 11A-D). Left DLPFC, medial / middle frontal cortex, and lateral occipital / fusiform cortex each showed a response to both the 1P and 2P stimulus for the associative and item-only trials, with a larger response to the 2P stimulus only in the associative trials. Left VLPFC, however, only responded to the 2P stimulus during associative trials, with no response during item-only trials. No significant clusters were identified in the reverse contrast during binding (item-only trials > associative trials, $p < 0.01$, corrected). Associative memory analyses were also performed focusing on the 1P and delay time periods of the encoding event, and there were no regions showing greater activity for associative trials relative to item-only trials during either time period. The only region showing significant subsequent associative memory effects during the delay period was located in right superior temporal gyrus, which showed greater suppression during associative trials relative to item-only trials; no regions showing significant subsequent associative memory effects were identified during the encoding of the 1P item.

In order to examine the specific contribution of MTL regions to the successful binding of associative information, active voxels from the associative memory contrast (associative minus item-only trials, $p < 0.05$) that overlapped with the anatomically defined MTL substructures were isolated. These active voxel clusters were located in left PRC and left ERC (Figure 12, A and B; Table 6). Due to the size of the active

voxel clusters in these small anatomical regions, these clusters did not survive cluster-size-based correction for multiple comparisons and, therefore, were reported as uncorrected values. Similar to the activity reported in left frontal regions and lateral occipital / fusiform, left perirhinal and entorhinal cortices showed a greater response during the encoding of 2P stimuli only when associative binding was successful. There were no voxels in MTL regions during the delay period showing greater activity for associative trials relative to item-only trials.

General item subsequent memory effects have been extensively explored in prior studies (beginning with Brewer, et al., 1998 and Wagner, Schacter, et al., 1998), and such analyses were not the focus of the current study. Nevertheless, noted is the single activation predictive of high-confidence subsequent item (only) memory ($p < 0.01$) in right lateral occipital / fusiform cortex. These findings of both item and associative memory effects in lateral occipital / fusiform cortex complement results from a previous study that found this area to be the only region of overlap between subsequent associative and item memory contrasts (Hales & Brewer, 2010).

Discussion

The current study identified subsequent memory effects in the MTL, PFC, and lateral occipital / fusiform cortex during associative encoding of temporally discontiguous images. Left frontal and lateral occipital cortices, like left PRC and ERC, showed increased activity during successful associative binding. Activity in

these regions during the inter-item delay, however, did not predict subsequent associative memory.

PRC / ERC involvement in associative memory formation

When controlling for item memory strength, subsequent associative memory effects for image pairs were found in left PRC and ERC in the present study. These results complement multiple studies that have reported the involvement of PRC, ERC, and other anterior regions of the MTL in successful associative encoding (Aminoff, et al., 2007; Chua, et al., 2007; Haskins, et al., 2008; Jackson & Schacter, 2004; Mayes, et al., 2007; Peters, et al., 2007; Pihlajamaki, et al., 2003; Rauchs, et al., 2008; R. Sperling, et al., 2003; Staresina & Davachi, 2009, 2010; Taylor, et al., 2006). A recent study examining MTL activity for a visual associative memory task in which subjects saw objects presented against one of two backgrounds (providing source information), found increased right PRC activity for correct source encoding (Peters, et al., 2007). The present finding of increased PRC activity during associative encoding has been supported in other studies examining memory for source information (Tendolkar, et al., 2007), picture pairs (Pihlajamaki, et al., 2003), word pairs (Jackson & Schacter, 2004), and visual landmarks and their specific contexts (Rauchs, et al., 2008), and the current study extends the involvement of the PRC to include the formation of associative memory for temporally discontiguous items.

Some studies, however, have reported PRC involvement only in item, and not associative, memory and, instead, highlight a separable role of the hippocampus in associative memory formation. A study examining the encoding of face-name pairs reported increased activity in anterior hippocampal formation for associative memory, while PRC activity was only increased for successful memory for the face items (Chua, et al., 2007). Staresina and Davachi (2008) examined the function of PRC and the hippocampus during the encoding of item/color associations with or without additional associated context information. Both PRC and the hippocampus showed increased activity for subsequently remembered item/color associations, while the hippocampus showed an additional increase in activity when the context was also remembered in the association. Authors concluded that PRC may contribute to item-level associative encoding, while the hippocampus is responsible for domain-general, including contextual, associative encoding (Staresina & Davachi, 2008). Nevertheless, the interpretation of PRC involvement in item-level encoding is complicated, as this activity may also represent increased response to associative encoding within a domain; such findings are consistent with the results of the current study, which reports greater activity in PRC and ERC during associative encoding of two visual objects, which are of the same domain.

A recent study, in which subjects were shown two words and instructed either to encode the two words as a single novel compound word or to encode the two words in a sentence, has provided a possible explanation for the seemingly different roles attributed to PRC (Haskins, et al., 2008). Increased activity was seen in left PRC

during the encoding of the words as a single unit compared to encoding the words as two separate words in a sentence. The results of Haskins et al. (2008) suggest that PRC is involved in the associative encoding of items that can be represented as a single unit. This concept of PRC involvement when associated items are unitized has also been discussed in a recent review (Diana, et al., 2007). To further examine the process of unitization in associative memory encoding, another recent study used fragmented objects that needed to be unitized when forming memory for the object and for the association between the object and its color (Staresina & Davachi, 2010). PRC showed increased activity when the object was remembered relative to forgotten and even greater activity when the object-color association was subsequently remembered. A recent study described a possible model for how temporally discontiguous items could be associated, where neocortical working memory regions maintain the percept for an item across a delay period allowing for concurrence between that active representation and a later one for associative binding (Hales & Brewer, 2010). This model provides a possible mechanism for how a unitized association could be formed for temporally discontiguous items based on concurrent percepts of the two items at the time of binding. Nevertheless, the present study only suggests left PRC and ERC involvement in successful associative encoding; future investigation would be needed to examine whether this involvement specifically predicts memory for a unitized percept that includes both objects or for a more flexible association of two separate items. Additionally, these findings do not exclude the

involvement of PRC in successful item encoding, but rather provide further evidence for PRC and ERC activity predicting successful associative encoding.

In addition to human imaging studies, the importance of PRC and ERC in associative encoding has been explored and supported by electrophysiological and lesion studies in non-human primates (Buckley & Gaffan, 1998; Buckmaster, Eichenbaum, Amaral, Suzuki, & Rapp, 2004; Fujimichi, et al., 2010; Higuchi & Miyashita, 1996; Miyashita & Chang, 1988; Miyashita, Kameyama, Hasegawa, & Fukushima, 1998; E. A. Murray, Gaffan, & Mishkin, 1993; E. A. Murray & Richmond, 2001; Sakai & Miyashita, 1991; Yanike, Wirth, Smith, Brown, & Suzuki, 2009; Yoshida, Naya, & Miyashita, 2003). Sakai and Miyashita (1991) examined neuronal activity in anterior inferotemporal (IT) cortex in macaque monkeys while they performed a paired-associates task. After memorizing pairs of Fourier descriptors, monkeys were shown one image of a pair (cue) and were then shown two simultaneous patterns, one of which was the cue's pair. During this memory task, the authors conducted extracellular recordings of single neurons in anterior IT cortex and discovered the presence of associative-memory-coding neurons (Sakai & Miyashita, 1991). A follow-up study examined the importance of intact connections between PRC / ERC and IT cortex for the formation of the associative memory representation in IT (Higuchi & Miyashita, 1996). Monkeys received anterior commissural transection and were then trained on the previously described visual paired-associates task. Following unilateral PRC and ERC lesions, there was no longer evidence of associative memory coding in anterior IT cortex. Authors concluded that the integrity

of PRC and ERC is necessary for the formation of associative memory representations for picture pairs in IT cortex (Higuchi & Miyashita, 1996).

The presence of increased activity in PRC and ERC in humans during the encoding of visual paired-associates reported in the present study is in line with such electrophysiological and lesion data from non-human primates; however, despite all of the support from primate research for the function of PRC in associative encoding, determining the timing of PRC involvement in associative encoding events would be difficult as monkeys require multiple presentations of the event in order to learn the task and association. Yanike et al (2009) recorded from PRC in monkeys learning new associations of a scene and an eye-movement location, and particular location-scene associations were selected in which a significant difference in cell firing rate was measured between the first 5-10 trials and the last 5-10 trials. Authors found PRC cells involved in learning this association that changed their firing rate during the scene, the delay period, or both; however, regardless of the time period of firing rate change, the monkey had already learned the association. In the present study, since all stimuli are presented only once, the only time period at which the association can be known is after the second stimulus is presented and the associated items can be bound. Therefore, the current study allows examination of the temporal component of PRC involvement in associative encoding that cannot be addressed in primate studies that involve repeated presentation of events during learning.

Recent studies have reported prestimulus MTL activity that is predictive of subsequent recollection of incidentally or intentionally encoded words (Gruber & Otten, 2010; Guderian, Schott, Richardson-Klavehn, & Duzel, 2009; Park & Rugg, 2010). Although the current study did not find delay period MTL activity differences between the conditions of interest (associative and item-only trials), these prior studies would suggest the presence of increased MTL activity just prior to the onset of subsequently remembered 2P items. It should be noted that, since the 2P item was subsequently remembered in both conditions, this activity might be expected to be similar in these trial conditions of interest.

Subsequent associative memory effects in left PRC and ERC were only seen in the current study at the time that the 2P stimulus was presented and the association could be formed; there was not a subsequent associative memory effect during the delay period between the 1P and 2P stimuli. Whether the MTL is involved in the maintenance of stimuli over a short delay is an active area of research without consensus. Human lesion and imaging studies looking at working memory report mixed results of MTL involvement in delay period maintenance; however, there is a common distinction across most of these studies. MTL involvement in delay period maintenance is often reported in studies that used non-verbal stimuli, such as faces or abstract pictures (Axmacher, et al., 2007; Ezzyat & Olson, 2008; Grady, McIntosh, Bookstein, et al., 1998; Hannula, et al., 2006; Hartley, et al., 2007; Monk, et al., 2002; Nichols, et al., 2006; Olson, Moore, et al., 2006; Picchioni, et al., 2007; Piekema, et al., 2006; Ranganath, et al., 2004; Ranganath & D'Esposito, 2001; Shrager, et al.,

2008; Stern, et al., 2001), whereas MTL involvement in delay period maintenance is *not* often reported in studies that used verbal stimuli, such as words or namable objects (Cave & Squire, 1992; Habeck, et al., 2005; Hales, et al., 2009; Kessler & Kiefer, 2005; Petit, et al., 1998; Shrager, et al., 2008; Talmi, Grady, Goshen-Gottstein, & Moscovitch, 2005), though exceptions to this dissociation exist (Cabeza, Dolcos, Graham, & Nyberg, 2002; Campo, et al., 2005; Mencl, et al., 2000; Olson, Page, Moore, Chatterjee, & Verfaellie, 2006; Oztekin, McElree, Staresina, & Davachi, 2009; Tesche & Karhu, 2000). While some researchers argue that the presence of MTL activity during delay period maintenance suggests MTL involvement in working memory, it is also possible that there is a categorical difference between maintaining verbalizable and non-verbalizable stimuli over a short delay and that working memory load capacity for these two types of stimuli is different. Therefore, maintenance of non-verbalizable stimuli may engage brain regions involved in long term memory encoding, such as MTL regions, even for short delays.

This reasoning has been supported in studies examining working memory processing during a delayed match-to-sample task and subsequent long-term recognition memory (see Hasselmo & Stern, 2006 for review; Schon, et al., 2005; Schon, Hasselmo, Lopresti, Tricarico, & Stern, 2004). These studies have shown that the involvement of MTL structures in active maintenance is correlated with subsequent long-term memory recognition. A recent study has additionally probed this effect by showing that MTL activity is further modulated by working memory load in a task involving the maintenance of two or four unfamiliar, trial-unique complex

visual outdoor scenes (Schon, Quiroz, Hasselmo, & Stern, 2009). Stern and colleagues also provide an alternative explanation for the presence of MTL activity during short delays in some studies, but not in others, as a distinction between the maintenance of familiar information versus novel information. Although PFC and parietal regions are commonly isolated for maintaining familiar representations during working memory delays, additional structures, including PRC / ERC, are recruited for creating a novel representation for maintenance (Hasselmo & Stern, 2006). The current results, using verbalizable stimuli depicting simple common objects and showing no maintenance activity in the MTL, are in line with studies that have provided distinctions regarding MTL activity during short-delay maintenance of verbalizable (or possibly familiar) and non-verbalizable (or possibly novel) stimuli.

Frontal involvement and functional dissociation in associative memory formation

In the current study, left DLPFC, VLPFC, and medial / middle frontal cortex all showed increased activity during the encoding of 2P stimuli that were subsequently recognized along with their corresponding associative pair (‘associative’ trials) compared to subsequently recognized 2P stimuli with forgotten associative information (‘item-only’ trials; Figure 11A-C). This finding of increased frontal activity for successful associative encoding is consistent with previous imaging, electrophysiology, and patient studies (Achim & Lepage, 2005; Davachi & Wagner, 2002; Dolan & Fletcher, 1997; Geuze, et al., 2008; Jackson & Schacter, 2004; Kapur,

et al., 1996; Montaldi, et al., 1998; L. J. Murray & Ranganath, 2007; Pihlajamaki, et al., 2003; Qin, et al., 2007; R. Sperling, et al., 2003; Staresina & Davachi, 2006, 2010; Weyerts, et al., 1997). Although these separate regions of the left frontal lobe all showed a subsequent associative memory effect, the response time course across the entire encoding event was categorically different in left VLPFC relative to left DLPFC and left medial / middle frontal cortex. Left DLPFC and medial / middle frontal cortex responded to both the 1P and 2P stimuli during associative and item-only trials, although the response to the 2P stimulus was larger for associative trials relative to item-only trials. Left VLPFC, however, only showed a response to the 2P stimulus for associative trials, with no response to the 1P stimulus or to either stimulus for item-only trials. Even though all three frontal regions predicted successful associative encoding, left VLPFC showed an increase in activity only during associative encoding, which is consistent with prior findings of selective VLPFC participation in associative memory formation (Blumenfeld, et al., 2010; Blumenfeld & Ranganath, 2006, 2007; L. J. Murray & Ranganath, 2007; Tanabe & Sadato, 2009; Wager & Smith, 2003).

Involvement of lateral occipital cortex in associative encoding

Increased left lateral occipital / fusiform activity was seen selectively for successful associative encoding in the present study. Lateral occipital cortex is commonly cited for its involvement in object recognition (Doehrmann, Weigelt,

Altmann, Kaiser, & Naumer, 2010; Grill-Spector, et al., 2001; Malach, et al., 1995; M. M. Murray, et al., 2004), and some recent studies have described its specific role in visual imagery (Deshpande, et al., 2010; Kaas, Weigelt, Roebroeck, Kohler, & Muckli, 2010; Lacey, et al., 2010; Schendan & Stern, 2008) and in object maintenance (Ferber, et al., 2005; Harrison & Tong, 2009). Lateral occipital cortex has also been found to play a role in the encoding of object-location source information (Cansino, et al., 2002). Additionally, a study examining lateral occipital – hippocampal correlations found increased functional correlations during rest following an associative encoding task with high subsequent memory performance (Tambini, Ketz, & Davachi, 2010). As an extension of these findings of lateral occipital involvement in associative memory, the current study showed that increased lateral occipital activity during encoding selectively predicted subsequent associative memory for object pairs, even when controlling for the memory strength of the item being encoded. Increased lateral occipital activity at the time of associative binding might reflect the creation of a newly unitized percept that, when accessed at retrieval, supports associative memory performance; however, further investigation would be needed to test such a putative underlying mechanism.

The current study confronts missing information regarding the time course of regional involvement in the associative encoding of temporally discontiguous visual objects pairs. Although the importance of PRC and ERC in associative memory

formation has been well established in primate lesion and electrophysiology studies, such studies could not have answered questions about when these regions are involved in the successful encoding event. By temporally separating the subjects' exposure to each item of a pair and by showing subjects each pair only once, the current study extends prior studies, demonstrating that increased activity in left PFC, lateral occipital cortex, and anterior MTL happens once the pair is completed and predicts successful associative encoding of temporally discontiguous visual object pairs when item memory strength is controlled. Although some of these regions showed delay activity suggestive of object maintenance, this activity is simply part of attempting to encode the association and is not sufficient to show subsequent associative memory effects. The increase of activity in these frontal, lateral occipital, and MTL regions might represent binding and mnemonic storage of the new percept that incorporates the pair of stimuli or a conceptual or verbal association that links the objects.

Acknowledgments

Chapter 4, in full, is a reprint of the material as it appears in Journal of Neurophysiology, 2011. Hales, Jena B.; Brewer, James B. The dissertation author was the primary investigator and author of this paper.

CHAPTER 5:

THE PATH TO MEMORY IS GUIDED BY STRATEGY: DISTINCT NETWORKS ARE ENGAGED IN ASSOCIATIVE ENCODING UNDER VISUAL AND VERBAL STRATEGY AND INFLUENCE MEMORY PERFORMANCE IN HEALTHY AND IMPAIRED INDIVIDUALS

Abstract

Given the diversity of stimuli encountered in daily life, a variety of strategies must be used for learning new information. Relating and encoding visual and verbal stimuli into memory has been probed using various tasks and stimulus-types. Engagement of specific subsequent memory and cortical processing regions depends on the stimulus modality of studied material; however, it remains unclear whether different encoding strategies similarly influence regional activity when stimulus-type is held constant. In this study, subjects encoded object pairs using a visual or verbal associative strategy during functional magnetic resonance imaging (fMRI), and subsequent memory was assessed for pairs encoded under each strategy. Each strategy elicited distinct regional processing and subsequent memory effects: middle frontal, lateral parietal, and lateral occipital for visually-associated pairs and inferior frontal, medial frontal, and medial occipital for verbally-associated pairs. This regional selectivity mimics the effects of stimulus modality, suggesting that cortical involvement in associative encoding is driven by strategy, and not simply by stimulus-type. The clinical relevance of these findings, probed in two patients with recent

aphasic strokes, suggest that training with strategies utilizing unaffected cortical regions might improve memory ability in patients with brain damage.

Introduction

While certain brain regions are commonly reported to show general subsequent memory effects, some regions only show effects for specific stimulus-types being encoded or tasks being used. During visual or picture-based encoding, subsequent memory effects have often been reported in regions including right prefrontal, superior parietal, lateral occipital, and fusiform cortex, whereas during verbal or word-based encoding, effects are often reported in regions including left inferior frontal, parietal, superior temporal, lingual, and medial frontal cortex (H. Kim, 2011).

An unanswered question remains, however, regarding whether these differences in regional memory responses for visual and verbal stimuli are due to the bottom-up processing of the stimuli or to the top-down strategy being used to form the memory. The influence that the implemented associative strategy has on regional activity is of considerable importance to the design and interpretation of memory studies. Whether instructed or uninstructed, subjects will use a strategy for encoding, retrieving, and relating items. If regional activity is dependent on the strategy employed, instructing subjects to perform a relational processing step during encoding could itself influence the subsequent memory effects. Given the large number of studies in which subjects are instructed to perform a relational processing step during encoding, a better understanding of what is driving these subsequent memory effects is needed.

Additionally, determining whether the strategy or the stimulus-type dictates which brain regions are more engaged in encoding could have clinical relevance. It is well established that regional neocortical atrophy occurs in neurodegenerative disorders (Dickerson, et al., 2009; Listerud, Powers, Moore, Libon, & Grossman, 2009; Mummery, et al., 2000). If the brain regions engaged during encoding are dependent on the stimulus-type, there is little flexibility in the system and patients will struggle when encountering stimuli that require the function of damaged regions for processing and encoding. However, if the brain regions engaged during encoding are driven by the strategy being employed, such findings could hold clinical significance in their implications for rehabilitation strategies for patients with regional brain damage or neurodegenerative disease.

Currently, it remains unclear whether regional encoding activity is fixed to the stimulus-type or driven by the employed strategy. Therefore, the present studies examine whether visual and verbal strategies influence regional subsequent memory effects if the stimulus-type is held constant. In Experiment 1, regional brain responses were examined using rapid-event-related functional magnetic resonance imaging (fMRI) while subjects associated pairs of visually-presented nameable objects using either a visual imagery or verbal rehearsal strategy. Despite the robust differences in regional subsequent memory effects seen when visual versus verbal stimuli are encoded, the prediction was that similar regional distinctions would be seen when the stimulus-type is held constant and subjects are instructed to use a visual versus a verbal strategy. Experiment 2, a modified behavioral version of Experiment 1, was

conducted in two patients recovering from recent aphasic strokes. By examining the impact of using an instructed visual or verbal associative encoding strategy relative to the patients' own natural strategy, the theoretical implications of Experiment 1 were applied to demonstrate potential clinical relevance.

Materials and Methods

Experiment 1

Subjects

Seventeen healthy volunteers (mean age = 24.8 ± 3.2 years, four males) were recruited from the University of California, San Diego (UCSD) community and the surrounding area. All subjects gave informed consent approved by the UCSD Institutional Review Board and had normal or corrected vision. Subjects received monetary compensation for their time. Two subjects were excluded from analyses due to poor behavioral performance.

Stimuli

Two-hundred and sixty-eight color images of everyday objects were used as stimuli in this experiment. Twelve images were used for practice trials prior to scanning to ensure that subjects understood the instructions. While in the scanner,

subjects were shown 256 images presented in concurrent pairs for encoding; each item was shown once resulting in 128 image pairs. One object from each pair was presented to the subject during the post-scan recognition test. Images were acquired from Rossion and Pourtois color Snodgrass images (Rossion & Pourtois, 2004) and Hemera object library (Hemera Technologies Inc).

Experimental Procedure

During the associative encoding task in the scanner, subjects were shown pairs of concurrently presented images, with each pair presented for 2 seconds followed by blank screen for 3 seconds (Figure 13A). All items were paired pseudorandomly to remove obvious semantic, verbal, or visual relationships within pairs. The order of the runs and the pairs assigned to each run were counterbalanced. A fixation cross was presented during jittered interstimulus intervals ranging between 1.5 and 10.5 seconds. The interstimulus intervals were calculated to optimize the study design for modeling the hemodynamic response to trials (Dale, 1999; Dale & Buckner, 1997). Subjects were instructed to encode and associate 64 pairs, split evenly among two functional runs, using the visual strategy of imagining the two items visually merged during the 3-second blank screen following the presentation of the pair without verbalizing the object names (e.g., Figure 13, “Visual”). Subjects were instructed to encode and associate the other 64 pairs, split evenly among two additional functional runs, using the verbal strategy of creating a compound word made up of the names of the two

objects and rehearsing it during the 3-second blank screen following the presentation of the pair without visualizing the objects (e.g., Figure 13, “Verbal”). Subjects were given a button box and were asked to press a button whenever a pair of objects appeared on the screen to make sure that subjects were attending to each image pair. One hundred and twenty-eight image pairs were presented to subjects in the scanner across four 331-second runs. Each image was presented once.

Following the encoding task in the scanner, subjects completed a self-paced post-scan recognition test examining subsequent memory for the associative pair and strategy used (Figure 13B). Subjects were shown one item from each pair previously viewed during the encoding task, i.e., the “cue” item. For each of the 128 stimuli, subjects were asked to verbally report to the examiner their answers to three questions. First, subjects were asked if they visually or verbally associated the cue item with its pair. Second, the examiner read aloud the names of three items, and subjects were asked to indicate which of those three choices was the pair of the cue item. Third, subjects were asked to report their confidence in identifying the correct pair: ‘Not Very,’ ‘Somewhat,’ or ‘Very’ confident. This recognition test lasted approximately 30 minutes.

Functional MRI Parameters

Subjects were scanned using a 3T GE scanner at the Keck Center for Functional MRI at the University of California, San Diego. Functional images were

acquired using gradient-echo, echo-planar, T2*-weighted pulse sequence (repetition time = 2.5 s; one shot per repetition; echo time = 30; flip angle = 90°; bandwidth = 31.25 MHz). Forty slices covering the brain were obtained perpendicular to the long axis of the hippocampus with 3.4 x 3.4 x 4 mm voxels. Field maps were acquired to measure and correct for static field inhomogeneities (S. M. Smith, et al., 2004). A T1-weighted structural scan was acquired in the same plane and with the same voxel size as the functional scans. A high resolution structural scan was also acquired sagittally using a T1-weighted (1 x 1 x 1 mm) inversion recovery prepared fast spoiled gradient recalled sequence.

Data Analysis

Structural data were transformed into Talairach space (Talairach & Tournoux, 1998) by AFNI using nearest-neighbor interpolation (Cox, 1996) after standard landmarks, including the anterior and posterior commissures, were manually defined on the anatomical scans. In order to improve medial temporal lobe (MTL) alignment between subjects, the region of interest large deformation diffeomorphic metric mapping (ROI-LDDMM) alignment technique (Miller, et al., 2005) was applied. Bilateral hippocampus and subregions of the parahippocampal gyrus were defined for each subject on Talairach transformed images. Previously described landmarks were used to define perirhinal and entorhinal cortices (Insausti, et al., 1998) and parahippocampal cortex (Stark & Okado, 2003). These defined anatomical regions of

interest for each subject were normalized using ROI-LDDMM to a modified model of a previously created template segmentation (Kirwan, et al., 2007).

After functional data from each run were field-map corrected (S. M. Smith, et al., 2004), slices were temporally aligned and co-registered using a three-dimensional image alignment algorithm, voxels outside the brain were eliminated using a threshold mask of the functional data, and functional runs were corrected for motion and concatenated, all using the AFNI suite of programs (Cox, 1996). A 4.0 mm FWHM Gaussian filter was also applied to smooth the functional data from each run. A general linear model was constructed using multiple regression analysis; six motion regressors obtained from the registration process were included along with eight behavioral regressors based on subsequent memory performance. Subjects' behavioral trials were sorted based on accuracy and subject ratings of associative memory confidence. Trials were first divided into those in which subjects were instructed to associate the items visually versus verbally. Each of those two groups of trials were then divided into one of four outcomes based on memory performance and confidence: 'high-confidence' if the correct pair item was identified by the subject with a response of "Very" confident; 'medium-confidence' if the correct pair was identified by the subject with a response of "Somewhat" confident; 'low-confidence' if the correct pair was identified by the subject with a response of "Not Very" confident; or 'incorrect' if the correct pair item was not identified. Therefore, there were eight trial outcomes: 'Visual-high-confidence,' 'Visual-medium-confidence,' 'Visual-low-confidence,' 'Visual-incorrect,' 'Verbal-high-confidence,' 'Verbal-

medium-confidence,' 'Verbal-low-confidence,' and 'Verbal-incorrect.' For each outcome, a hemodynamic response function was derived from the fMRI data using signal deconvolution with tent basis functions and a defined time window of 17.5 seconds following the onset of each pair of items (Cox, 1996). Multiple linear regression analysis was used to examine activity for 'high-confidence' correct items encoded using a visual versus a verbal associative strategy (i.e., 'Visual-high-confidence' versus 'Verbal-high-confidence'). To examine subsequent memory effects within each associative encoding strategy, a weighted approach was used to identify brain regions that responded linearly to the four memory conditions (i.e., incorrect < low-confidence < medium-confidence < high-confidence).

Functional data underwent the same Talairach and ROI-LDDMM transformations as were applied to the anatomical data. Whole brain voxel-wise *t*-tests ($p < 0.05$, two-tailed) carried out across all 15 subjects were conducted to examine which brain regions showed more activity for successful associative encoding using a visual versus verbal strategy and which regions showed a significant linearly weighted subsequent memory effect within each strategy separately. In order to correct for multiple comparisons and yield a whole brain significance value of $p < 0.05$ corrected for all comparisons (based on Monte Carlo simulations), functional clusters of least 12 contiguous voxels were identified in these conditions. When a whole brain significance value of $p < 0.001$ was used for illustrative purposes, functional clusters of least 4 contiguous voxels were required in order to correct for multiple

comparisons. Average hemodynamic response functions were extracted for each condition and cluster of interest.

Experiment 2

Subjects

Participants included two female patients with focal lesions localized to the left inferior frontal lobe due to a very recent stroke (Figure 18A). Patient 1, age 79, was tested 37 days post-stroke, and Patient 2, age 46, was tested 13 days post-stroke. Both subjects gave informed consent approved by the UCSD Institutional Review Board and had normal or corrected vision. Subjects received monetary compensation for their time.

Additional Patient Information

Patient 1 was a 79-year-old female with hypertension, hyperlipidemia, left subclavian steel syndrome, and tobacco use. She had been in her normal state of health until the day of admission, when she noted, upon making a phone call, that she was unable to speak. Evaluation in the UCSD emergency department revealed a National Institute of Health Stroke Scale of 4 for severe Broca's nonfluent aphasia and a subtle facial droop, and given that less than three hours had passed since the onset of

symptoms, the patient received tissue plasminogen activator. Computed tomography suggested severe atherosclerotic disease interpreted to be the result of long-term tobacco use. MRI showed an acute ischemic stroke in the anterior middle cerebral artery distribution, and magnetic resonance angiography showed high grade stenosis versus blockade of the anterior insular division of the left middle cerebral artery. She was kept in the ICU for 24 h for close monitoring and antiplatelet therapy was initiated. The patient was ambulatory and had no detectable motor deficits. Physical therapy, occupational therapy, and speech therapy were consulted and followed the patient during her stay. She was discharged with near complete resolution of her speech symptoms.

Patient 2 was a 46-year-old female with no significant past medical history who awoke on the day of admission with an inability to speak, except to answer ‘yes’ or ‘no.’ Upon presentation to the hospital, her National Institute of Health Stroke Scale was 2 for severe Broca’s nonfluent aphasia. There were no other neurologic abnormalities. She was started on aspirin 325 mg daily immediately following her admission. An MRI was obtained confirming an acute stroke in the left frontal lobe as well as a punctuate infarct in the right temporal lobe. There was also an old subclinical right frontal lobe stroke noted on MRI. Magnetic resonance angiography was normal. Hypercoagulability screening was negative. Physical therapy, occupational therapy, and speech therapy were consulted and followed the patient during her stay. She was discharged with ability to create full sentences, but remained with inappropriate pauses in speech, some difficulties in spelling, and occasional dropped prepositions,

pronouns and articles. She was ambulatory and had no motor deficits. She was sent home on 325 mg of aspirin daily and was asked to discontinue her oral contraceptive.

Stimuli

Two-hundred and fifty-six of the stimuli used in Experiment 1 were used in Experiment 2.

Experimental Procedure

The task used for behavioral testing was presented to the subjects on a laptop. Subjects were shown eight sets of encoding and retrieval runs. All items were paired pseudorandomly to remove obvious semantic, verbal, or visual relationships within pairs, and stimulus pairs were randomly assigned to each run. During each encoding run, subjects were shown 16 pairs of concurrently presented images. Each pair was presented for 2 seconds followed by a 3-second blank screen and 5-second fixation cross before the next pair was presented. Following the 16^{th} pair, subjects were given approximately 10 seconds of a distracter task, in which they were asked to count backwards by a certain interval from a particular starting number (e.g., “Count backwards aloud from 47 by 4s…”). Once they counted four numbers aloud, the experimenter advanced to the retrieval run. Subjects were given a retrieval run following each encoding run. During retrieval, subjects were shown one item from

each of the 16 pairs at the top of the screen and three choice images at the bottom of the screen. The position of the correct pair, which was one of the three choice images, varied pseudorandomly between left, center, and right locations. The lure images were two unpaired items from the prior encoding run, so that all three choice images were from the same encoding session. Subjects responded by verbally identifying or pointing to their choice image, and the experimenter pressed the key that corresponded with the selected image, which advanced the run to the next question. The retrieval runs were self-paced. List presentation order allowed assessment for practice effects. For the first three encoding runs, subjects were instructed to associate and remember the pairs and they were not told to use any particular strategy. For the fourth and eighth encoding runs, subjects were given the verbal strategy instructions used in Experiment 1. For the fifth, sixth, and seventh runs, subjects were given the visual strategy instructions used in Experiment 1.

Data Analysis

The number of pairs correctly identified for each run was calculated, and averages were calculated for each strategy (own, verbal, and visual).

Results

Experiment 1

Behavioral Analysis

Subjects identified the correct associative pair on 65% (± 4% SEM) of visual trials and on 58% (± 3% SEM) of verbal trials. Of these trials, subjects reported that they were "Very" confident on 39% (± 5% SEM) of the visual-correct trials and on 20% (± 3% SEM) of the verbal-correct trials.

fMRI Analysis

Controlling the type of stimulus and focusing on successfully encoded associative pairs, the effects of using a visual versus a verbal strategy could be isolated. Brain regions were identified where the size of the BOLD response was greater when subjects successfully encoded pairs of items with high confidence using the visual associative strategy relative to the verbal associative strategy and vice-versa. Regions identified by this contrast ($p < 0.05$, corrected for multiple comparisons) are listed in Table 7. Greater response for visually- relative to verbally-encoded pairs was seen in bilateral middle frontal gyrus (BA 6), inferior and superior parietal cortices (BA 40 and 7), and lateral occipital cortex (BA 19 / 39; Figure 14). There were a large number of voxels showing a greater response for verbally- relative to visually-encoded pairs at this threshold causing single clusters to encompass multiple peaks of activation; for illustration, a threshold of $p < 0.001$, corrected for multiple comparisons, was used in order to highlight distinct foci of activity for this contrast. Regions identified at this threshold are also listed in Table 7. Greater response for

verbally- relative to visually-encoded pairs was seen in left inferior frontal (BA 45) and precentral (BA 4) gyri and bilateral frontal operculum (BA 45 / 47 / 13), medial frontal cortex (BA 6), and medial occipital cortex (BA 19, 18, 30/18; Figure 15). Given that the type of stimulus was the same for both conditions and the only difference was the use of a visual or verbal associative strategy, these differences in regional activity for associative encoding are, therefore, driven by the utilized strategy.

Within-strategy subsequent memory effects were examined using a linear weighted model to isolate regions consistent with the following listing from least to greatest: incorrect, correct with low confidence, correct with medium confidence, and correct with high confidence ($p < 0.05$, corrected). Regions isolated using this model for visually and verbally encoded pairs are listed in Table 8. Under a visual associative strategy, positive subsequent memory effects were seen in left inferior frontal (BA 9, 47) and middle frontal (BA 6) gyri (Figure 16). Under a verbal associative strategy, positive subsequent memory effects were seen in left medial frontal gyrus (BA 6), prefrontal cortex, and medial occipital cortex (BA 18; Figure 17). Left prefrontal regions showed subsequent memory effects for both the visual and verbal encoding strategies. While these regions had distinct foci of peak intensity, there was some overlap of functional clusters between the two conditions.

Experiment 2

Behavioral Analysis

Patient 1 had difficulty with the task, performing poorly in all three strategy conditions. She correctly identified the pair in 42% of trials using her own strategy, 38% of trials using a verbal strategy, and 42% of trials using a visual strategy. All three values are close to that of chance (i.e., 33%). Patient 2, however, showed differences in behavioral performance due to strategy; she identified the correct pair in 77% of trials using her own strategy, 59% of trials using a verbal strategy, and 100% of trials using a visual strategy. The behavioral results are represented in Figure 18B. Practice effects were not evident for either patient across the eight retrieval runs, as percent correct scores for each run were as follows: Patient 1- 38% (own-strategy), 38% (own), 50% (own), 44% (verbal), 38% (visual), 31% (visual), 56% (visual), 31% (verbal); Patient 2- 81% (own-strategy), 75% (own), 75% (own), 56% (verbal), 100% (visual), 100% (visual), 100% (visual), 63% (verbal).

Discussion

The current study examined the effects of using a visual-strategy compared to a verbal-strategy for associative encoding. Subjects were shown the same type of stimulus (i.e., visually-presented drawings of nameable objects) under both associative encoding strategies, which allowed isolation of regional brain responses due to the utilized strategy (Experiment 1). This design also allowed within-strategy subsequent memory effects to be compared between the two associative encoding strategies. Based on the finding of greater left inferior frontal involvement in using a verbal

associative strategy relative to a visual strategy, patients with focal lesions localized to this region were tested on a modified behavioral version of this study (Experiment 2). Although one patient had impaired memory performance for all strategies, one patient showed impaired performance when using the verbal strategy relative to her own strategy, but improved performance when using the visual strategy relative to her own strategy.

Effects of strategy

Prior studies examining the encoding of visual or verbal stimuli have reported different patterns of cortical activity for each stimulus-type, in which visual-stimulus encoding often involves regions including right prefrontal, superior parietal, lateral occipital, and fusiform cortex, while verbal-stimulus encoding often involves regions including left inferior frontal, parietal, superior temporal, lingual, and medial frontal cortex (Achim, et al., 2007; Baker, et al., 2001; Bernstein, et al., 2002; Brewer, et al., 1998; Cansino, et al., 2002; Demb, et al., 1995; Deshpande, et al., 2010; Ferber, et al., 2005; Fletcher, et al., 2002; Fletcher, et al., 2003; Gottlieb, et al., 2010; Grady, McIntosh, Rajah, et al., 1998; Grill-Spector, et al., 2001; Harrison & Tong, 2009; Heun, et al., 1999; Hocking & Price, 2009; Iidaka, et al., 2000; Kapur, et al., 1994; Kapur, et al., 1996; Kirwan, et al., 2008; Kohler, et al., 2000; Lacey, et al., 2010; Lee, et al., 2000; Park & Rugg, 2008; Prabhakaran, et al., 2000; Rama, et al., 2001; Rugg, et al., 2002; Uncapher & Wagner, 2009; Wagner, Poldrack, et al., 1998). Kim (2011)

recently published a meta-analysis of 74 fMRI studies looking at subsequent memory effects for item or associative encoding of verbal or pictorial material. This meta-analysis indicated that left inferior frontal gyrus was more active for encoding verbal material, while bilateral fusiform, occipital, hippocampal, and posterior parietal regions were more active for encoding pictorial material.

In accordance with such findings, the present study found distinct regions recruited for encoding visual- versus verbal-associations, even though the same type of stimulus was presented under both conditions. Furthermore, these distinct regions were the same as those that have often been reported when visual versus verbal stimuli are encoded. The present findings, therefore, suggest that the differences in reported activity during studies using different types of stimuli are driven by the strategies subjects are using and are not simply due to the types of stimuli they encounter.

Within-strategy subsequent memory effects

Within-strategy subsequent memory effects were also seen in regions more responsive to a particular strategy. Given that both encoding conditions involved associating the same type of stimulus, these differences in subsequent memory effects can be attributed to the subjects' use of the two different instructed strategies. While most of those effects were in regions selective to that strategy, some regions showed within-strategy subsequent memory effects for the strategy that did not recruit that region as strongly. For example, left inferior frontal gyrus was more active during

successful verbal encoding than during successful visual encoding (Figure 15), but showed subsequent memory effects within both strategies (Figures 16 and 17).

The current findings support the claim that some cortical regions engaged during the processing of an event are also important for its successful encoding (Rugg, et al., 2002). In line with the "task-dependency" principle, which suggests that the type of task influences the neural correlates of episodic encoding (Otten & Rugg, 2001), the cortical regions with activity predictive of successful encoding depended on whether subjects were associating the items visually or verbally. The current study extends what is known about subsequent memory activity by indicating that even a single stimulus-type can engage diverse subsequent memory networks dictated by the utilized encoding strategy.

Implications for encoding studies

Evidence that using different encoding strategies influences regional responses, even when the stimuli remain constant, has important implications for designing and interpreting studies of successful memory formation. Without instruction, subjects will likely use a strategy related to the type of stimuli they are encoding; this explanation fits with the patterns of cortical activity reported when studies use visual versus verbal stimuli. For example, a prior study examining the encoding of visual object pairs in which subjects were not instructed to use any particular associative strategy found increased activity in cortical regions including left prefrontal, inferior parietal, and

middle occipital cortices (Hales, et al., 2009), all of which were engaged during visual encoding in the present study. Subjects' individual predilection for one strategy over another may also have an effect, and is a topic for further examination, but such individual differences are expected to cancel out or have minimal impact on group data as more robust group effects dominate the resulting activations. In the absence of explicit strategy instruction, strategy remains influenced by the selected stimulus-type or modality.

Examining brain activity in response to the use of different encoding strategies is an important area of research; however, the current findings have cautionary implications. Many studies have examined different levels of processing, i.e., deep versus shallow encoding or relational versus item encoding. If the instructions for the two types of processing differ in their demand on using visual or verbal encoding strategies, there could be confounding effects between strategy use and level of processing. Given the current findings that explicit strategy use dominates over the implicit effects of the presented stimulus-type, such potential confounds are an important consideration for designing future studies.

Potential clinical applications

Impairments that result from neurological disease or damage can extend beyond primary cognitive findings, such as in the verbal or visuospatial domains, to impact memory. Once the affected brain regions have been identified, an important

component of rehabilitation is targeting and retraining intact brain regions and pathways to reorganize and compensate for the impairment. The processes and treatments involved in the functional reorganization of motor pathways have been extensively studied in patients after suffering a stroke (Ward, 2004). Theoretically, the same principles could be applied to rehabilitating patients with damage in non-motor brain regions that cause different functional deficits. For example, following a stroke or focal damage to the left inferior frontal lobe, a patient is likely to be aphasic, and although other brain regions remain unaffected, this patient can have disproportionate difficulty remembering grocery lists or verbal directions. However, the results from Experiment 1 suggest that the brain regions engaged during an encoding task are not locked to the stimulus-type, but are flexible and can be controlled by top-down influences of the employed strategy. Therefore, individuals might improve memory performance by using a strategy that avoids the damaged tissue.

This hypothesis was tested in Experiment 2 using a modified behavioral version of Experiment 1 in two patients with recent strokes localized to the left inferior frontal lobe. Although the two patients suffered damage to very similar brain regions, their behavioral performances on the task differed. Patient 1 barely performed above chance levels of 33% correct for any of the three strategies, suggesting poor general memory in this older individual. Patient 2, however, was younger and, aside from the isolated infarction, in otherwise good health. She exhibited some memory impairment when instructed to use her own associative encoding strategy, and this deficit became more pronounced when she performed the task using a verbal strategy.

Greater impairment with using a verbal strategy was not surprising given the finding of enhanced left inferior frontal engagement during verbal associative encoding in Experiment 1. However, when Patient 2 was instructed to abandon the verbal strategy and only use a visual associative encoding strategy, her performance improved to 100% for all three runs. This behavioral performance improvement occurred despite her reluctance to use a strategy that she thought would be suboptimal, as she considered herself to be a 'verbal person.' Her impaired memory performance when using her own strategy was possibly due to her continued use of a strategy that was no longer ideal given her brain damage. By abandoning the verbal strategy, she was no longer relying on the integrity of this brain region and showed marked improvement in her memory performance.

The results of the first experiment elucidate how engagement in a particular associative strategy dictates which brain regions are recruited for encoding. Such findings are relevant to both past and future investigation into regional brain involvement in encoding. In addition, the outcome of the second experiment gives hope that the potential implications of these findings may extend beyond basic research and towards developing possible targets within clinical treatment, in that a possible adaptive approach might be to teach patients to rely upon memory strategies that avoid damaged brain regions and engage spared regions.

Acknowledgments

Chapter 5, in full, is a reprint of the material as it was submitted for consideration for publication. Hales, Jena B.; Brewer, James B. The dissertation author was the primary investigator and author of this paper.

CHAPTER 6:

DISTINCT PARIETAL AND FRONTAL CONTRIBUTIONS TO SEQUENTIAL OBJECT-LOCATION ASSOCIATIVE ENCODING

Abstract

Frontoparietal involvement in top-down, goal-directed attention and visuospatial encoding has been strongly supported; however, the contributions of frontal and parietal regions to these processes remain controversial. This study used fMRI to examine associative encoding of sequentially presented spatial cues and object stimuli. The spatial cue preceded the centrally-displayed visual object by a jittered delay interval to isolate object encoding with location information from object encoding without location information. For confidently remembered objects, superior parietal regions were modulated by attempted visuospatial binding regardless of success. In contrast, the response in medial / middle frontal regions was predictive of successful visuospatial binding.

Real-world objects tend to have associated locations, and commonly in daily life, an object needs to be remembered along with its location. Prefrontal and medial temporal regions have often been the focus of studies examining general subsequent memory effects (beginning with Brewer, et al., 1998 and Wagner, Schacter, et al., 1998); however, more recently, the contribution of parietal regions to episodic encoding has gained attention (see Uncapher & Wagner, 2009 for review), particularly when spatial processing is required (see Husain & Nachev, 2007 for review). Frontoparietal activity has been widely reported in tasks involving spatial working memory (Bledowski, et al., 2010; Diwadkar, et al., 2000; Haxby, et al., 2000; Piekema, et al., 2010; Sala, et al., 2003; Schon, et al., 2008; Ungerleider, et al., 1998; Wager & Smith, 2003) and visuospatial associative encoding (Cansino, et al., 2002; Gould, et al., 2005; Gould, et al., 2003; Hannula & Ranganath, 2008; Haxby, et al., 1991; Kesner, 2009; Postma, et al., 2008; Sommer, Rose, Glascher, et al., 2005; Sommer, Rose, Weiller, et al., 2005; van Asselen, et al., 2009). Neuroimaging studies of object-location encoding, in which subjects were shown pictures of objects in particular locations and were subsequently tested on these spatial associations, found subsequent memory effects for object-location binding in superior parietal and prefrontal regions (Cansino, et al., 2002; Gould, et al., 2005; Gould, et al., 2003; Sommer, Rose, Weiller, et al., 2005). Additionally, a recent study examining patients with focal damage due to ischemic or hemorrhagic stroke reported impairment in object-location binding in patients with left posterior parietal cortex lesions (van Asselen, et al., 2009). This frontoparietal involvement in spatial encoding has also

been salient in reviews of findings from human (Postma, et al., 2008) and rat (Kesner, 2009) studies.

Although frontoparietal regions have been strongly implicated in visuospatial encoding, the contribution of particular subregions has been a matter of discussion. Some recent reviews have described a dorsal-ventral distinction in frontoparietal involvement in episodic memory through its role in attention (Cabeza, et al., 2008; Uncapher & Wagner, 2009). Corbetta and Shulman (2002) performed an extensive review of neurophysiological and psychological findings regarding visual attention. They established and described two separate attention systems: a dorsal frontoparietal network for goal-directed, top-down attention and a ventral frontoparietal network for stimulus-driven, bottom-up attention. Additionally, they discussed superior parietal and frontal involvement in top-down visuospatial attention. Extending this dual-process model for attention to episodic memory, Cabeza et al. (2008) described their attention to memory model, AtoM, which complements and applies the dorsal-ventral distinction within the frontoparietal attention network. In a recent review, Uncapher and Wagner (2009) acknowledged the additional involvement of parietal regions in successful encoding and addressed this role in light of the dual-attention perspective on parietal activity. They presented converging evidence that dorsal posterior parietal cortex is more active during the encoding of subsequently remembered events of all stimulus types, but particularly when involving spatial attention.

Despite this evidence supporting a dorsal frontoparietal network for controlling goal-directed attention within visuospatial encoding, unanswered questions remain regarding the specific contributions of frontal and parietal regions to the different components of this memory formation process. The current study was designed to tease apart the components of visuospatial encoding by temporally separating the spatial cue from the presentation of the object. By varying the presence or absence of location information in the cue, the successful encoding of individual objects with or without prior location instruction and with or without successful spatial binding could be examined.

Seventeen healthy volunteers (mean age = 25.3 ± 2.8 years, seven males) were recruited from the University of California, San Diego (UCSD) community and the surrounding area. All subjects gave informed consent approved by the UCSD Institutional Review Board, had normal or corrected vision, and received monetary compensation for their time. Three subjects were excluded from analyses, two for having poor behavioral performance (with three and zero ‘correct location’ trials while the other subjects had no fewer than ten ‘correct location’ trials) and one for having magnetic resonance signal artifact that interfered with analysis and led to insufficient quality of functional data. Stimuli consisted of 168 color images of everyday objects (Bakker, Kirwan, Miller, & Stark, 2008). While undergoing functional magnetic resonance imaging (fMRI), subjects were sequentially shown single 2 x 2 grids, with or without an identified quadrant, followed by an object. Figure 19A illustrates the timing of the 128 location-object pair trials. Subjects were instructed that if the grid

had a circle in one of the quadrants (“Location” trial), to imagine and remember the following object as located in that quadrant, and if the grid was blank (“No-Location” trial), to remember the object without spatial information. Subjects received an equal number of Location and No-Location trials. Following the scan, subjects performed a self-paced recognition test of object and spatial memory for each of the 128 objects. Subjects were asked to make object-memory and spatial-memory judgments for each of the 128 objects presented during the scan, and 40 additional novel objects were included for the object-memory judgment only (see Figure 19B). Prior to scanning, each subject was shown one grid-object pair (not used during testing) as a practice trial to ensure understanding of the instructions.

Subjects were scanned using a 3T GE scanner at the Keck Center for Functional MRI at the University of California, San Diego. Functional images were acquired using gradient-echo, echo-planar, T2*-weighted pulse sequence (repetition time = 2.5 s; one shot per repetition; echo time = 30; flip angle = 90°; bandwidth = 31.25 MHz). Forty slices covering the brain were obtained perpendicular to the long axis of the hippocampus with 3.4 x 3.4 x 4 mm voxels during the four 395-minute functional runs. Field maps were acquired to measure and correct for static field inhomogeneities (S. M. Smith, et al., 2004). A T1-weighted structural scan was acquired in the same plane and with the same voxel size as the functional scans. A high resolution structural scan was also acquired sagittally using a T1-weighted (1 x 1 x 1 mm) inversion recovery prepared fast spoiled gradient recalled sequence.

Structural data were transformed into Talairach space (Talairach & Tournoux, 1998) by AFNI using nearest-neighbor interpolation (Cox, 1996) after standard landmarks, including the anterior and posterior commissures, were manually defined on the anatomical scans. Medial temporal lobe (MTL) alignment between subjects was then optimized using the region of interest large deformation diffeomorphic metric mapping (ROI-LDDMM) alignment technique (Miller, et al., 2005; for more details on these methods see Hales & Brewer, 2011).

For two subjects, one functional run (out of four) was discarded due to scanner malfunction or excessive subject motion identified visually during pre-analysis quality checks. After functional data from each run were field-map corrected (S. M. Smith, et al., 2004), slices were temporally aligned and co-registered using a three-dimensional image alignment algorithm, voxels outside the brain were eliminated using a threshold mask of the functional data, and functional runs were corrected for motion and concatenated all using the AFNI suite of programs (Cox, 1996). A 4.0 mm FWHM Gaussian filter was also applied to smooth the functional data from each run. A general linear model was constructed using multiple regression analysis; six motion regressors obtained from the registration process were included along with six behavioral regressors based on subsequent memory performance (three subjects only had five behavioral regressors due to very strong memory performance). Subjects' behavioral trials were sorted based on object-memory accuracy and confidence and spatial-memory accuracy. The objects remembered with high confidence ("definitely old") were divided into four trial types based on the accuracy of the spatial judgment:

(1) the correct location quadrant was identified, ‘correct location;’ (2) the correct location quadrant was not identified, ‘incorrect location;’ (3) the lack of a location quadrant was correctly identified, ‘correct no-location;’ (4) the lack of a location quadrant was not identified, ‘incorrect no-location.’ Only ‘correct location, ‘incorrect location,’ and ‘correct no-location’ trials were included for group analyses. Additional trials, modeled but not included in further analyses, consisted of all objects rated as “new,” which were grouped as ‘forgotten’ trials, and objects rated as “maybe old” or “probably old,” which were grouped as ‘weak-memory’ trials. Signal deconvolution with tent basis functions and a defined time window of 15 seconds following the onset of each object was used to derive hemodynamic response functions from the fMRI data (Cox, 1996). Multiple linear regression analyses were used to separately examine the activity for all three conditions.

Functional data underwent the same Talairach and ROI-LDDMM transformations as were applied to the anatomical data. Whole brain voxel-wise *t*-tests ($p < 0.001$, two-tailed) carried out across all 14 subjects were conducted to examine positive regional responses to ‘correct location,’ ‘incorrect location,’ and ‘correct no-location’ trials, and functional clusters of least 4 contiguous voxels were identified in each analysis to yield a whole brain significance value of $p < 0.001$ corrected for all comparisons (based on Monte Carlo simulations). In order to isolate areas involved in forming object-location associations, regions significantly active for ‘correct location’ but not for ‘correct no-location’ trials were isolated. Functional voxels showing this contrast were identified by exclusively masking the results of the ‘correct location’

clustered *t*-test with the results of the 'correct no-location' clustered *t*-test (each at $p < 0.001$, and then clustered at 4 contiguous voxels). Responses to 'incorrect location' trials were then examined in order to isolate regions modulated by (1) *intent* to associate spatial information during object encoding versus (2) *success* in object-location binding. Within the isolated functional clusters, those voxels with significant activity for 'incorrect location' trials suggested that the area was responsive for associating spatial information with object encoding regardless of binding success; those voxels that were exclusively active for 'correct location' trials suggested that the area's activity was predictive of successful object-location binding. For illustrative purposes, average hemodynamic response functions were extracted for each condition for the 15-second time period following the onset of the object within the five largest clusters (responses were averaged across two of these clusters that were located in the same anatomical region).

Object memory did not differ between Location and No-Location trials, as subjects confidently remembered 72% (± 4% SEM) of the objects and 70% (± 4% SEM) of the objects for each trial-type, respectively ($t_{(13)} = 0.63$, $p > 0.5$). Of those confidently remembered objects, 55% (± 5% SEM) had a correctly identified associated quadrant location and 60% (± 4% SEM) had a correct 'no-location' judgment. Location responses were selected from six choices, one of which was an 'unsure' judgment (Figure 19B).

During the scan, the presentation of the visual object was temporally separated from the spatial cue thereby allowing the isolation of visual object encoding with prior location information from visual object encoding without prior location information. Brain regions involved in forming object-location associations were identified as those with activity for 'correct location' trials ($p < 0.001$, corrected for multiple comparisons) that were nonoverlapping with regions active for 'correct no-location' trials ($p < 0.001$; Table 9). Within the five largest isolated functional clusters, one of the two contrasts, *intent* versus *success* of object-location binding, yielded a clearly predominant response (> 80% of the cluster volume) (Figure 20A). The greatest response in bilateral superior parietal cortex (BA 7) was for attempting to associate spatial information with object encoding. In this region, increased activity was seen for successful object encoding when location information was to be associated, regardless of whether the location was remembered or forgotten (Figure 20B). Therefore, these findings suggest that simple intention to link spatial components to a successfully encoded object strongly drives superior parietal lobe regardless of binding success.

In contrast, the predominant response in bilateral medial frontal and left middle frontal cortex (BA 6) was for successful object-location binding. In this region, increased activity was seen for successful object-location binding relative to successful encoding of objects for which associated location information was absent or forgotten (Figure 20C). In other words, greater involvement of medial / middle frontal regions was predictive of object-location binding success.

In daily life, people encounter objects that need to be associated with a different location from where that event is occurring. This study is believed to be the first to look at forming visuospatial memories for objects and previously cued locations. Such a design allowed the isolation of object encoding with or without prior location information. As a result, the specific involvement of frontal and parietal regions to visuospatial encoding were disentangled, as parietal regions were modulated by the attempt to bind the object to a location, regardless of success, while frontal region responses were predictive of binding success.

Although some prior studies have reported subsequent visuospatial memory effects in both frontal and parietal regions (Cansino, et al., 2002; Sommer, Rose, Weiller, et al., 2005), these studies have used object stimuli that were presented to subjects in the cued location. The current study, however, found a dissociation in how frontal and parietal regions were modulated during visuospatial encoding when the location cue was not visually concurrent with the presented object. Therefore, when a cued location was provided, subject needed to maintain that location across the delay in order to associate and encode the following object with that location. Given the established role of parietal regions in attention, and especially spatial attention, it's possible that the responses seen in parietal regions in the present study are attentional; however, this would suggest that increased spatial attention did not influence subsequent visuospatial binding success, which would be in contrast to previous studies which found that selective attention influenced binding success (e.g. Uncapher & Rugg, 2009; Uncapher & Wagner, 2009). Nevertheless, these findings suggest a

model for how frontal and parietal regions contribute to visuospatial encoding, in which attempted binding of object and spatial information engages superior parietal regions, while binding success is predicted by additional medial / middle frontal response (Figure 21). The unique design of the current study allowed examination of the specific contributions of parietal and frontal regions to visuospatial associative encoding and demonstrated that these regions are differentially engaged by spatial binding attempt versus success.

Acknowledgments

Chapter 6, in full, is a reprint of the material as it was submitted for consideration for publication as a brief communication. Hales, Jena B.; Brewer, James B. The dissertation author was the primary investigator and author of this paper.

CHAPTER 7:

CONCLUSIONS

The studies described in this dissertation have thoroughly examined the coordination and contribution of brain region activity to successful associative memory formation and have tackled existing questions in this area of neuroscience research using behavioral memory testing and functional magnetic resonance imaging (fMRI). These findings have addressed how the brain attempts to form and succeeds in forming associative memories for temporally-discontiguous stimuli and have found that using different associative strategies influences which brain regions are engaged in encoding. Furthermore, this research found a potential clinical approach for treatment of domain-related cognitive and memory deficits in patients with focal brain damage due to stroke or other neurological disease or damage, in that memory might be improved through an adaptive strategy designed to avoid damaged, and engage spared, brain regions.

Chapter 2 presented the first study which looked at associative encoding of sequentially presented visual objects using a novel paradigm to temporally separate the associative cue from the binding of the objects (Hales, et al., 2009). This design elucidated the dissociable contributions of prefrontal and medial temporal regions to associative encoding using fMRI. Although prior studies had reported similar involvement of prefrontal and medial temporal lobe (MTL) regions in forming associative memories, this study revealed involvement of both regions at binding, but

only prefrontal response to the associative cue. Both prefrontal and medial temporal responses to a visual stimulus were modulated by the presence or absence of preceding associative instruction; however, each region subserves a different function in the maintenance and binding of visual stimuli into memory.

Chapter 3 presented the second study, which used the same paradigm to explore subsequent memory for associations between temporally discontiguous stimuli and the involvement of working memory in bridging the temporal gap between to-be-associated events using fMRI (Hales & Brewer, 2010). This study proposed a model for associating temporally-discontiguous events, in that neocortical working memory regions maintain neural representation of an item across a delay, allowing concurrence between that active representation and later ones for hippocampal binding. This study provided evidence for a functional dissociation between frontoparietal regions, which were more active for binding associative information across time, and posterior cortical regions, which were more active for forming individual memories of visual objects. Such findings suggested coordination between regions involved in working and long-term memory in the ability to associate information across discrete events into memory.

Chapter 4 presented the third study which used a similar paradigm, using fMRI, to examine the temporal aspect of successful associative memory formation to identify when activity in medial temporal and additional neocortical processing regions, including prefrontal and lateral occipital cortex, is predictive of associative

memory formation (Hales & Brewer, 2011). Using a fixed delay period between the presentation of the first and second object of each pair allowed analysis of the entire time course of each trial. Although primate lesion and electrophysiology studies have established the importance of anterior MTL regions, including perirhinal and entorhinal cortices, in associative memory formation, this study extends those findings by demonstrating that increased activity in left prefrontal cortex, lateral occipital cortex, and anterior MTL happens once the associative pair is completed. Additionally, such activity is predictive of successful associative encoding of temporally discontiguous visual object pairs when item memory strength is controlled. Increased activity during the delay period within pairs, suggestive of object maintenance, occurred in some of these regions; however, such increases were not sufficient to show subsequent memory effects and were likely due to attempting to encode the association.

Chapter 5 presented the fourth study which examined the unanswered question of whether differences in regional activity and subsequent memory effects seen when different stimulus-types are being encoded, e.g., visual versus verbal stimuli, are also seen when different encoding strategies, e.g., visual versus verbal, are used with a constant stimulus-type. In other words, are regional processing and subsequent memory effects driven by the stimulus-type being encoded or by the encoding strategy being employed? The findings for encoding visual nameable object pairs using a visual versus verbal associative strategy, using fMRI, were similar to those previously reported for encoding visual versus verbal stimuli, respectively, suggesting that

engagement in a particular associative strategy dictates which brain regions are recruited for encoding. Relevance of these findings may influence the interpretation of past and future studies of regional brain involvement in encoding. The potential clinical impact of these findings was probed using a modified behavioral version of this study in two patients recovering from recent left inferior frontal lobe strokes. The results of the fMRI study suggested that verbal encoding should be impaired in these patients given the increased involvement of left inferior frontal regions in verbal, relative to visual, associative encoding. As expected, the use of a verbal encoding strategy further impaired memory performance; however, using the visual strategy improved one patient's performance even beyond that when using her own natural associative encoding strategy. While further study is needed into the potential treatment benefits of encoding strategy training, this result gives hope that the potential implications of these findings may extend beyond basic research towards developing possible targets within clinical treatment and that a possible adaptive approach might be to teach patients to rely upon memory strategies that avoid damaged brain regions and engage spared regions.

Chapter 6 presented the fifth and final study, which used fMRI to examine visuospatial associative encoding when the spatial cue and object stimulus were temporally separated, allowing isolation of object encoding with or without prior location information. Frontoparietal activity has been associated with visuospatial encoding; however, the specific contributions of frontal and parietal regions to this process had not been disentangled. By separating the spatial cue from the encoding of

the object so that they were not visually concurrent, this study found a dissociation in how these two regions were modulated during visuospatial encoding when the object was remembered with high confidence. Superior parietal regions were modulated by attempted visuospatial binding, regardless of success, whereas the response in medial and middle frontal regions was predictive of successful visuospatial binding.

Together, the studies in this dissertation have shown how different brain regions involved in working memory processing and long-term memory encoding contribute to and are coordinated in attempting to form and successfully forming associative memories for visual object and object-location pairs. The real-world process of associating events across time was examined in a research setting, thereby allowing the distinct contributions of specific brain regions to associative object and visuospatial encoding to be disentangled from the active networks commonly described in prior studies. Additionally, the driving impact that encoding strategy has on regional involvement in associative memory formation has implications for future development both in basic research and for potential clinical treatments.

TABLES

Table 1: Significantly active brain regions for paired stimuli versus unpaired stimuli (2P versus 2U).

	#Volume	**x**	**y**	**z**	***t*-values**
L DLPFC (BA 9/46)	3904	-46	14.4	25.5	5.54
L VLPFC (BA 45)	2816	-46.6	22.1	5	5.49
L Superior Frontal (BA 6)	2624	-4.5	11.3	52.4	6.65
L Middle Frontal (BA 6)	2176	-25.6	0.2	51.6	7.18
L Angular (BA 39)	1344	-28.6	-60.3	32.2	4.60
L Parahippocampal (BA 36)	896	-26.3	-35.3	-14.8	5.55
L Middle Occipital (BA 19)	640	-48.9	-57.9	-3	4.12
R Cingulate (BA 31)	640	26.4	-48.8	25.1	4.11
L Middle Temporal (BA 21)	576	-53	-30.8	-6.1	5.93
R Cerebellum	512	29.7	-51.7	-27.9	5.12
R Supramarginal (BA 40)	512	51.1	-47.3	33.4	-3.95
L Inferior Temporal (BA 20)	448	-50.3	-51.7	-13.6	4.90
L Inf Parietal (BA 40)	448	-48.5	-32.1	35.5	5.55
R Insula (BA 47)	384	31.4	17.3	2.5	4.03
L Inferior Parietal (BA 40)	320	-42	-49.6	45.9	3.68
L Caudate	256	-14	10.2	4.1	3.25
R Supramarginal (BA 40)	256	54	-51.1	20.2	-4.18
L Supramarginal (BA 40)	256	-41	-43	35.2	3.92
L Precentral (BA 6)	256	-46	-0.7	48.8	4.74

Table 2: Significantly active brain regions for two paired stimuli (3.5-sec ISI) versus two unpaired stimuli (3.5-sec ISI).

	#Volume	**x**	**y**	**z**	***t*-values**
L DLPFC (BA 9)	4480	-47.3	7.5	35.3	5.93
L Angular (BA 39)	3584	-32.6	-56.4	35.5	5.82
L Medial Frontal (BA 6)	1280	-5.4	5.3	52.5	6.71
L Middle Temporal (BA 21)	704	-47	-46.6	5.8	4.50
L Fusiform, (BA 37)	512	-37.4	-43.3	-8.6	4.05
R Cuneus (BA 19)	512	19	-83.9	30.7	-3.79
R Superior Temporal (BA 39)	512	32.1	-52.7	31.6	5.18
R Cerebellum	384	1	-38.1	-14.8	3.91
L Middle Frontal (BA 6)	384	-27.3	-7.1	46.2	3.80
L Middle Temporal (BA 39)	320	-39.5	-50.2	10.9	5.39
L Superior Frontal (BA 10)	320	-31.6	48.8	17.7	3.68

Table 3: Significantly active brain regions for associative versus item-only trials.*

$p < 0.05$**	#Volume	x	y	z	*t*-values
L Precuneus (BA 7)	35904	-26	-65	28	5.2375
L Precentral Gyrus (BA 6)	31424	-26	-9	52	5.0144
R Cerebellum	11392	30	-69	-24	4.4381
L Striatum	6848	-18	7	8	4.4458
R Lingual Gyrus (BA 18)	5760	10	-77	4	4.4084
R Precuneus (BA 31)	3264	22	-69	20	4.3196
L Cerebellum	1408	-14	-53	-40	3.4985
R Cerebellum	1344	18	-41	-28	3.245
L Cuneus (BA 17)	1280	-10	-81	12	3.4166
R Precentral Gyrus (BA 6)	1152	22	-13	52	3.9336
R Middle Frontal Gyrus (BA 10)	1088	34	35	20	3.2486
L Precentral Gyrus (BA 4)	1088	-26	-25	60	3.4927
L Midbrain	1024	-6	-21	-8	3.8523
R Striatum	960	22	-5	16	4.089
L Cerebellum	832	-10	-57	-4	3.4716
L Cerebellum	704	-6	-41	-24	2.5972
L Cerebellum	704	-14	-61	-16	4.1222
L Inferior Frontal Gyrus (BA 47)	640	-50	39	-8	3.4677
L Thalamus	640	-18	-13	4	3.2927
R Superior Frontal Gyrus (BA 8)	640	18	27	48	-2.9286
R Hippocampus	576	30	-33	-8	3.4074
L Lingual Gyrus (BA 18)	576	-18	-81	-4	2.8385
L Parahippocampal Gyrus (BA 19)	576	-22	-53	0	3.4153
L Putamen	512	-30	3	4	2.858
R Precuneus (BA 7)	512	6	-61	44	2.6297

*coordinates correspond to the voxel of maximum intensity for each cluster

**corrected for multiple comparisons

Table 4: Significantly active brain regions for item-only versus forgotten trials.*

$p < 0.05$**	#Volume	x	y	z	*t*-values
R Parahippocampal Gyrus (BA 36)	9728	26	-37	-12	3.6068
L Fusiform Gyrus (BA 37)	5184	-42	-49	-12	3.795
R Insula (BA 13)	4224	26	-29	20	3.9061
L Posterior Cingulate (BA 30)	2816	-26	-49	20	3.1384
L Inferior Occipital Gyrus (BA 18)	1408	-30	-89	-4	3.9172
L Cingulate Gyrus (BA 31)	960	-26	-25	36	3.5273
L Cingulate Gyrus (BA 31)	896	-18	-33	32	3.4189
Brainstem	832	6	-13	-28	3.1858
R Posterior Cingulate (BA 23)	768	2	-33	16	2.8386
L Thalamus	576	-22	-25	4	2.7505
R Cingulate Gyrus (BA 32)	576	18	15	36	2.8948
R Precuneus (BA 31)	576	18	-53	32	2.8237
L Cerebellum	512	-2	-41	-12	3.3703
L Fusiform Gyrus (BA 20)	384	-38	-1	-20	3.3649
L Cerebellum	384	-22	-45	-16	2.5557
R Thalamus	320	22	-25	4	2.6238
R Superior Temporal (BA 41)	320	34	-41	12	3.5759
R Cuneus (BA 19)	320	22	-85	36	2.6615
L Precuneus (BA 19)	320	-18	-85	44	3.1007
R Medial Frontal Gyrus (BA 6)	320	2	-5	48	2.9164

*coordinates correspond to the voxel of maximum intensity for each cluster
**corrected for multiple comparisons

Table 5: Behavioral Results.

Memory Question	**Memory Outcome**	**Percent of Trials**	**Average Trials / Subject**
Item	High Confidence	61% ± 5% SEM*	76.1 ± 6.1 SEM
Association	Associative	76% ± 5% SEM†	59.9 ± 7.3 SEM
	Item-Only	24% ± 5% SEM†	16.2 ± 3.0 SEM

*percent of all trials
†percent of High Confidence Item trials

Table 6: Significantly active brain regions for associative versus item-only trials.*

$p < 0.01$[†]	**#Volume**	**x**	**y**	**z**	***t*-values**
L Medial/Middle Frontal (BA 6)	1984	-18	-1	56	4.6394
L Lateral Occipital (BA 19)	1216	-46	-57	-4	4.0167
L Dorsolateral Prefrontal (BA 46)	704	-38	31	12	4.3769
L Ventrolateral Prefrontal (BA 47)	512	-42	35	-4	4.7694
R Superior Parietal/Postcentral (BA 7)	320	14	-45	72	4.3278
$p < 0.05$[‡]	**#Volume**	**x**	**y**	**z**	***t*-values**
L Entorhinal Cortex	128	-17	-18	-20	2.7346
L Perirhinal Cortex	128	-25	1	-26	2.6658

[*]coordinates correspond to the voxel of maximum intensity for each cluster

[†]corrected for multiple comparisons

[‡]uncorrected for multiple comparisons (active voxels for associative versus item-only trials overlapping with anatomically defined MTL substructures

Table 7: Regional effects of associative strategy on high-confidence encoding.

Region	BA	Volume*	x	y	z	*t*-values
Visual > Verbal[†]						
L / R middle frontal gyrus	6	1088	-26	-9	56	3.46
	6	1088	22	-9	56	3.52
L / R inferior parietal lobule	40	1856	58	-29	40	4.56
	40	3136	-54	-29	36	4.26
	40	1472	34	-41	40	3.32
L / R superior parietal lobule	7	1920	-18	-73	52	3.79
	7	1216	14	-65	52	3.29
L / R lateral occipital cortex	39	6144	46	-69	24	5.80
	19	5824	-30	-81	36	4.52
Verbal > Visual[†]						
R cingulate	30	326592	22	-57	8	7.01
sub-clusters at higher threshold[‡]						
L inferior frontal gyrus	45	1344	-42	19	4	6.69
L / R frontal operculum	47/13	576	-30	23	0	5.80
	45/13	320	30	27	8	5.39
B medial frontal gyrus	6	896	-2	-5	64	6.56
L precentral gyrus	4	832	-50	-9	48	5.45
L postcentral gyrus	5	256	-26	-37	60	4.61
L / R medial occipital cortex	30/18	8320	22	-57	8	7.01
	19	448	-26	-61	0	5.66
	19	320	-18	-65	4	5.47
	18	256	-22	-73	16	5.16
L / R cingulate	31	320	-2	-17	44	5.26
	30	256	22	-49	12	5.11
L white matter	-	576	-30	-49	4	6.00
	-	256	-30	-41	20	5.18
	-	256	-30	-37	24	5.35
R cerebellum	-	3328	30	-65	-48	4.88
	-	896	26	-33	-24	3.29
Brain stem	-	1664	-2	-29	-32	3.31

*cluster volumes (mm^3); coordinates correspond to the voxel of maximum intensity for each cluster
[†]$p<0.05$ corrected for multiple comparisons
[‡]$p<0.001$ corrected for multiple comparisons

Table 8: Regional subsequent memory effects within a visual or verbal associative strategy.

Region	BA	Volume*	x	y	z	*t*-values
Visual subsequent memory regions[†]						
L inferior frontal gyrus	47	2176	-42	35	0	3.40
	9	832	-34	11	24	2.91
L middle frontal gyrus	6	2688	-26	11	52	4.88
Verbal subsequent memory regions[†]						
L prefrontal cortex	45	15232	-26	35	16	7.32
L medial frontal gyrus	6	1216	-6	15	44	4.41
L medial occipital cortex	18	2240	-10	-69	-4	3.35
L superior temporal gyrus	13	17600	-42	-45	20	5.50
R insula	13	1536	26	27	12	3.77
	-	1728	38	-65	-28	3.37
R white matter	-	20032	30	-45	4	5.65
	-	2048	22	11	24	3.50
	-	1152	26	-5	24	3.33

*cluster volumes (mm^3); coordinates correspond to the voxel of maximum intensity for each cluster; only positive activations listed

[†]$p<0.05$ corrected for multiple comparisons

Table 9: Regions activated by the object-location associative encoding task.*

Region	BA	Volume†	% of volume predicting successful binding‡	x	y	z
L superior parietal	7/40	6208	11	-27	-57	47
L / R medial frontal	6	3584	86	-4	8	55
L middle frontal	6	2496	82	-30	-4	53
R superior parietal	7	2176	12	26	-57	44
L middle frontal	6	1536	88	-46	3	38
L fusiform	37	1344	48	-39	-47	-11
R inferior frontal	9/6	1152	67	40	3	32
L middle frontal	9	704	82	-39	31	32
L inferior parietal	40	640	70	-49	-32	42
R cerebellum	-	640	100	40	-47	-22
R fusiform	37	512	25	44	-57	-8
L cerebellum	-	512	100	-29	-50	-21
R cerebellum	-	448	43	29	-53	-22
R middle frontal	9	256	100	31	33	27
L white matter	-	256	100	-38	0	25

*coordinates correspond to cluster center of mass; $p<0.001$ corrected for multiple comparisons

†cluster volumes (mm^3)

‡the remaining % of the cluster also responded to incorrect location trials

FIGURES

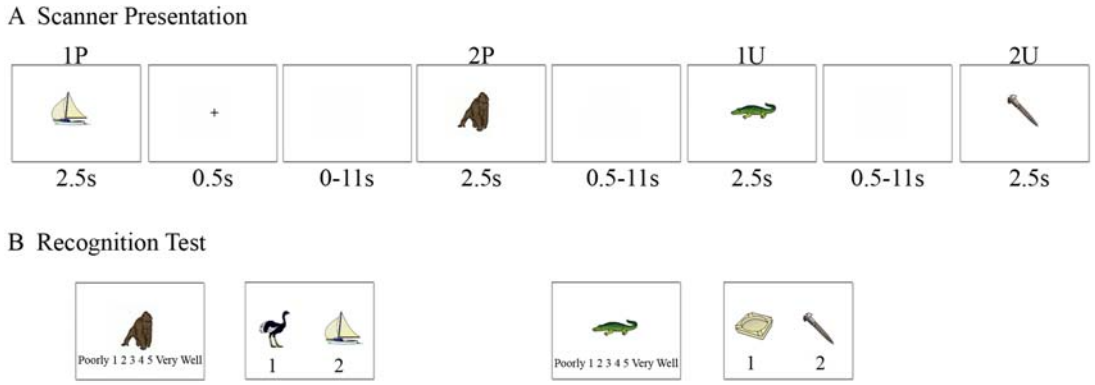

Figure 1: Experimental design. (A) Schematic depiction of the scanner presentation of two paired and two unpaired stimuli. For the first 0.5 sec of a 0.5- to 11-sec ISI, the associative memory instruction of a plus-sign is present between two images that should be paired (1P and 2P) and is not present between two images that should remain unpaired (1U and 2U). (B) Schematic depiction of the recognition test conducted following the scan. Participants were asked if they remember seeing the image in the scanner ("poorly" if they think it is a novel item; "very well" if they remember seeing the item). If the image was presented in the scanner, participants were then shown a second screen with two choice images; they were asked to report which image (1 or 2) was the associated pair if the target image was paired or to report if the target image was unpaired (3).

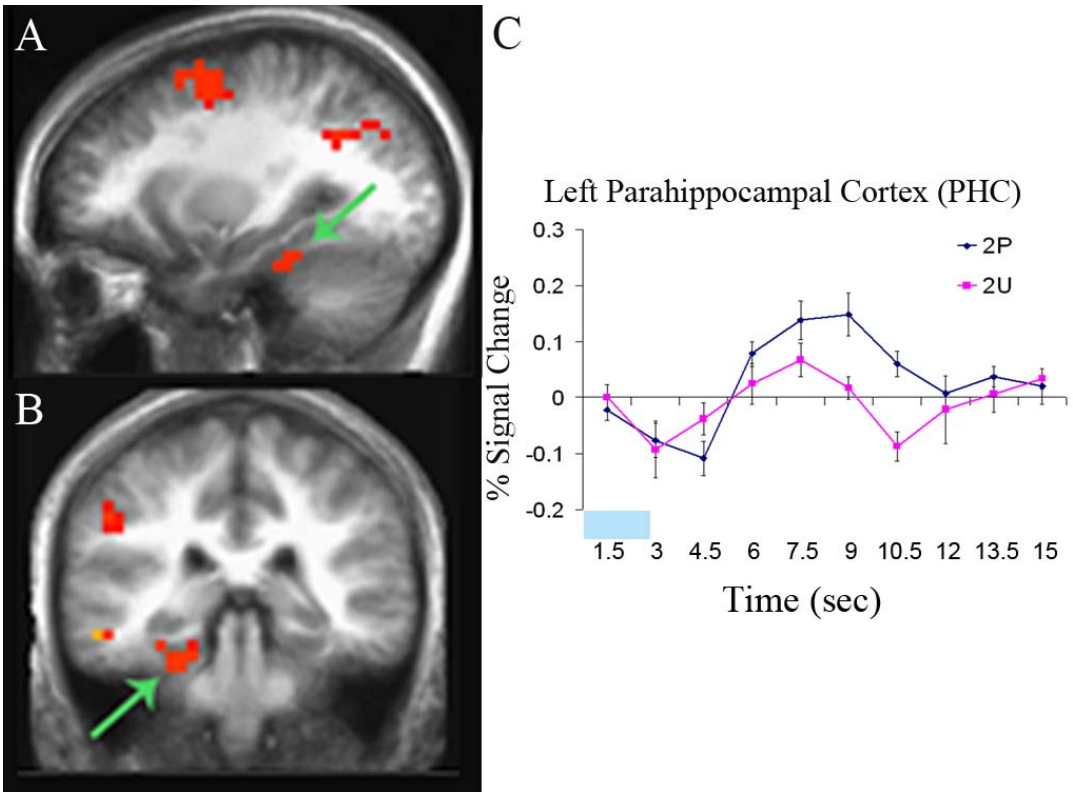

Figure 2: Increased activity in left PHC during the encoding of the second paired (2P) stimuli versus the second unpaired (2U) stimuli. Statistical activation maps illustrating greater activation ($p < .01$) during the encoding of 2P versus 2U stimuli are superimposed on sagittal (A) and coronal (B) slices of mean anatomical scan images across all 13 subjects; arrows indicate the left PHC cluster used for time-course analysis. (C) Time-course of activity in left PHC beginning with the onset of 2P stimuli (blue) and 2U stimuli (pink) demonstrates activity during item encoding, with increased activity during associative encoding. The time of stimulus presentation is represented by the light blue block. The y-axis represents percent signal change, the x-axis is time in seconds (sec), and the error bars represent the standard error of the mean.

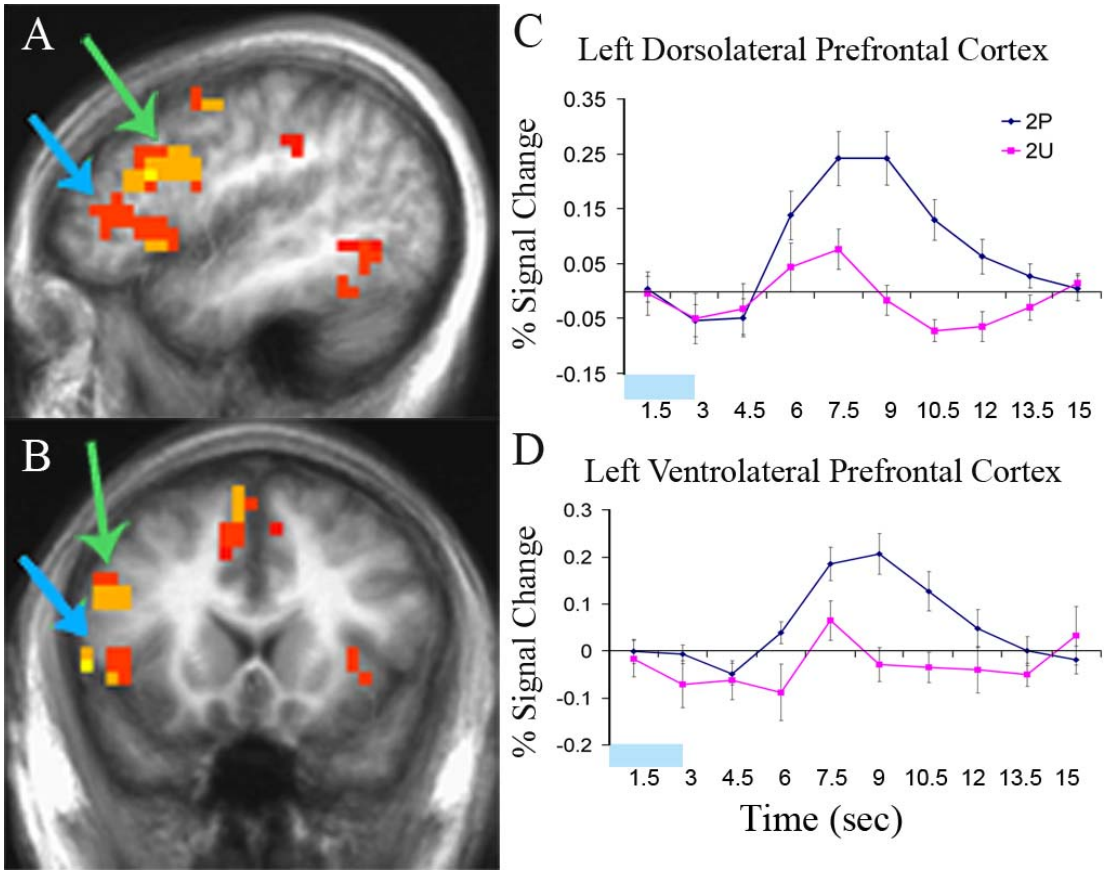

Figure 3: Increased activity in left DLPFC and left VLPFC during the encoding of the second paired (2P) stimuli versus the second unpaired (2U) stimuli. Statistical activation maps illustrating greater activation ($p < .01$) during the encoding of 2P versus 2U stimuli are superimposed on sagittal (A) and coronal (B) slices of the mean anatomical scan images across all 13 subjects; arrows indicate left DLPFC (green) and left VLPFC (blue) clusters used for time-course analysis. (C) Time-course of activity in left DLPFC beginning with the onset of 2P stimuli (blue) and 2U stimuli (pink) demonstrating activity during item encoding, with increased activity during associative encoding. The time of stimulus presentation is represented by the light blue block. (D) Time-course of activity in left VLPFC for the same comparison demonstrates activity only during associative encoding, with no significant response during the encoding of individual items.

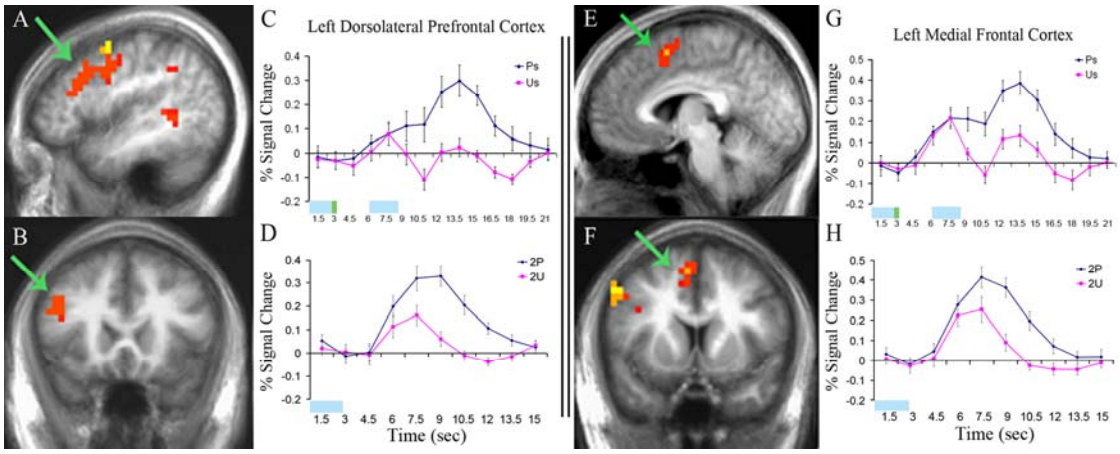

Figure 4: Initiation of activity increase in left DLPFC and left medial frontal cortex at onset of associative memory instruction. Statistical activation maps illustrating greater activation ($p < .01$) during the encoding of two paired images (with a 3.5-sec ISI) versus two unpaired images (with a 3.5-sec ISI) are superimposed on sagittal (A, E) and coronal (B, F) slices of mean anatomical scan images across all 13 subjects; arrows indicate the left DLPFC (A, B) and left medial frontal (E, F) clusters used for time-course analysis. *C, G,* Time-courses of activity in left DLPFC (C) and left medial frontal cortex (G) beginning with the onset of the first image of two paired images (blue) and the first image of two unpaired images (pink) demonstrate divergence at the onset of associative instruction. The time of stimulus presentation is represented by the light blue block, and the time of associative instruction presentation is represented by the green block. *D, H,* Time-courses of activity in left DLPFC (D) and left medial frontal cortex (H) during the presentation of 2P (blue) and 2U (pink) stimuli illustrate the enhanced response to the second stimulus in the associated condition. The time of stimulus presentation is represented by the light blue block.

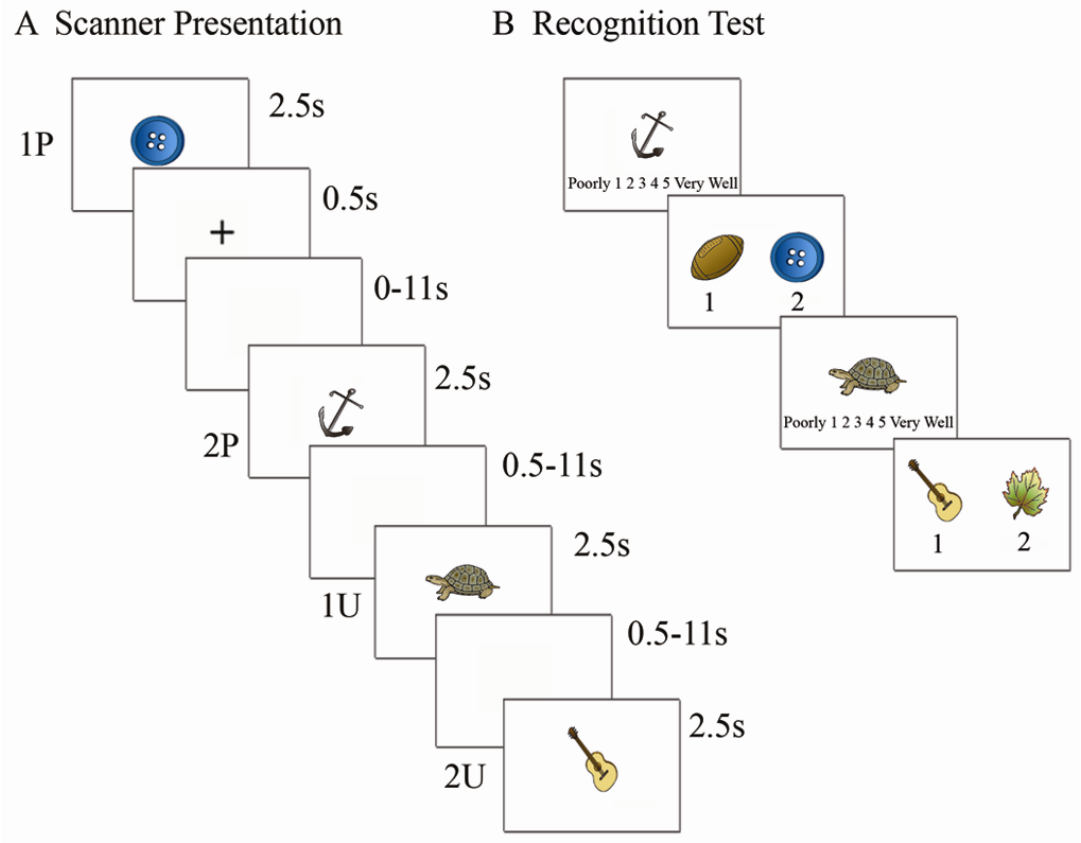

Figure 5: Experimental design. (A) Example of the encoding task used in the scanner illustrating the presentation of two paired and two unpaired stimuli. A plus-sign, cuing the association of the preceding stimulus (1P) with the one to follow (2P), is presented for the first 0.5s of a 0.5-11 second ISI only between paired images and not between unpaired images (1U and 2U). Each stimulus is presented for 2.5 seconds. (B) Example of the post-scan recognition test. Subjects were shown stimuli previously viewed during the encoding task as well as novel stimuli, and they were asked if they remember seeing the image in the scanner, responding “1” (poorly) through “5” (very well). If the object was included in the encoding task, a follow up question was provided where subjects were shown two choice stimuli (both of which had been previously viewed) and were asked which object (1 or 2) was the associated pair (if paired) or to respond 3 if the target was unpaired.

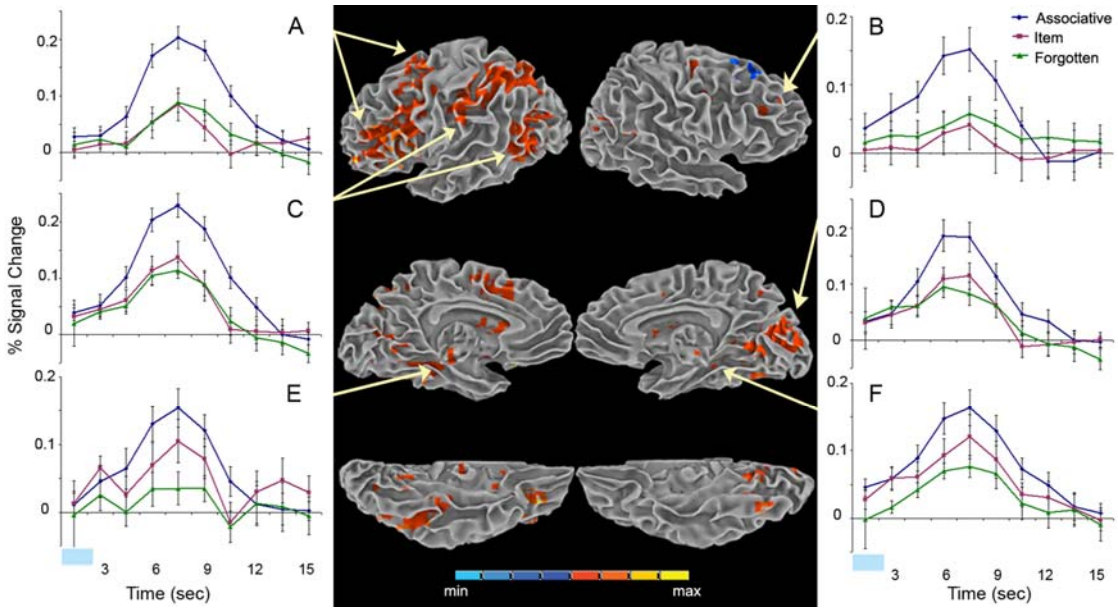

Figure 6: Activity in bilateral frontal and parietal neocortical regions predicts memory for associative information only. Activity in bilateral regions of posterior MTL, extending into lateral temporal and occipital cortices, predicts memory for associative information, but also is influenced by memory for items. Yellow arrows indicate left prefrontal (extending both lateral and medial) (A), right prefrontal (B), left lateral parietal and occipital (C), right precuneus (D), and bilateral posterior MTL (E and F) clusters used for time-course analyses. Statistical activation maps for regions showing significantly increased activity ($p < 0.05$, corrected for multiple comparisons) for associative trials compared to item-only trials are overlaid on the smooth white matter surface of the Talairach and Tournoux N27 average brain. Graphs depicting the time course of percent signal change in these regions for each condition beginning with the onset of stimuli following a plus-sign, 2P. The blue block represents the time of stimulus presentation. The error bars illustrate the standard error of the mean, the y-axis represents the percent signal change, and the x-axis represents time in seconds from stimulus onset.

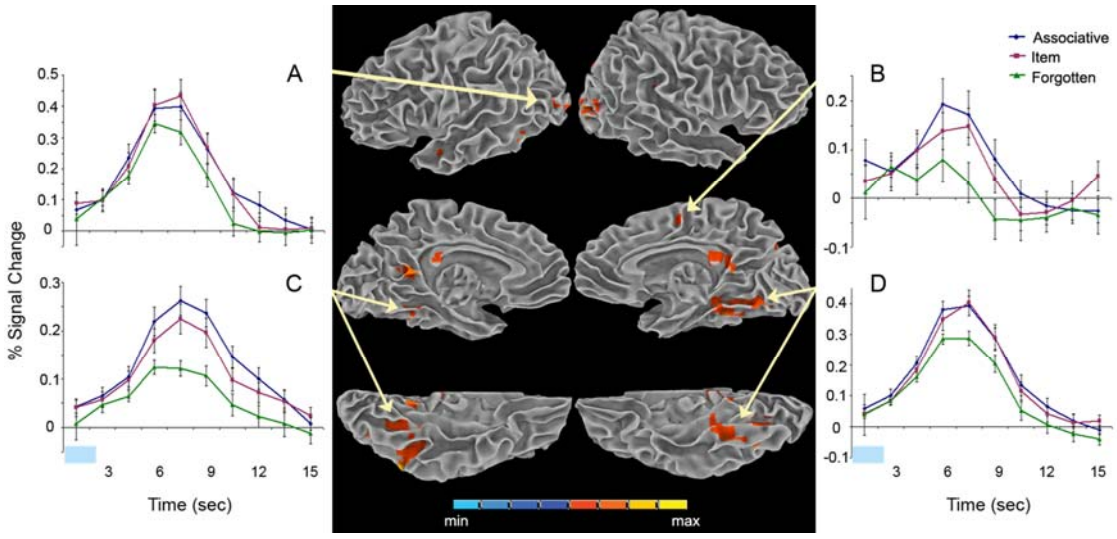

Figure 7: Activity in bilateral occipital and right medial frontal neocortical regions predicts memory for items, regardless of additional memory for associative information. Activity in bilateral regions of posterior MTL, regions similar to those defined functionally in the previous contrast, predicts memory for items, but also is influenced by additional associative memory. Yellow arrows indicate left occipital (A), right medial frontal (B), and bilateral posterior MTL (C and D) clusters used for time-course analyses. Statistical activation maps for regions showing significantly increased activity ($p < 0.05$, corrected for multiple comparisons) for item-only trials compared to forgotten trials are overlaid on the smooth white matter surface of the Talairach and Tournoux N27 average brain. Graphs depicting the time course of percent signal change in these regions for each condition beginning with the onset of stimuli following a plus-sign, 2P. The blue block represents the time of stimulus presentation. The error bars illustrate the standard error of the mean, the y-axis represents the percent signal change, and the x-axis represents time in seconds from stimulus onset.

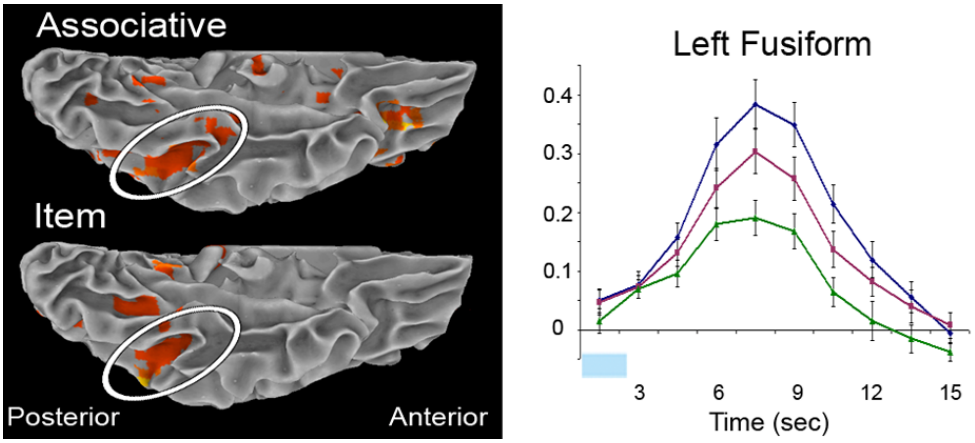

Figure 8: (Left) Left fusiform cortex predicts memory for items and is influenced by additional memory for associative information. White circles indicate the left fusiform cluster, the only region of overlap between the "associative memory" and "item memory" contrasts; this region was then used for time-course analysis. Statistical activation maps for regions showing significantly increased activity ($p < 0.05$) for associative compared to item-only trials, "associative memory," and for item-only compared to forgotten trials, "item memory," are overlaid on the left hemisphere ventral smooth white matter surface of the Talairach and Tournoux N27 average brain. (Right) Graph depicting the time course of percent signal change in the identified cluster in each condition beginning with the onset of stimuli following a plus-sign, 2P. Activity in left fusiform shows a stepwise increase from forgotten to item-only to associative trials. The blue block represents the time of stimulus presentation. The error bars illustrate the standard error of the mean, the y-axis represents the percent signal change, and the x-axis represents time in seconds from stimulus onset.

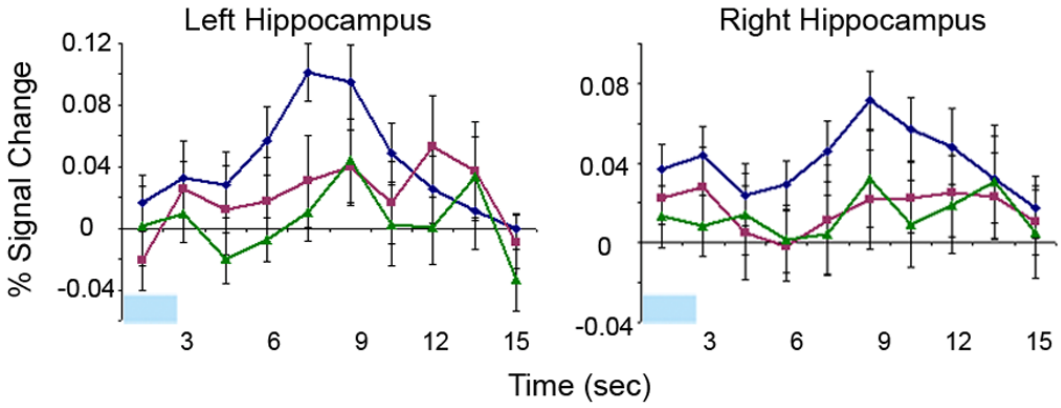

Figure 9. Bilateral hippocampus predicts memory for associative information. Graphs depict the time course of percent signal change in left and right hippocampus for each condition beginning with the onset of stimuli following a plus-sign, 2P. Voxels functionally defined in posterior MTL from the "associative memory" and "item memory" conditions extended into multiple anatomical brain regions; therefore, time courses of activity were extracted from those voxels that overlapped with anatomically defined bilateral hippocampus. The blue block represents the time of stimulus presentation. The error bars illustrate the standard error of the mean, the y-axis represents the percent signal change, and the x-axis represents time in seconds from stimulus onset.

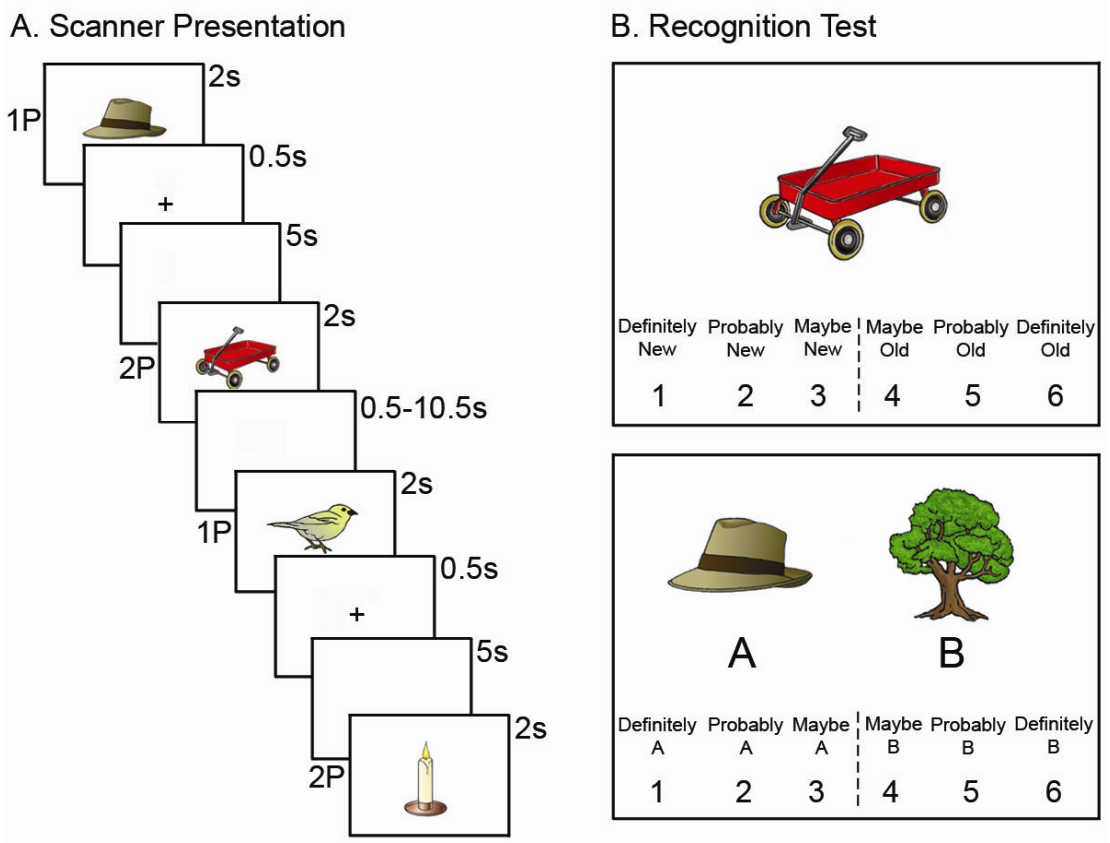

Figure 10: Experimental design. *A:* example of the encoding task used in the scanner illustrating the sequential presentation of 4 stimuli in pairs of 2 (1P-2P and 1P-2P). Each stimulus was presented for 2 s. After the 1P stimulus, a plus-sign cued the association of the preceding stimulus (1P) with the following stimulus (2P). The plus-sign was presented for 0.5 s, followed by a 5-s interitem delay. A jittered intertrial interval lasting 0.5-10.5 s separated each 2P stimulus from the next 1P stimulus. *B:* example of the post-scan recognition test. Subjects were shown 2P stimuli previously viewed during the encoding task as well as novel stimuli, and they were asked to rate their confidence that the picture (e.g., wagon) was new or that it was shown during the scan (old) on a scale from "1, definitely new" to "6, definitely old." If the target stimulus was included in the encoding task, a follow-up question was provided where subjects were shown 2 choice stimuli, A and B (both of which were previously shown during encoding), and were asked to rate their confidence that the target stimulus was paired with image A (e.g., hat) or B (e.g., tree) on a scale from "1, definitely A" to "6, definitely B."

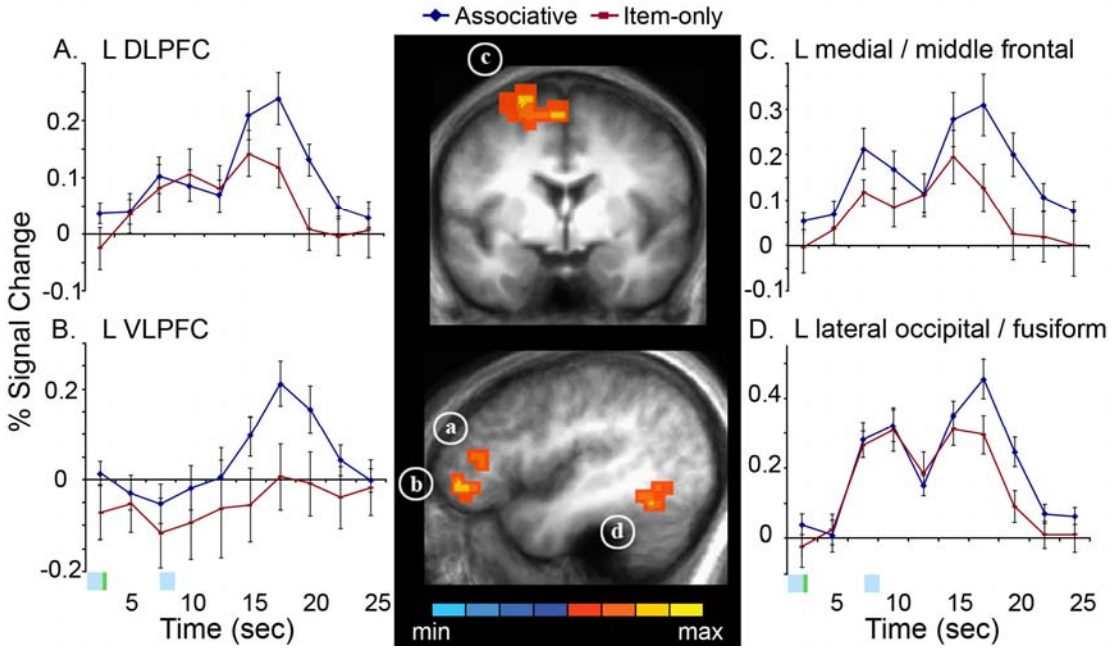

Figure 11: Activity in left frontal and lateral occipital regions predicts the successful associative binding of items. Statistical activation maps for regions showing increased activity during binding ($p < 0.01$, corrected for multiple comparisons) for associative trials compared to item-only trials are overlaid on sagittal and coronal slices of mean anatomical scan images across all 15 subjects. Functional clusters located in left (L) dorsolateral prefrontal cortex (DLPFC; *A*), ventrolateral prefrontal cortex (VLPFC; *B*), medial / middle frontal cortex (*C*), and lateral occipital / fusiform cortex (*D*) were used for time-course analyses. Graphs depict the time course of percent signal change in these regions for each condition beginning with the onset of the first stimulus of each pair, 1P. The blue bar represents the time of stimulus presentation, and the green bar represents the time of associative instruction presentation (plus-sign). The error bars represent the standard error of the mean.

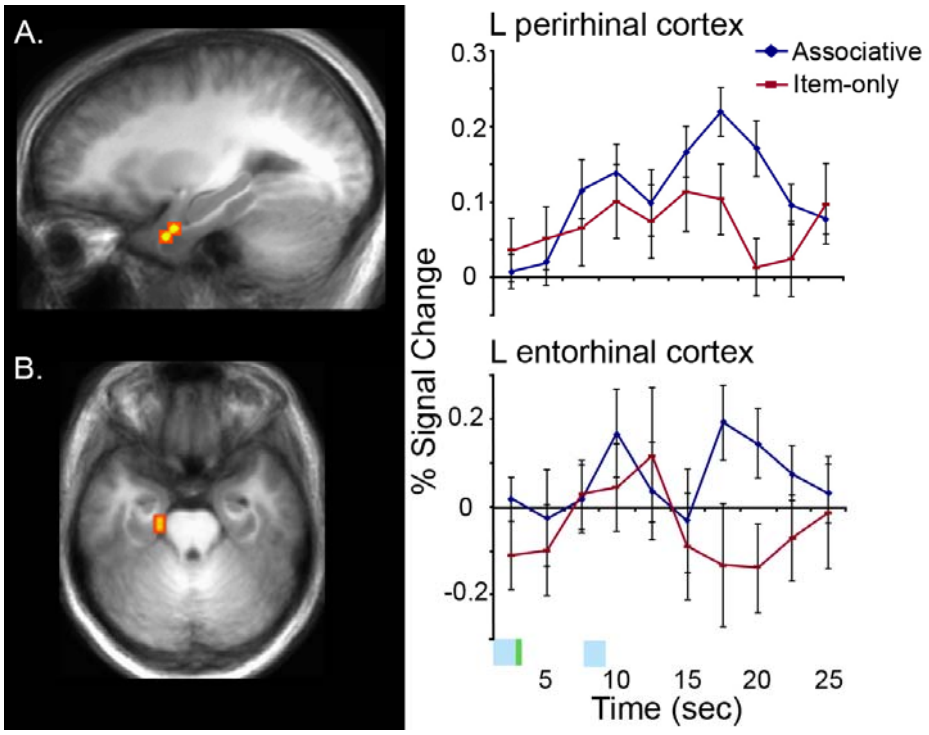

Figure 12: Activity in left perirhinal and entorhinal cortex predicts the successful associative binding of items. Statistical activation maps for regions showing increased activity during binding ($p < 0.05$, uncorrected) for associative trials compared to item-only trials are overlaid on sagittal and axial slices of mean anatomical scan images across all 15 subjects. Graphs depict the time course of percent signal change in left perirhinal and entorhinal cortices for each condition beginning with the onset of the first stimulus of each pair, 1P. These clusters were isolated from voxels functionally defined in the contrast of associative memory trials relative to item-only memory trials ($p < 0.05$) that were located in anatomically defined MTL regions, left perirhinal and entorhinal cortices. The blue bar represents the time of stimulus presentation, and the green bar represents the time of associative instruction presentation (plus-sign). The error bars represent the standard error of the mean.

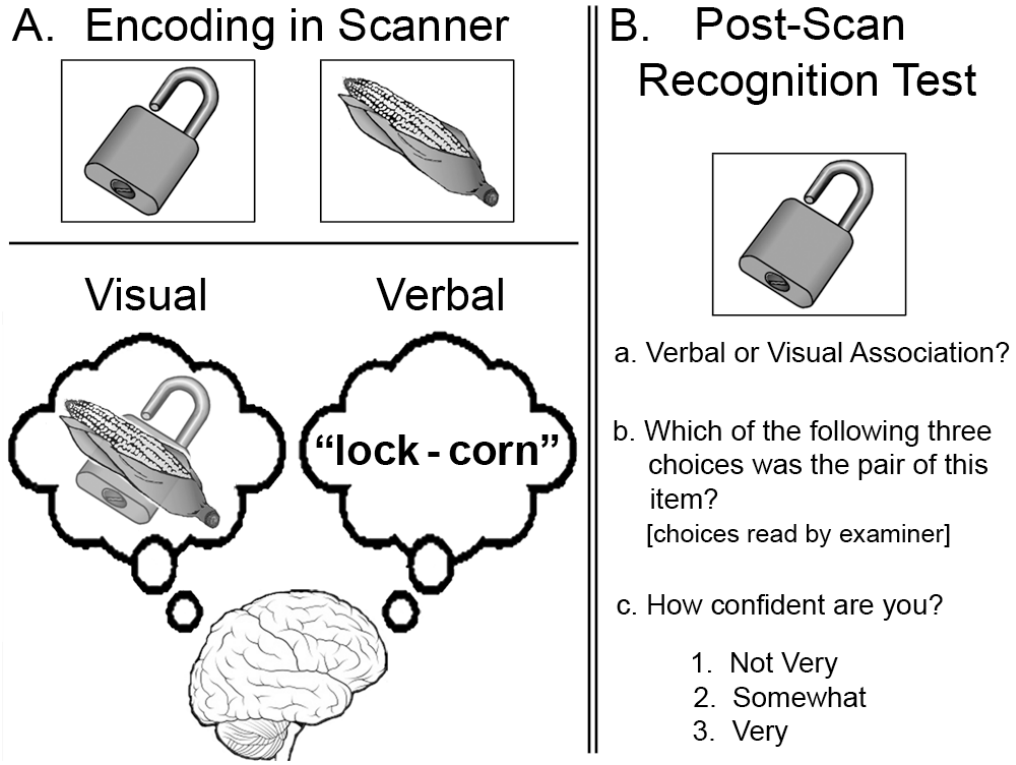

Figure 13: Experimental design. *A,* Example of the encoding task used in the scanner illustrated with a sample pair of objects. Each stimulus pair was presented for 2 seconds, followed by 3 seconds of blank screen during which subjects associated the objects using the instructed strategy. Under the visual associative encoding condition, subjects were instructed to visualize the two objects as merged, without verbalizing their names. Under the verbal associative encoding condition, subjects were instructed to combine and rehearse the names of the two objects, without visualizing the objects. Following the 3-second blank screen and before the next pair was presented, a fixation cross appeared on the screen for a jittered 1.5-10.5-second interstimulus interval. *B,* Example of the post-scan recognition test. Subjects were shown one object from each pair previously viewed during the encoding task, and they were asked to verbally report to the experimenter their answers to three questions (a, b, and c). After the subjects reported if each item was part of a visual or verbal association (a), the experimenter read the subjects three choice pair items, one of which was the correct pair. Subjects then reported which of those three choices they recognized as the pair (b) and their confidence in selecting the correct pair (c).

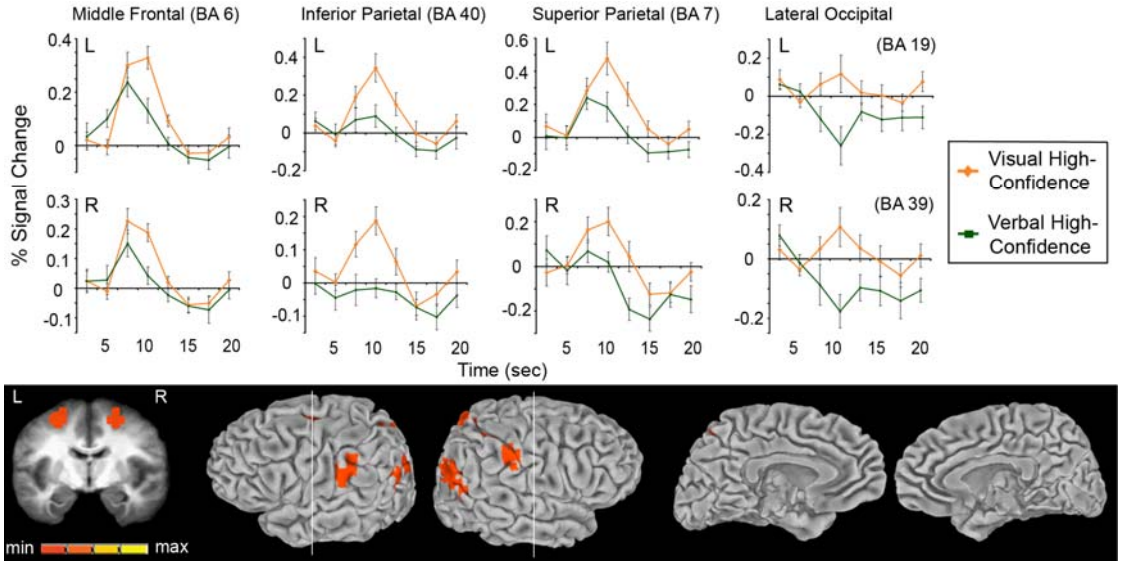

Figure 14: Visual associative encoding engages bilateral middle frontal, lateral parietal, and lateral occipital regions. Statistical activation maps for regions showing increased activity during highly-confident associative encoding using the visual strategy relative to the verbal strategy ($p < 0.05$, corrected for multiple comparisons) are overlaid on the pial surface of the Talairach and Tournoux N27 average brain and on a coronal slice of a mean anatomical scan image across all 15 subjects. Functional clusters located in bilateral middle frontal (BA 6), inferior and superior parietal (BA 40 and 7), and lateral occipital (BA 19, 39) regions were used for time-course analyses. Graphs depict the time course of percent signal change in these regions for the visual and verbal associative encoding of object pairs subsequently recognized with high-confidence. The error bars illustrate the standard error of the mean, the y-axis represents the percent signal change, and the x-axis represents time in seconds from stimulus pair onset.

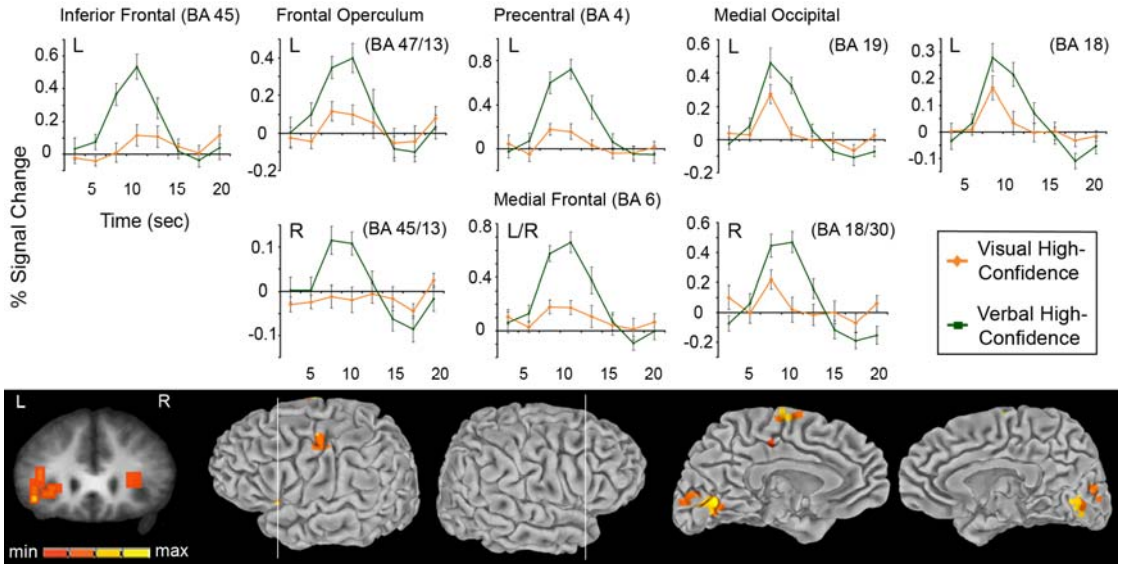

Figure 15: Verbal associative encoding engages bilateral inferior frontal, medial frontal, and medial occipital regions. Statistical activation maps for regions showing increased activity during highly-confident associative encoding using the verbal strategy relative to the visual strategy ($p < 0.001$, corrected for multiple comparisons) are overlaid on the pial surface of the Talairach and Tournoux N27 average brain and on a coronal slice of a mean anatomical scan image across all 15 subjects. Functional clusters located in left inferior frontal (BA 45), bilateral frontal operculum (BA 47/13, 45/13), left precentral (BA 4), bilateral medial frontal (BA 6), and bilateral medial occipital (BA 19, 18, 18/30) regions were used for time-course analyses. Graphs depict the time course of percent signal change in these regions for the visual and verbal associative encoding of object pairs subsequently recognized with high-confidence. The error bars illustrate the standard error of the mean, the y-axis represents the percent signal change, and the x-axis represents time in seconds from stimulus pair onset.

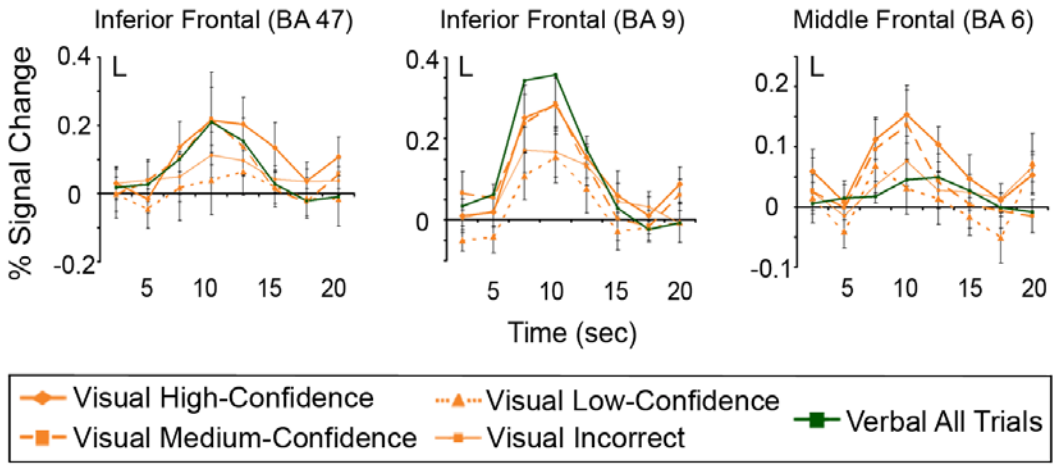

Figure 16: Visual strategy influences regional subsequent memory effects. Graphs depict the time course of percent signal change for regions identified using a linear weighted model of increasing subsequent memory confidence, from subsequently forgotten to subsequently recognized with high-confidence pairs, under the visual associative encoding strategy ($p < 0.05$, corrected). Functional clusters located in left inferior frontal (BA 47, 9) and left middle frontal (BA 6) regions were used for time-course analyses. The error bars illustrate the standard error of the mean, the y-axis represents the percent signal change, and the x-axis represents time in seconds from stimulus pair onset.

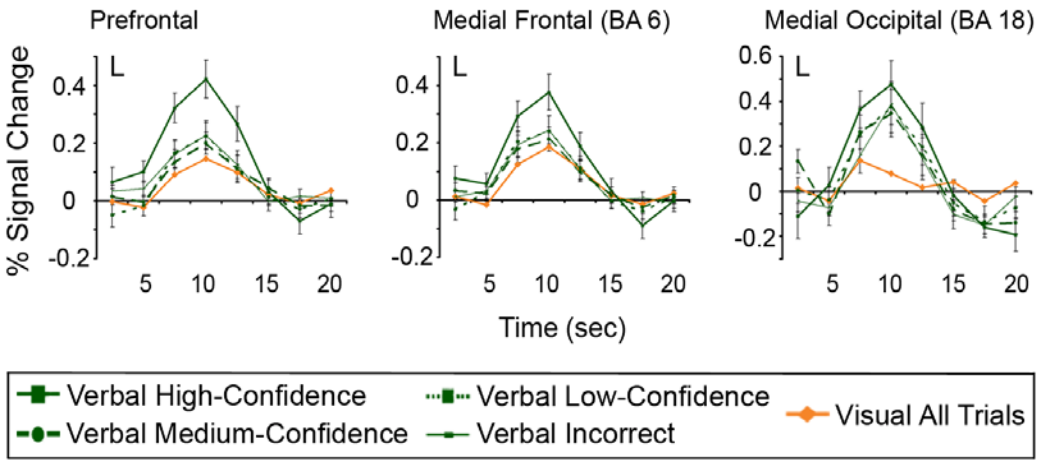

Figure 17: Verbal strategy influences regional subsequent memory effects. Graphs depict the time course of percent signal change for regions identified using a linear weighted model of increasing subsequent memory confidence, from subsequently forgotten to subsequently recognized with high-confidence pairs, under the verbal associative encoding strategy ($p < 0.05$, corrected). Functional clusters located in left prefrontal, left medial frontal (BA 6), and left medial occipital (BA 18) regions were used for time-course analyses. The error bars illustrate the standard error of the mean, the y-axis represents the percent signal change, and the x-axis represents time in seconds from stimulus pair onset.

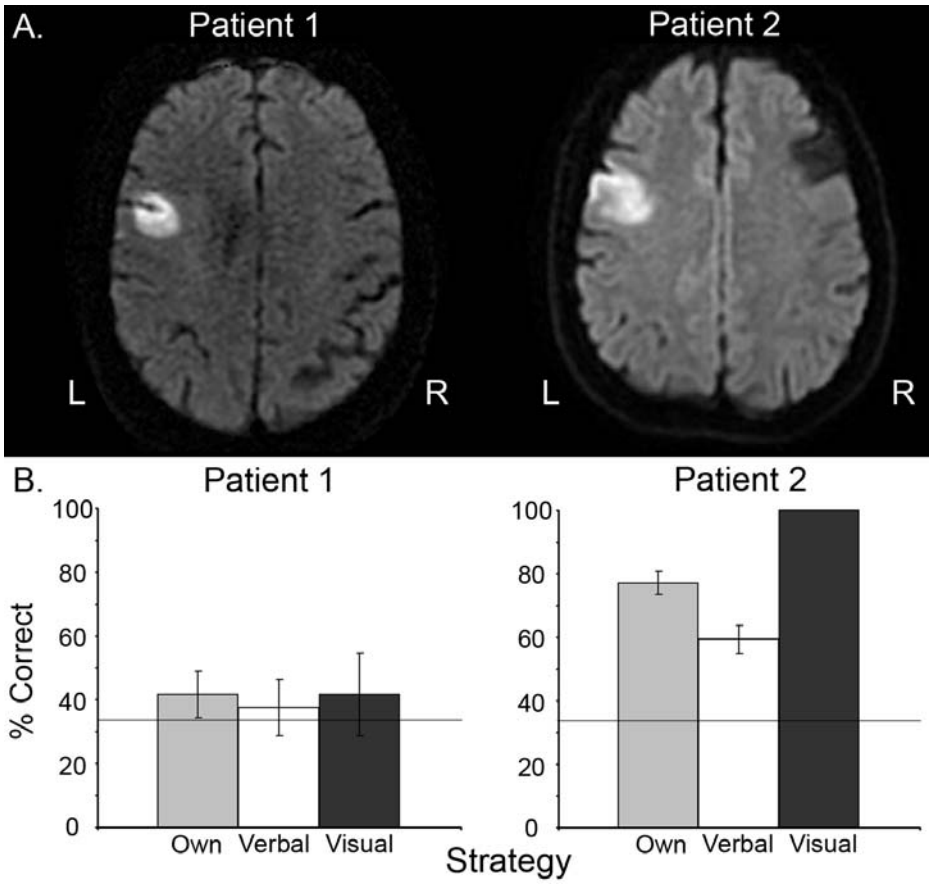

Figure 18: Encoding strategy influences memory performance in patient with focal brain damage. *A,* Axial diffusion-weighted brain images for Patient 1 and 2 following strokes localized to the left inferior frontal lobe. *B,* Graphs depict each patient's recognition memory performance for pairs encoded using their own strategy (light grey), the verbal strategy (white), and the visual strategy (dark grey). Patient 1 performed close to chance (33%) under all three encoding strategy conditions. For Patient 2, relative to her memory performance when using her own strategy, she showed further impairment under the verbal strategy, but improvement under the visual strategy. The error bars illustrate the standard deviation, the y-axis represents the percent of trials in which they selected the correct pair, and the horizontal dashed line marks the chance level of 33% correct.

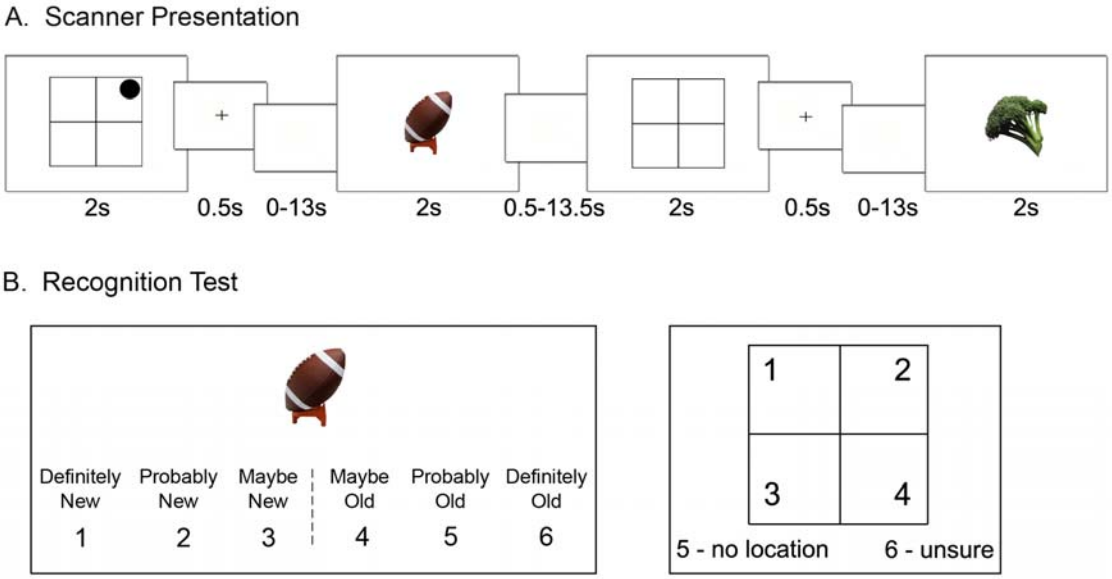

Figure 19: Experimental design. *A,* Example of the encoding task used in the scanner illustrating the sequential presentation of a spatial cue (with present or absent location information) and an object. A trial consisted of a 2-sec spatial cue grid, followed by a 0.5-sec associative cue (plus-sign), a blank screen jittered delay of 0 to 13 sec, and finally a 2-sec object. A blank screen was present during an intertrial interval of 0.5 to 13.5 sec. The jittered delay periods and intertrial intervals were calculated to optimize the study design for modeling the hemodynamic response to trials (Dale, 1999; Dale & Buckner, 1997). When a circle was present in one of the grid quadrants, subjects were instructed to imagine and remember the following object (e.g., football) as located in that quadrant. When the grid was blank, subjects were instructed to just remember the object (e.g., broccoli), without spatial information. *B,* Example of the post-scan recognition test. Subjects were shown each object previously viewed during the encoding task as well as novel objects, and they were asked to rate their confidence that the picture (e.g., football) was new or that it was shown during the scan (old) on a scale from "definitely new" to "definitely old." If the object was included in the encoding task, subjects were asked a follow-up question regarding the object's associated spatial information. Subjects responded 1-4 to identify the object's associated location, 5 to select that the object had no location, or 6 to say they were unsure about the object's location.

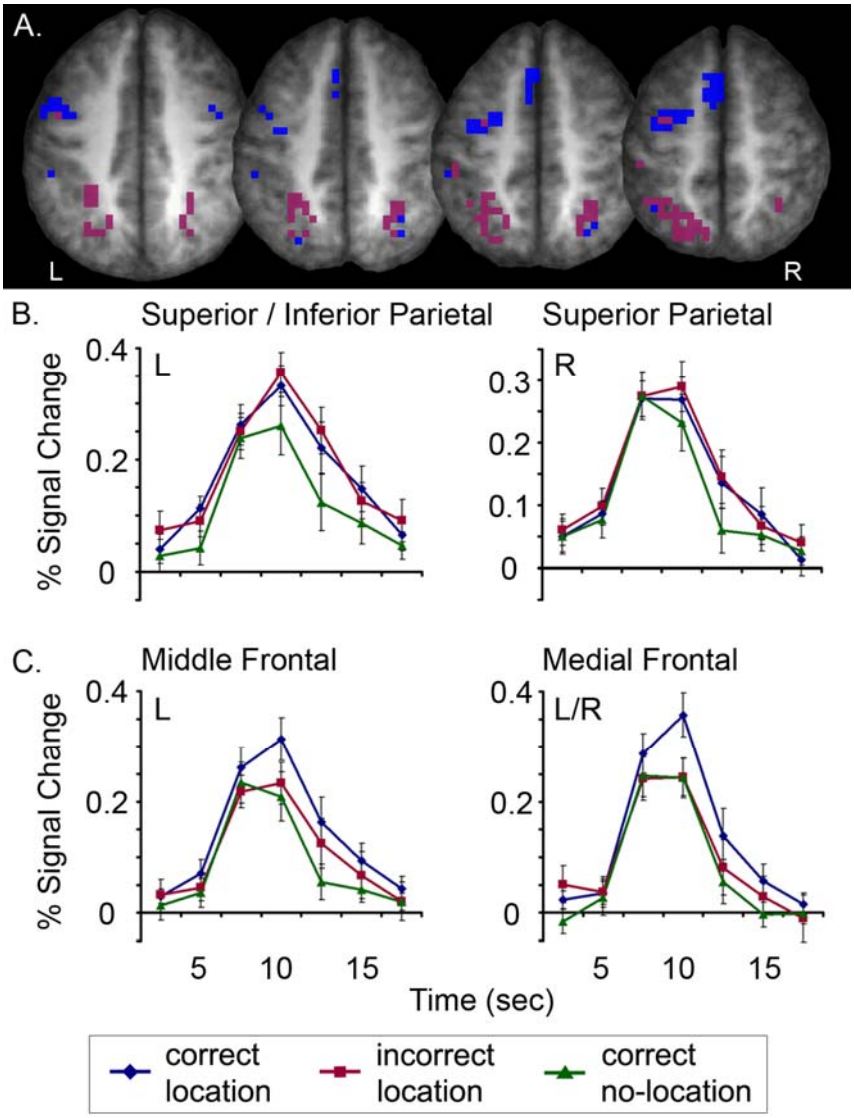

Figure 20: Superior parietal and medial / middle frontal regions are differently engaged by visuospatial binding attempt versus success. *A*, Statistical activation maps for regions showing increased activity for successful (blue) versus attempted (purple) object-location binding ($p < 0.001$, corrected for multiple comparisons) are overlaid on axial slices of mean anatomical scan images across all 14 subjects. Functional clusters located in left (L) superior / inferior parietal (BA 7/40), right (R) superior parietal (BA 7), left (L) middle frontal (BA 6), and bilateral (L/R) medial frontal (BA 6) regions were used for time-course analyses. Graphs depict the time course of percent signal change in these regions for each condition beginning with the onset of the object stimulus. The error bars represent the standard error of the mean.

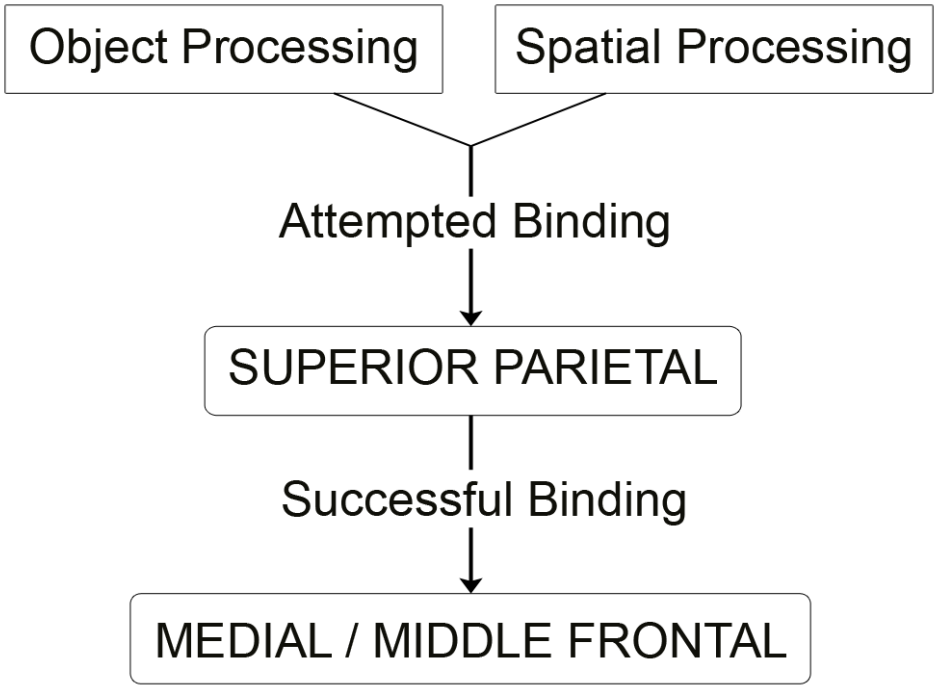

Figure 21: Model of visuospatial encoding. Attempted visuospatial binding requires both object and spatial processing and modulates the response in superior parietal regions, regardless of binding success. Medial / middle frontal regions, in contrast, are modulated by successful visuospatial binding.

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