Title
Imaging frontal and medial temporal lobe interaction during memory retrieval and disentangling the effects of the default network

Permalink
https://escholarship.org/uc/item/002971x6

Author
Gimbel, Sarah Israel

Publication Date
2010

Peer reviewed|Thesis/dissertation
UNIVERSITY OF CALIFORNIA, SAN DIEGO

Imaging Frontal and Medial Temporal Lobe Interaction During Memory Retrieval and Disentangling the Effects of the Default Network

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

Doctor of Philosophy

in

Neurosciences

by

Sarah Israel Gimbel

Committee in charge:
Professor James B. Brewer, Chair
Professor Adam R. Aron
Professor John T. Serences
Professor Larry R. Squire
Professor John T. Wixted

2010
The dissertation of Sarah Israel Gimbel is approved, and is acceptable in quality and form for publication on microfilm and electronically:

Chair

University of California, San Diego

2010
DEDICATION

I dedicate this dissertation to my family, and to those who might as well be family. To Mom – you were my first mentor and co-author and you taught me what it means to be a scientist. To Dad – you asked me every day when I came home from school if I discovered radium that day, and you have supported me through all of my scientific endeavors, even when they didn’t include medical school. David – thanks for pushing me to finish my dissertation, so that I can graduate before you do. Jeremy – thank you for being the best husband a girl could wish for, and especially for making me dinner while I was writing and pretending to understand what I’m talking about when I tell you about my research. To the members of the Brewer lab past and present – thank you for your guidance, help, support, and most of all friendship. Specifically to Jena, my lab wife – thank you for every smile, every kind word, every look over a paper, a script, or a graph, every birthday cake, and every trip to the bathroom. I can’t imagine having done this without you. And last but most certainly not least, to Jim – thank you for your high fives, your wisdom, your patience, your expertise, your consoling words, your encouraging words, and most of all, your guidance and support throughout the past five years.
# TABLE OF CONTENTS

Signature Page ........................................................................................................ iii

Dedication ................................................................................................................ iv

Table of Contents ................................................................................................... v

Acknowledgments ................................................................................................. vi

Vita ......................................................................................................................... vii

Abstract ................................................................................................................ ix

Chapter 1: Introduction ......................................................................................... 1

Chapter 2: Going their separate ways: Dissociation of hippocampal and
dorsolateral prefrontal activation during episodic retrieval and post-retrieval processing .......................................................... 15

Chapter 3: Elaboration versus suppression of cued memories: Influence of memory recall instruction on default network, retrieval network, and hippocampal activity ........................................ 40

Chapter 4: Reaction time, memory strength, and fMRI activity during memory retrieval: Hippocampus and default-mode network are differentially responsive during recollection and familiarity judgments .................................................................................. 57

Chapter 5: Conclusions ......................................................................................... 70

Tables ..................................................................................................................... 75

Figures ................................................................................................................... 79

References ............................................................................................................. 94
ACKNOWLEDGMENTS

I would like to acknowledge Professor James Brewer for his invaluable advice and support throughout my graduate school career and as the chair of my dissertation committee. Additionally, I would like to acknowledge Professors Adam Aron, John Serences, Larry Squire, and John Wixted for their excellent guidance and support.

I would also like to acknowledge the members of the Brewer Laboratory who were a constant support throughout graduate school and made my research so much more enjoyable and more productive than it would have been as a solitary venture. I would particularly like to thank Jena Hales, Tyler Seibert, and Elizabeth Murphy for their support, guidance, and friendship during this process.

Chapter 2, in full, is a reprint of the material as it appears in Journal of Cognitive Neuroscience, 2010. Israel, Sarah L.; Seibert, Tyler M.; Black, Michelle L.; Brewer, James, B. The dissertation author was the primary investigator and author of this paper.

Chapter 3, in part, has been submitted for consideration for publication. Gimbel, Sarah I.; Brewer, James B. The dissertation author was the primary investigator and author of this paper.

Chapter 4, in full, has been submitted for consideration for publication. Gimbel, Sarah I.; Brewer, James B. The dissertation author was the primary investigator and author of this paper.

This work was supported by NINDS 1K23 NS050305-1 and the General Electric Medical Foundation.
VITA

2005 Bachelor of Arts, Stanford University
2007 Master of Science, University of California, San Diego
2010 Doctor of Philosophy, University of California, San Diego

PUBLICATIONS

S. I. Gimbel*, J. B. Brewer. Reaction time and fMRI activity during memory retrieval: Hippocampus and default network are differentially influenced by reaction time during recollection and familiarity judgments. (submitted)


*Name change from Sarah Laurel Israel to Sarah Israel Gimbel
RESEARCH EXPERIENCE

1999-2000  San Diego Neurosciences Institute
            Advisors: Dr. Chiara Cirelli and Dr. Giulio Tononi

2000-2003  San Diego Neurosciences Institute
            Advisor: Dr. Paul Shaw

2002-2004  Stanford Center for Narcolepsy, Stanford University
            Advisor: Dr. Emmanuel Mignot

2003       Centre for Marine Science, University of Queensland, Brisbane, Australia
            Advisor: Dr. Ove Hoegh-Guldberg

2004       Department of Psychiatry and Behavioral Sciences, Stanford University
            Advisor: Dr. Allen Reiss

2004-2005  San Diego Neurosciences Institute
            Advisor: Dr. Ralph Greenspan

2005-2010  Department of Neuroscience, University of California, San Diego
            Advisor: Dr. James Brewer
ABSTRACT OF THE DISSERTATION

Imaging Frontal and Medial Temporal Lobe Interaction During Memory Retrieval and Disentangling the Effects of the Default Network

by

Sarah Israel Gimbel

Doctor of Philosophy in Neurosciences
University of California, San Diego, 2010
Professor James B. Brewer, Chair

Exploring how the medial temporal lobe interacts with different areas of the brain during memory tasks is an important component in understanding the dynamics of memory retrieval. To achieve this goal, functional magnetic resonance imaging (fMRI) was used to determine how the frontal and medial temporal lobes interact during memory retrieval and subsequent use of recollected information and how memory retrieval may integrate with or affect default network activity. The first study used blocked and event-related fMRI to examine hippocampal activity during long term memory recollection and post-retrieval processing of paired items. Subjects were
asked to make living/nonliving judgments about items visually presented (classify) or about items retrieved from memory (recollect-classify). In addition, active (odd/even digit classification) and passive (fixation) baselines were used to differentiate task-related activity from default network activations. During the ‘recollect-classify’ task, activity in the anterior hippocampus was selectively reduced relative to ‘classify’ and baseline tasks (active and passive), and hippocampal activity was inversely correlated with bilateral DLPFC activity. The finding was that frontal and hippocampal activity are dissociated during memory retrieval and post-retrieval processing. The second study examined the effects of retrieval instruction on brain regions implicated in episodic memory retrieval. The finding was that the default network showed a greater decrease in activation for poorly-remembered than strongly-remembered responses regardless of whether subjects were instructed to suppress the cued material or to perform non-elaborative or elaborative retrieval. The hippocampus showed an increase in activation only with successful memory recall. Further examination revealed that the retrieval network, commonly identified by differences in activation during successful retrieval and baseline, seems to be modulated somewhat by task instruction, but not recall success. The hippocampus showed differential activity based on top-down modulation elicited by retrieval instructions while the default network did not. The third study examined recollection and familiarity with attention to reaction-time to explore its contribution to regional activations. The finding was that the hippocampus is functionally dissociated from other regions of the retrieval-network during recollection. Portions of the retrieval-network are generally influenced by reaction-
time and show suppressed signal when subjects are task-engaged in either recollection or familiarity; suppression is greater for longer trials. The hippocampus, however, shows a positive response only for recollection trials, where activation is greater for longer recollection trials, but not longer familiarity trials. It is concluded from these experiments that the hippocampus is dissociated from the rest of the default network during tasks of memory retrieval.

While many studies have examined how the hippocampus, pre-frontal cortex, retrieval network, and default network are related to memory retrieval, these studies take into account additional components of the memory retrieval tasks like reaction time and false alarm rate in order to disentangle memory retrieval itself from related components. Prior studies have shown functional connectivity of the hippocampus and the default network, but these studies, taken together, suggest that hippocampus is affected by task instruction as well as task success, and is dissociated from the default network during tasks involving memory retrieval. The summation of these studies exposes how the modulation of activity in non-memory related networks in the brain may affect activation attributed to memory retrieval, and why it is so important to take these confounds into account in memory recall studies.
CHAPTER 1:
INTRODUCTION

A long-term objective of many memory researchers is to understand how different structures of the medial-temporal lobe (MTL) contribute to memory encoding and retrieval. While understanding how these structures interact is important for understanding how memory processes work, it also has important implications for patient populations, since substructures of the MTL are damaged early in Alzheimer’s disease. Thus, understanding how substructures of the MTL are involved in memory may aid in the development of neuropsychological measures that aim to detect the earliest stages of Alzheimer’s disease. Beyond examining the specific substructures of the MTL, the overarching goal of this work is to understand how the MTL interacts with different areas of the brain during memory retrieval. To achieve this goal, functional magnetic resonance imaging (fMRI) was used to determine how the frontal lobes, retrieval network, default network, and medial temporal lobes interact during memory recall and subsequent use of recollected information.

Memory Systems

Memory has been broadly defined as the capacity of the nervous system to change as a result of experience (Tulving, 2000). Memory is not a single entity but consists of several separate components that depend on different brain systems. Within long term memory, the primary division is made between non-declarative, implicit
memory basically manifested in behavioral changes, and declarative, explicit memory, where one can hold in mind the product of the act of memory. Declarative memory is further divided into semantic memory, whose function is to mediate the use of general knowledge, and episodic memory, whose function is to mediate the encoding of and conscious access to the personally experienced past (Squire & Zola-Morgan, 1991; Tulving, 2000). The studies employed here use episodic memory retrieval and suppression to examine the neural bases of recall in different regions of the brain.

**Memory Recall**

Knowledge about the function of the hippocampus and surrounding MTL regions and their relationship to memory has been greatly advanced by the study of patients with MTL damage (Scoville & Milner, 1957). With recent advances in neuroimaging, it has become possible to study these memory processes in adults with intact memory. Several imaging and electrophysiological studies have found that activity in the human hippocampus is modulated during the encoding and retrieval of memories (Anderson, et al., 2004; Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998; Dolan & Fletcher, 1997; Dolan & Fletcher, 1999; Fernandez, et al., 1999; Gabrieli, Brewer, Desmond, & Glover, 1997; Gabrieli, Brewer, & Poldrack, 1998; Greicius, et al., 2003; Henke, Buck, Weber, & Wieser, 1997; Jackson & Schacter, 2004; Meltzer & Constable, 2005; Nyberg, McIntosh, Houle, Nilsson, & Tulving, 1996; Rombouts, et al., 1997; Rugg, Fletcher, Frith, Frackowiak, & Dolan, 1997; Wagner, Schacter, et al., 1998, see Henson, 2005 for review). While increases in hippocampal activity are
most often observed during the retrieval processes, decreases in activity of hippocampal and adjacent parahippocampal regions have also been noted (Gonsalves, Kahn, Curran, Norman, & Wagner, 2005). Task-related decreases in hippocampal and wider MTL activity have been noted during volitional suppression of unwanted memories and have been correlated with subsequent forgetting of information presented (Anderson et al. 2004, Depue et al. 2007). It was unknown, however, if these decreases represent a neural mechanism of memory suppression, or if they are related to another aspect of the task employed in these studies.

Memory recall is seldom independent of other cognitive processes called upon during daily function; rather, memory recollection is the initial step in a multitude of processes working together to perform everyday tasks. Memory recall is a complex process involving not only the retrieval of specific details from long term memory storage, but also the search required to find the memory, internal monitoring of its accuracy, and sense of how strong the memory is. Memory recall does not happen in a vacuum, but the products of recall are held in mind for some time while further cognitive processing occurs (Daselaar et al., 2007). In memory studies it is difficult to distinguish between the recall event and further processing following recall. A feature often overlooked in studies of memory retrieval is the interplay between brain regions subserving retrieval and later processing of the retrieved information. These studies will explore neural activity during retrieval and post-retrieval processing and how the hippocampus and surrounding regions are modulated during these tasks.
Recollection and Familiarity

Many studies of memory recognition use the ‘remember / know’ paradigm to test recollection and familiarity (Mandler, 1980; Rajaram, 1996). Subjects are instructed to judge a stimulus as ‘remember’ if they not only remember the item, but also remember specific details about the encoding event. If they remember the item but have no additional memory surrounding the conditions of the encoding events, they are asked to judge the item with ‘know.’ In order to identify the brain bases of recollection- and familiarity-based episodic retrieval, the ‘remember / know’ paradigm is used in behavioral studies as well as functional neuroimaging studies to determine how these aspects of memory differ and if they are separable in the brain.

It remains unclear how recollection and familiarity are distinguished in the medial temporal lobe and other memory-related structures. The dual process model of memory recall suggests that recollection and familiarity are separate processes, supported by the hippocampus and parahippocampal gyrus, respectively (Brown & Aggleton, 2001; Fortin, Wright, & Eichenbaum, 2004; Mandler, 1980; Yonelinas, et al., 2002). This theory asserts that recollection and familiarity depend on different underlying processes and are fundamentally different in the nature of their response. Other studies promote a signal detection model, where recollection and familiarity are both based on the hippocampus and both relate to memory strength and performance (Donaldson, 1996; Haist, Shimamura, & Squire, 1992; Hirshman & Master, 1997; Johnson, Hashtroudi, & Lindsay, 1993; Manns, Hopkins, Reed, Kitchener, & Squire, 2003; Wais, Wixted, Hopkins, & Squire, 2006; Wixted & Squire, 2004; Wixted &
Stretch, 2004). In this model there is a spectrum of memory strength, where ‘remember’ responses correspond to stronger memories and ‘know’ responses correspond to weaker memories (Donaldson, 1996; Dunn, 2004). The following studies take into account reaction time and memory strength in order to determine their effects on hippocampal activity during recollection and familiarity-based judgments. Given the effects that these components of memory have on other brain regions, it is possible that they are contributing to differences observed in the hippocampus during recollection and familiarity memory judgments.

Lesion and Imaging Studies

Lesion studies suggest that the hippocampus not only mediates memory encoding, but also is involved in memory consolidation and retrieval (Bayley & Squire, 2005; Cohen & Squire, 1980; Scoville & Milner, 1957). Studies of patients with medial temporal lobe lesions have greatly furthered our understanding of brain regions necessary for different components of memory encoding, consolidation, and retrieval. Lesion studies have also added to the understanding of how recollection and familiarity may be supported by different regions of the brain. Recollection and familiarity seem to be differentially affected by MTL lesions in different regions. In patients with hippocampal lesions as well as in animal models of hippocampal amnesia, recollection is reduced when compared to controls, but familiarity is unaffected (Aggleton & Brown, 1999; Eichenbaum, Yonelinas, & Ranganath, 2007;
Fortin, et al., 2004; Yonelinas, et al., 2002). Across multiple studies, patients with medial temporal lobe lesions showed decreased memory process estimates for recollection compared with patients with non-medial temporal lobe lesions, while there was no difference between the two patient groups for familiarity (Skinner & Fernandes, 2007).

Functional magnetic resonance imaging has enhanced our understanding of memory processing and has allowed researchers to study regional brain activity during tasks of encoding and retrieval in a non-invasive way. Consistent with findings from hippocampal lesion literature, fMRI investigations into the neural bases of recollection and familiarity in humans have found greater hippocampal activity during “remember” judgments than during “know” judgments (Cabeza, Rao, Wagner, Mayer, & Schacter, 2001; Cansino, Maquet, Dolan, & Rugg, 2002; Eldridge, Knowlton, Furmanski, Bookheimer, & Engel, 2000; Schacter, Alpert, Savage, Rauch, & Albert, 1996). However, these studies have not controlled for reaction time and confidence, which will be addressed below.

While memory recall affects medial temporal lobe structures, it also relies on activity in other regions of the brain to support recall and each of the subcomponents of the recall process. Subregions of the parietal lobe and of the temporal lobe show greater activation specifically for recollection (inferior parietal lobe, lateral parietal lobe, and lateral temporal cortex) (Henson, Rugg, Shallice, Josephs, & Dolan, 1999; Montaldi, Spencer, Roberts, & Mayes, 2006; Wheeler & Buckner, 2004; Yonelinas,
Otten, Shaw, & Rugg, 2005). Recollection has been associated with increased activity in the superior and inferior posterior parietal cortex (Vilberg & Rugg, 2008). Posterior parietal regions have also consistently shown a retrieval success effect, seen for deeply encoded words versus shallowly encoded words (Shannon & Buckner, 2004) as well as for old versus new items (for a review, see Rugg & Henson, 2002)). While these regions appear to be active during successful memory retrieval, and perhaps particularly for retrieval of additional details, the precuneus, a subregion of the parietal lobe, shows increases in activity for both recollection and familiarity (Henson, Rugg, et al., 1999; Henson, Shallice, & Dolan, 1999; Sharot, Delgado, & Phelps, 2004). Examination of non-medial temporal lobe regions implicated in memory recall aids in the understanding of how brain structures work in concert to facilitate the retrieval of memories from long term memory storage.

Memory Suppression

The active suppression of a memory has been found to drive down activity in the hippocampus below levels seen during encoding and retrieval of memories (Anderson et al. 2004) and a fixation cross baseline (Depue et al. 2007). Anderson and Green (2001) found that unwanted memories could be suppressed, resulting in a difficulty in accessing these memories at a later time. They later hypothesized that unwanted memories are suppressed by recruiting the lateral prefrontal cortex to disengage the hippocampus (Anderson et al. 2004). They found that prefrontal cortex
was more active and activity in the hippocampus was further reduced during memory 
suppression than during recall. Depue and colleagues (2007) found that the prefrontal 
regions of the brain are more active in a ‘no-think’ memory suppression task than in a
‘think’ memory recall task, suggesting their involvement in controlling the
suppression of memories. They also found a decrease in hippocampal activation
during active memory suppression, and suggested that Broadmann Area 10
(frontopolar region) has modulatory effects on inferior frontal gyrus and middle
frontal gyrus, leading to a subsequent decrease in hippocampal activity. The studies
presented here examine memory suppression and memory recollection in the same
group of subjects to determine the neural correlates of active memory suppression and
memory recall, and whether there are common brain regions that are suppressed across
the two tasks.

Since similar activity has been observed during active memory suppression
and memory recall, it is possible that activity attributed specifically to memory recall
or suppression might be more generally related to the overarching components
necessary for the performance of a task. Since the cognitive processes that lead to
hippocampal suppression have not yet been identified, it is possible that frontal lobe
activity associated with post-retrieval processing may be linked with observed
hippocampal suppression. This dissertation examines whether hippocampal
suppression occurs not only during active memory suppression, but also during post-
retrieval processing following memory recollection.
Default Network

In the absence of a task or stimulus, activation in the hippocampal formation correlates with activation in the medial and lateral parietal, medial prefrontal, and anterior temporal regions (Vincent, et al., 2006). This is a network of regions defined as the “default network.” Raichle et al. (2001) proposed the idea of a default network of human brain function, taken from the idea that a set of regions in the cortex is more active in the resting state than during the performance of tasks requiring external attention.

It has been proposed that the activation of the default network is actually mind-wandering, and that a reduction in processing demands is accompanied by an increase in mind-wandering and default network activation (Mason, et al., 2007). The precuneus is one of the most active regions of the brain during a “resting state” in which attention is not directed to an outside stimulus. This pattern of activation and the correlation of increased precuneus activity with increased self-reflection processes characterizes the activity commonly observed throughout the default network (Cavanna 2007). However, it was found that the posterior regions of the network correspond closely with the regions involved in memory recollection (Wagner, Shannon, Kahn, & Buckner, 2005). Posterior parietal cortex activation is modulated by recollection, but not by familiarity-based recognition.
Stark and Squire (2001) found that when an even/odd digit classification task was compared to a fixation-cross baseline, the default network showed deactivation (less activity during the even/odd digit classification than during passive fixation). This highlights the importance of examining the effects of baseline activity during memory recollection tasks. The inclusion of active and passive baseline tasks is necessary to better interpret the level of activity in the MTL related to a particular task and to dissociate task related activity from activation related to default network modulation. These studies investigate the hemodynamics of the default network to determine in what circumstances the hippocampus is part of the default network and in which circumstances they are dissociated.

Retrieval Network

The retrieval network is defined as a set of regions more active for correct and detailed memory retrieval than for unsuccessful or less strong memory retrieval. In a meta-analysis of memory tasks and their modulation of the parietal lobe, Wagner et al. (2005) found increased BOLD activation in subregions of the parietal lobe across multiple memory experiments with different manipulations and comparisons of remember / know judgments, correct rejections, false alarms, and misses (Dobbins, Rice, Wagner, & Schacter, 2003; Eldridge, et al., 2000; Henson, Rugg, et al., 1999; Wheeler & Buckner, 2004). While these studies used different kinds of stimuli and different comparisons, they all found an increase in activity in precuneus, lateral parietal cortex, posterior cingulate, retrosplenial cortex, and intraparietal sulcus.
Whether the comparison was old versus new judgments, hits versus correct rejections, hits versus misses, source hits versus source misses, or any other “stronger” memory vs. “weaker” memory comparison, positive activation was seen in this network of regions. The studies outlined below delve more deeply into retrieval network regions and how they are affected by strong and poor memory retrieval. Specifically, their observed divergence from hippocampal activity is addressed.

Memory Strength and Reaction Time in Episodic Memory Retrieval

Confident memory retrieval is performed faster than retrieval with lower confidence or judgments of familiarity (Dewhurst, Holmes, Brandt, & Dean, 2006; Rotello & Zeng, 2008; Wixted, 2009; Wixted & Stretch, 2004). Based on previous findings of default network activity and its modulation based on task load, these differences in time-on-task would be expected to influence activity in the default network regions. ‘Remember’ responses typically have a significantly shorter reaction time than ‘know’ responses both when there is a two step old/new judgment followed by a recollection/familiarity judgment or when a recollection/familiarity one step judgment is made on its own (Dewhurst, et al., 2006). Therefore, the greater amount of activity observed in the retrieval network could, in fact, be less suppression in default network regions during tasks that are performed faster and more easily. Since reaction time and confidence are confounding components uncontrolled in most studies that use the ‘remember / know’ paradigm, the ability to constrain ‘remember’ and ‘know’
judgments by reaction time and confidence may help determine which medial
temporal lobe substructures contribute to recollection and familiarity and how retrieval
network / default network activity is affected by different processes involved in
memory retrieval.

Memory strength could also influence activity in the medial temporal lobe and
retrieval network. In a study of high and low confidence memory recognition
judgments, activity in the medial temporal lobe and posterior regions of the default
network was greater with high confidence recall (Kim & Cabeza, 2009). Kim and
Cabeza (2009) acknowledge that reaction time for low confidence retrieval was longer
than for high confidence retrieval, but only find a significant correlation between
reaction time and signal change in the left posterior prefrontal cortex. While
controlling for confidence eliminates differences in reaction time, controlling reaction
time might not eliminate differences in confidence (Wixted, 2009). Therefore, by
examining both confidence and reaction time within the same study, one could
determine how these parameters affect observed neural activity.

Summary

While there has been much research devoted both to memory retrieval and to
frontal lobe processing, little has been done to determine the exact contribution of the
frontal lobe, default network, or retrieval network to memory recollection. The
experiments in this dissertation seek to further the understanding of how activity in
these regions and in the hippocampus modulates during memory recollection and memory suppression. This work seeks to explore the relationship between frontal and medial temporal lobes in order to progress the frontier of understanding about frontal lobe and medial temporal lobe related disease, such as fronto-temporal dementia and Alzheimer’s disease. By studying the modulation of frontal processing and its effects on hippocampal suppression and if that suppression is concurrent with memory increases or decreases, we will be able to determine how frontal lobe activity and medial temporal lobe activity modulate in an anticorrelated fashion to mediate memory retrieval. This understanding may have implications for treating disorders such as Alzheimer’s disease where patients have problems with memory recollection or post-traumatic stress disorder where patients rely upon the ability to suppress unwanted memories.

In the following chapters, I examine three aspects of hippocampal activity and whole-brain memory function: 1) which component of BOLD activation is due to memory retrieval itself versus other components of retrieval; 2) how hippocampus, retrieval network, and default network are modulated by task instruction and success; 3) how default network is dissociated from hippocampus during recollection and familiarity memory recall.

In Chapter 2, I assess the dissociation of prefrontal cortex and hippocampus in a memory recall test employing a non-verbal test of memory recollection. I report that hippocampus and dorsolateral prefrontal cortex are dissociable during memory recollection with post-retrieval processing, and this activity is separate from the
default network of brain function. In Chapter 3, I assess the neural bases of memory suppression and memory recall in one group of subjects. I report that hippocampus acts unlike either the default network or the retrieval network during strong- or poor-memory retrieval, and the hippocampus shows an interaction of task instruction and recall success. In Chapter 4, I assess the dissociation of the hippocampus and default network in a remember / know memory test, taking into account reaction time and false alarm rate as factors that may affect activity in these regions. I report that hippocampus and default network respond differently to increased reaction time in trials of recollection and familiarity and have dissociated activity during both types of memory recall.

These three studies, taken together, start to examine how hippocampal activity is part of or distinct from activity in the frontal lobe, retrieval network, and default network during tasks involving memory retrieval. This work not only adds to a growing body of evidence that memory recall affects different brain regions in distinct ways, but also has implications for the study of patients who experience memory deficits due to degeneration in specific brain regions.
CHAPTER 2:
GOING THEIR SEPARATE WAYS: DISSOCIATION OF HIPPOCAMPAL AND DORSOLATERAL PREFRONTAL ACTIVATION DURING EPISODIC RETRIEVAL AND POST-RETRIEVAL PROCESSING

Abstract

Hippocampal activity is modulated during episodic memory retrieval. Most consistently, a relative increase in activity during confident retrieval is observed. The dorsolateral prefrontal cortex (DLPFC) is also activated during retrieval, but may be more generally activated during cognitive-control processes. The “default network,” regions activated during rest or internally focused tasks, includes hippocampus, but not DLPFC. Therefore, DLPFC and hippocampus should diverge during difficult tasks suppressing the default network. It is unclear, however, whether a difficult episodic memory retrieval task would suppress the default network due to difficulty or activate it due to internally directed attention. We hypothesized that a task requiring episodic retrieval followed by rumination on the retrieved item would increase DLPFC activity, but paradoxically reduce hippocampal activity due to concomitant suppression of the default network. In the present study, blocked and event-related fMRI were used to examine hippocampal activity during episodic memory recollection and post-retrieval processing of paired-associates. Subjects were asked to make living/nonliving judgments about items visually presented (classify) or items retrieved from memory (recall-classify). Active and passive baselines were used to differentiate task-related
activity from default network activity. During the ‘recall-classify’ task, anterior hippocampal activity was selectively reduced relative to ‘classify’ and baseline tasks, and this activity was inversely correlated with DLPFC. Reaction time was positively correlated with DLPFC activation and default network/hippocampal suppression. The findings demonstrate that frontal and hippocampal activity are dissociated during difficult episodic retrieval tasks and reveal important considerations for interpreting hippocampal activity associated with successful episodic retrieval.
Introduction

Memory recollection is seldom independent of other cognitive processes that are called upon to perform routine activities. Rather, memory retrieval is recruited alongside several processes working in concert to perform everyday tasks. Often, the products of recollection are held in mind for some time while further cognitive processing occurs (Buckner, 2003; Daselaar, et al., 2008; Moscovitch, 1992; Wagner, Maril, Bjork, & Schacter, 2001). When an item is retrieved from memory, working memory processes may be called upon to both monitor the validity of the memory retrieved (post-retrieval monitoring; (Rugg & Wilding, 2000)) and perform processes necessary in pursuit of a cognitive task. Thus, interplay between long term memory (LTM) and working memory (WM) may be required to perform many real-world tasks that involve post-retrieval processing.

Similarly, tasks designed to gauge memory strength involve post-retrieval processing as subjects ruminate on the products of retrieval to determine whether the item was strongly or weakly recognized. Prior imaging studies have shown increases in hippocampal activity during successful LTM retrieval. Retrieval of information from LTM activates hippocampus particularly when items have been deeply encoded (Dobbins, et al., 2003; Dolan & Fletcher, 1997; Gabrieli, et al., 1997; Greicius, et al., 2003; Ranganath & Rainer, 2003; Schacter, et al., 1995; Weis, et al., 2004; Zeineh, Engel, Thompson, & Bookheimer, 2003) and recollection is made with high
It is unclear how brain imaging results are influenced by the additional component of post-retrieval processing included in studies where subjects make confidence judgments. Interpretation of hippocampal activity during these tasks is further complicated by the fact that the hippocampus is part of the default network, an interconnected set of brain regions that are active during mind wandering (Mason, et al., 2007) or during internally directed thought (Esposito, et al., 2006; Fransson, 2006; Gusnard, Akbudak, Shulman, & Raichle, 2001; McKiernan, Kaufman, Kucera-Thompson, & Binder, 2003; Raichle, et al., 2001). Thus, these regions are often maximally deactivated during more difficult tasks requiring an external focus of attention. Indeed, activity in medial temporal lobe (MTL) regions, specifically posterior parahippocampus, has been shown to be reduced by active versus passive non-mnemonic tasks (Stark & Squire, 2001). On the other hand, recognition tasks activate a set of “retrieval network” brain regions that overlap with the default network, including the precuneus, posterior cingulate, retrosplenial cortex, and lateral parietal cortex (Buckner & Vincent, 2007; Vincent, et al., 2006). It is plausible that making and judging a confident recognition of an item may be quicker and easier than making and judging a less confident recognition of an item. Thus, there is an alternative interpretation of increased retrieval network and hippocampal activity during confident recollection; confident recollection judgments lead to less suppression of the default network than do judgments of familiarity.
Activity in dorsolateral prefrontal cortex (DLPFC) may be related less to retrieval itself than to cognitive control or post-retrieval monitoring. Prior studies have found that activity in the DLPFC is not directly tied to retrieval mode (Kapur, et al., 1995) or to retrieval success (Rugg, Fletcher, Frith, Frackowiak, & Dolan, 1996). Henson, Rugg, Shalice, and Dolan (2000) found increased activity in the right DLPFC for low-confidence judgments, which require more monitoring before a decision is made. In a non-mnemonic task, Fleck, Daselaar, Dobbins, and Cabeza (2006) found that DLPFC activity is not based on continuous monitoring, but rather is dependent on discontinuous evaluation of ongoing events.

No prior imaging studies have directly addressed frontal and hippocampal activity dissociations during episodic memory retrieval and post-retrieval processing. However, studies of active memory suppression have shown inversely correlated activity in these two regions, suggesting a dynamic interplay between frontal and hippocampal regions at retrieval (Anderson, et al., 2004; Depue, et al., 2007). An episodic retrieval task that requires subjects to make a judgment on the products of retrieval might be expected to similarly activate DLPFC and suppress hippocampal regions if the default network is driven more generally by task difficulty. The opposite result would be expected if the default network is active during internally directed thought, including memory retrieval processes and post-retrieval rumination. To test these competing hypotheses, we included active and passive baselines in our studies of memory recall to identify classic default network suppression and compare it to suppression associated with the memory task.
To directly investigate frontal and hippocampal memory dissociations during episodic memory retrieval and post-retrieval processing, the present study examined frontal and hippocampal interaction during retrieval of information from LTM and further classification of that information. This task was contrasted with a task in which subjects classified items that were visually presented. Subjects were asked to make living/nonliving judgments about items retrieved from memory (recall-classify), and in a control task, subjects made living/nonliving judgments on visually presented items (classify). In addition, active (odd/even digit classification) and passive (fixation) baselines were used, allowing comparison of the task to different baselines that have been shown to influence MTL activity. Based on studies that suggest recruitment of frontal lobe circuitry in post-retrieval processing (Moscovitch, 1992), we expected to see greater recruitment of DLPFC during a task that required post-retrieval classification than during simple classification of items visually presented. We predicted that this activity would be correlated with trial-by-trial reaction time (RT) and expected default network regions/hippocampus to show the inverse pattern of activity.

A block-design experiment revealed increased DLPFC activity and suppressed hippocampal activity during the recall-classify task. This hippocampal region showed no difference in activity during even/odd discrimination, fixation, and classify tasks. To further examine the temporal basis of the observed hippocampal suppression, a rapid event-related design was used to replicate the findings and explore the time-course of the activity. The time-course was then separated based on RT within each
task type, showing that DLPFC is more active and hippocampus is more suppressed during memory recall trials with longer RTs.

Methods

Subjects. Twenty-two healthy right-handed subjects were recruited from the University of California, San Diego community and the surrounding area. Twelve subjects (mean age = 23.83 ± 3.01 years, 5 male) participated in Experiment 1 and ten subjects (mean age = 22.75 ± 3.37 years, 5 male) participated in Experiment 2. Two subjects (male) were excluded from Experiment 2 due to scanner and response-recording device technical issues. Subjects were paid $40 for their participation and gave informed consent approved by the Institutional Review Board of the University of California, San Diego.

Stimuli. Stimuli were 256 color drawings of common objects selected from Rossion and Pourtois color Snodgrass images (Rossion & Pourtois, 2004). Drawings were paired randomly into 128 pairs. Pairs were screened to remove those with obvious visual or semantic relationships.

Experiment 1 - Block design. Experiment 1 examined magnetic resonance blood oxygen level dependent (BOLD) response during classification judgments made on items retrieved from LTM (recall-classify) or items visually presented (classify). In addition, active (even/odd discrimination) and passive (fixation) baselines were
assessed. Prior to the scan, subjects learned pairs of images using a study task that
provided a high degree of retrieval accuracy in a behavioral pilot (range: 70%-93%
correct). During this study phase of the experiment, which took place approximately
30 minutes before scanning, subjects saw 128 pairs of items and were instructed to
remember which items were paired together. Two images were presented side-by-side
for 3 seconds, and each pair of items was presented three times during the course of
the study session.

During scanning, subjects were presented with two adjacent noise-mask-filled
boxes on the viewing screen, one outlined in black and one outlined in either red or
green (Fig. 1). After 1 second, a single image from the study set appeared in either the
black or the green box for 0.5 seconds. The green box indicated that the subject should
classify the presented item as ‘living’ or ‘nonliving.’ The red box indicated that the
subject should recall and classify the pair of the presented item. Subjects were given
1.5 seconds to make a judgment of ‘living’ or ‘non-living’ for each image seen (green
trial) or recalled (red trial) and were instructed not to respond if unable to recall the
item. ‘Recall-classify’ and ‘classify’ blocks each included 8 trials of one condition,
and these were interspersed with blocks of 16 odd/even judgments (1.5 seconds each)
or 24 seconds of fixation cross. There were four blocks of each condition in each of 4
runs. Runs lasted 395 sec, and were separated by 2-3 minute breaks.
**Block-design fMRI data analysis.** Using the AFNI (Cox, 1996) suite of programs, data from each run were reconstructed. Slices were temporally aligned and co-registered with a 3D registration algorithm. Voxels outside the brain were removed using a threshold mask of the functional data. Functional runs were corrected for motion and concatenated. For each of the four conditions the raw signal was averaged from 9 to 24 seconds of each 24 second block for all twelve subjects. The initial 9 seconds were excluded to avoid confounds from the previous block. The 16 blocks of each condition were then averaged together to get one average activation trace at each voxel for each of the four conditions. Standard landmarks were defined manually on the anatomical scans, and then the anatomical and functional scans were transformed into Talairach space (Talairach & Tournoux, 1998) using AFNI nearest neighbor interpolation (Cox, 1996). Voxel-wise t-tests (two-tailed) were performed to compare average BOLD signal across conditions. Because of the small volume of our area of interest (hippocampus), clusters were defined with a connectivity of 4mm between voxel centers and including at least 5 voxels (for a whole-brain corrected p-value of .05). Alphasim was used to correct for multiple comparisons inside the brain and to obtain cluster significance. Clusters consisting of voxels significant at p<.001 (corrected for multiple comparisons) were displayed on a statistical map overlaid onto an average structural image, and were used to extract average activity in each region.

**Experiment 2 - Event-related.** To replicate and further explore the time-course of task-related activity elicited by the block-design study, an event-related design was used to examine frontal and hippocampal activity during the ‘recall-classify’ and
‘classify’ conditions contrasted with a fixation baseline. In this study, subjects had a study session identical to the block-design study and were asked to perform the ‘recall-classify,’ ‘classify,’ and fixation tasks in the scanner. During scanning, subjects were presented with two adjacent noise-mask-filled boxes on the viewing screen, one outlined in black and one outlined in either red or green (Figure 1). After 0.5 seconds, an image appeared in either the black or the green box for 0.5 seconds. Instructions were identical to those of the block experiment. Subjects were asked to make a judgment of ‘living’ or ‘non-living’ for each image seen or recalled (2 s), and to respond with ‘unsure’ if they could not recall the pair. Error trials (unsure, incorrect, and no-response) were excluded from the analysis. Trials were jittered with 0, 1.5, 3, or 4.5 seconds of fixation baseline. Each subject underwent a single session of four scans lasting 362 sec each.

**Event-related fMRI data analysis.** Data from each run were reconstructed. Slices were temporally aligned and co-registered with a 3D registration algorithm. Voxels outside the brain were removed using a threshold mask of the functional data. Functional runs were corrected for motion. A general linear model was constructed using multiple regression analysis, and included six motion regressors from the registration process and regressors for ‘recall-classify’ and ‘classify’ condition correct and incorrect responses. Standard landmarks were defined manually on the anatomical scans, and then the anatomical and functional scans were transformed into Talairach space (Talairach & Tournoux, 1998) using AFNI nearest neighbor interpolation (Cox, 1996). For the ‘recall-classify’ and ‘classify’ conditions, a hemodynamic response was
estimated for the 15 seconds following the onset of the stimulus using signal
deconvolution. Voxel-wise t-tests (two-tailed) were performed to compare average
BOLD signal between conditions. Because of the small volume of our area of interest
(hippocampus), clusters were defined with a connectivity of 4mm between voxel
centers and including at least 5 voxels. These clusters, significant at p<.05 (two-tailed
and corrected for multiple comparisons) were displayed on a statistical map overlaid
onto an average structural image, and the average hemodynamic response function
was then extracted for each cluster of interest.

Correlation analysis. The time-course of the seed region of interest was
extracted and a contrast regressor for ‘recall-classify’ and ‘classify’ conditions was
obtained to construct the interaction regressor (Heekeren, Marrett, Bandettini, &
Ungerleider, 2004). This was used in the correlation analysis to determine the
correlation of brain regions with the seed region chosen (hippocampus). Correlation
coefficients were obtained showing areas in the brain that were more correlated in the
‘recall-classify’ task than in the ‘classify’ task. Correlation coefficients were converted
to Z-scores, analyzed with a t-test, and clustered at a threshold of p<.05 (corrected for
multiple comparisons).

Response Time analysis. To further explore the event-related data, correct trials
in the ‘recall-classify’ and ’classify’ conditions were separated into two groups within
each condition: trials where the response time (RT) was > +1 standard deviation from
the mean and trials where the RT was < -1 standard deviation from the mean for each
subject (see Table 1 for individual RT means and average SDs). For the ‘recall-classify’ and ‘classify’ conditions, a hemodynamic response was estimated for the 15 seconds following the onset of the stimulus using signal deconvolution. Voxel-wise t-tests (two-tailed) were performed to compare average BOLD signal between long and short RT trials, separately analyzed in the ‘recall-classify’ and ‘classify’ conditions. The average hemodynamic response function was then extracted for the DLPFC and hippocampal clusters identified in the initial ‘recall-classify’ minus ‘classify’ contrast.

*fMRI Imaging Parameters.* Imaging was done in a 3T 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 s, one shot per repetition, echo time = 30, flip angle = 90, bandwidth = 31.25 MHz). Twenty-two slices covering the entire brain were acquired perpendicular to the long axis of the hippocampus with 4 x 4 x 7 mm voxels, allowing greater summation of activity along the hippocampal axial plane (Brewer & Moghekar, 2002). A T1-weighted high resolution (1 x 1 x 1 mm), three-dimensional magnetization-prepared rapid gradient echo or fast spoiled gradient recalled anatomical dataset was collected. A structural scan was acquired in the same slice locations as the functional images for use in confirming alignment of functional data to the high-resolution anatomical scan.

Results
Experiment 1: fMRI Results – Block, Behavioral Results. The mean RTs after the onset of the stimulus differed ($F(2,33) = 22.41, p< .001$) for the ‘recall-classify’ condition (937 ± 57 msec), ‘classify’ condition (484 ± 57 msec), and even/odd discrimination (677 ±18 msec). Post hoc Bonferroni tests indicated that RT for the ‘recall-classify’ task was significantly longer than for the ‘classify’ task ($p< .01$) and even/odd discrimination ($p< .05$). RT for the ‘classify’ task was significantly shorter than for even/odd ($p< .001$). Subjects responded in 73 ± 4% of trials for the ‘recall-classify’ task and made correct judgments in 86 ± 2% of those trials. Subjects responded in 97 ± 1% of ‘classify’ trials and made correct judgments in 98 ± 1% of those trials.

fMRI results: ‘recall-classify’ vs. ‘classify.’ As depicted in Figure 2, bilateral anterior hippocampus showed BOLD responses that were significantly lower for ‘recall-classify’ than for ‘classify’, even/odd, or fixation (each $p<.001$, corrected). In bilateral DLPFC (Brodmann Area 9), BOLD response was significantly higher for ‘recall-classify’ than for ‘classify’, even/odd, and fixation ($p<.01$, corrected) and was higher for ‘classify’ than for even/odd and fixation ($p<.05$, corrected). A list of clusters significantly different in the ‘recall-classify’ and ‘classify’ conditions at $p<.001$, corrected, can be found in Table 2.

fMRI results: Correlation analysis. Using the left hippocampus as a seed region, a correlation analysis was performed using ‘recall-classify’ and ‘classify’ tasks as regressors to determine areas of activity more correlated with the observed decrease
in hippocampal activity during the ‘recall-classify’ condition. Left and right hippocampus were positively correlated with each other and inversely correlated with bilateral DLPFC (Figure 3, $p<.05$, corrected). The hippocampus was positively correlated with bilateral middle frontal gyrus as well as bilateral precentral and superior temporal gyri and inversely correlated with bilateral fusiform, parahippocampal, anterior cingulate, and occipital gyri.

**fMRI results: Default Network.** The even/odd minus fixation (EO-FIX) activation map of the present study shows activity decreases in precuneus, posterior cingulate, and other midline structures, similar to prior published results describing “default network” activity (ie. areas that are more active for easier tasks) (for a list of significant clusters, see Table 3). Stark and Squire (2001) used an EO-FIX contrast to show that MTL regions may be part of the default network. A comparison between the present EO-FIX contrast and the Stark and Squire EO-FIX contrast reveals similar activity maps (Figure 4; 4A reprinted with consent from the Proceedings of the National Academy of Sciences of the United States of America, 2001). Both studies show activation in the posterior parahippocampal regions in addition to posterior cingulate and other midline structures. Activation maps from the EO-FIX contrast from the current experiment were compared to activation maps from the ‘recall-classify’ versus ‘classify’ contrast to determine regions of overlap between the default network and activation due to the experimental condition. To show that the current ‘recall-classify’ versus ‘classify’ contrast results in MTL activation distinct from the
default network, an overlap analysis was done comparing activations from the EO-FIX and ‘recall-classify’ versus ‘classify’ contrasts.

Comparison of the activation maps of ‘recall-classify’ versus ‘classify’ and EO-FIX revealed MTL regional suppression for the experimental conditions that was spatially distinct from that attributable to the default network defined by the contrast of EO-FIX (Figure 5). While the ‘recall-classify’ versus ‘classify’ contrast revealed significant clusters in the bilateral anterior hippocampus, insular cortex, and DLPFC, the EO-FIX contrast revealed significant clusters in the posterior cingulate, insular cortex, and bilateral posterior parahippocampus. While many of the regions commonly defined as part of the default network showed less activity in both of these contrasts, EO-FIX showed decreased activity in posterior parahippocampus while a suppression of the anterior hippocampus was only observed in the task requiring memory retrieval. The overlap analysis showed no overlapping voxels in the MTL. This comparison reveals that the default-network-related modulation of MTL activity, which replicated the Stark and Squire (2001) findings, is different than the hippocampal suppression revealed by the ‘recall-classify’ versus ‘classify’ contrast.

*Experiment 2: fMRI Results – Event-Related with Fixation Baseline*

*Behavioral Results.* The mean RTs differed for ‘recall-classify’ (1552 ± 69 msec) and ‘classify’ (1060 ± 63 msec) conditions. RT for ‘recall-classify’ was significantly longer than for ‘classify’ (t(7) = 8.54, p< .001). Subjects responded in 80 ± 5% of trials for the ‘recall-classify’ task and made correct judgments in 90 ± 1% of those
trials. Subjects responded in 96 ± 1% of ‘classify’ trials and made correct judgments in 97 ± 1% of those trials. Only these correct judgments were used in further analysis.

fMRI Results. Cluster maps of the difference in activation in the ‘recall-classify’ and ‘classify’ conditions showed significant differences ($p<.05$, corrected) in the right hippocampus and left DLPFC. Hippocampus showed less activation in the ‘recall-classify’ condition, while DLPFC showed more activity during this task (Figure 6). These clusters were used as a mask to extract average impulse response curves for the twelve subjects, which revealed increases in DLPFC activity (Figure 6A, left) that corresponded to decreases in hippocampal activity (Figure 6B, left). As in Experiment 1, in a correlation analysis, activity in the right HC was more anticorrelated with activity in the DLPFC for the ‘recall-classify’ condition than for the ‘classify’ condition ($t(7) = 3.106, p<.01$).

Clusters defined in the original contrast were used for further analysis within each trial type, and differences in the right hippocampus and left DLPFC for ‘recall-classify’ and ‘classify’ trials with longer and shorter reaction times were examined. Left DLPFC (Figure 6A, right) showed greatest amounts of activation for the ‘recall-classify’ trials with longer reaction times and intermediate activation for the ‘recall-classify’ trials with shorter reaction times. Activation in the ‘classify’ trials with the longer reaction times overlapped with activation for ‘recall-classify’ trials with shorter reaction times. DLPFC activation for the ‘classify’ trials with the shorter reaction times was lowest. The right hippocampus (Figure 6B, right) showed a decrease in
Discussion

These experiments examined brain activity associated with memory retrieval followed by working with the information retrieved. During Experiment 1, BOLD activation in the anterior hippocampus was significantly reduced for ‘recall-classify’ compared with ‘classify,’ even/odd discrimination, and fixation. Hippocampal suppression was correlated with an increase in activity in DLPFC. In Experiment 2 the findings were replicated and extended to show the time-course of hippocampal activity with a reduction of BOLD signal in the ‘recall-classify’ condition below the ‘classify’ condition. A separation of the activity by response time showed greatest activity in DLPFC and greatest suppression of activity in hippocampus for the memory task trials with the longest reaction times. These experiments demonstrate that hippocampal activity is dissociated from prefrontal activity during a retrieval task requiring post-retrieval processing; reduced activity in the hippocampus is distinct from the default-network MTL activity defined by comparing active versus passive baseline tasks.

Dissociation of frontal and hippocampal activity. The results of these studies showed that DLPFC was most active and hippocampus was least active during the ‘recall-classify’ task. In imaging studies, DLPFC has been linked with numerous...
mnemonic and non-mnemonic functions, including LTM retrieval (Lundstrom, et al., 2003; Nolde, Johnson, & D'Esposito, 1998; Nyberg, et al., 1995; Ranganath, Johnson, & D'Esposito, 2000; Wager & Smith, 2003; Wagner, Desmond, Glover, & Gabrieli, 1998), maintenance and manipulation of items in working memory (Cabeza & Nyberg, 2000), decision-making (Fleck, et al., 2006), set shifting (Zanolie, et al., 2008), and task difficulty (Braver, et al., 1997; Manoach, et al., 1997). Perhaps most relevant to the present study are its role in search processes subserving memory retrieval and its role in working memory (see D'Esposito, 2007 for review). DLPFC areas are activated when more information needs to be stored in working memory (Braver, et al., 1997; Rypma, Berger, & D'Esposito, 2002; Rypma, Prabhakaran, Desmond, Glover, & Gabrieli, 1999; Smith & Jonides, 1997). The ‘recall-classify’ task had components of recollection that would engage search processes, and post-retrieval processing that would engage working memory to hold the retrieved information in mind so classification could be performed. Thus, the dissociation of DLPFC and hippocampal activity observed during the ‘recall-classify’ condition might have been enhanced by engagement of search processes before LTM retrieval, working memory following LTM retrieval, or both. Following search and correct retrieval of an item from LTM, the hippocampal network might be suppressed as WM systems come online to work with the information retrieved. Such suppression may be relevant to minimize memory intrusion during post-retrieval processing.

Direct connections between prefrontal cortex and MTL have been established through anatomical studies of the primate brain (Goldman-Rakic, Selemon, &
Schwartz, 1984), and these connections have been examined noninvasively in humans using directional diffusion weighted neuroimaging (Takahashi, Ohki, & Kim, 2007). Such findings provide a neuroanatomic basis for previous evidence of top-down modulation of MTL activity by prefrontal cortex (Buckner, Koutstaal, Schacter, Dale, et al., 1998; Buckner, Koutstaal, Schacter, Wagner, & Rosen, 1998; Gazzaley, Cooney, Rissman, & D'Esposito, 2005; Takahashi, Ohki, & Miyashita, 2002). The inversely correlated activity in prefrontal and MTL regions observed in the present study suggests that these two regions exhibit a dissociable functional response. Directed study of temporally linked prefrontal-MTL interaction will provide further information regarding the functional linkage between these regions.

*Increases and decreases in hippocampal activity associated with memory retrieval.* Prior studies have shown increases in hippocampal activity both during memory encoding (Davachi, et al., 2003; Fernandez, et al., 1999; Lepage, Habib, & Tulving, 1998; Stern, et al., 1996; Uncapher & Rugg, 2005) and retrieval (Brewer, et al., 1998; Dobbins, et al., 2003; Dolan & Fletcher, 1997; Eldridge, et al., 2000; Greicius, et al., 2003; R. Henson, 2005; Kahn, Davachi, & Wagner, 2004; Nyberg, et al., 1996; Ranganath & Rainer, 2003; Rugg, Henson, & Robb, 2003; Schacter, et al., 1995; Weis, et al., 2004; Zeineh, et al., 2003). A meta-analyses of PET studies found greater activation in the rostral portions of the hippocampus for encoding and greater activation in the caudal portions of the hippocampus for retrieval (Lepage, et al., 1998). In each of these PET and fMRI studies the subjects were shown an image or word and asked if they recognized it as previously seen or were cued to remember a
word. The tasks employed in these studies did not require holding the retrieved item in
mind for further processing. The clearest distinction between the tasks in the prior
studies and those used in the current study is that the current ‘recall-classify’ task
demanded search, retrieval, and working with the item retrieved and did not rely solely
upon recognition or cued-recall.

The current findings are relevant to the interpretation of hippocampal activity
differences during memory retrieval. Many studies have examined ‘old’ versus ‘new’
item contrasts at recognition and have reported greater hippocampal activity for
confidently identified items (Brewer & Gabrieli, 1997; Daselaar, Fleck, & Cabeza,
2006; Gabrieli, et al., 1997; Slotnick & Schacter, 2004). One confound is that making
such ‘old’ judgments requires less effort, less search, and presumably less frontal
processing than judging an item as ‘new.’ Similarly, studies have reported greater
hippocampal activity for ‘remember’ judgments (or items retrieved with high
confidence) relative to ‘know’ judgments (or items retrieved with low-confidence)
(Eldridge, et al., 2000; Hockley & Consoli, 1999; Wixted & Stretch, 2004). Low-
confidence retrieval might require more search, effort, and frontal processing than
high-confidence retrieval and, in light of the current findings, would be expected to
lead to decreased hippocampal activity. In fact, examination of the parameter
estimates reported by Yonelinas, Otten, Shaw, & Rugg (2005) found that the
hippocampus showed essentially no response for items judged as “remember,” but
negative parameter estimates for items judged as “familiar.” In addition, a number of
regions showing a similar decreased response for familiar judgments have been
identified as default network regions (ventromedial frontal and posterior cingulate).

An additional consideration arises for such imaging studies that employ a retrieval task that includes a subsequent judgment of memory strength. The post-retrieval processing required for subjects to assess and report memory strength may, itself, influence frontal and hippocampal activity. The neural bases of the judgments themselves and the differential influence of memory strength upon them remains unknown and has yet to be addressed through experimentation.

*Memory retrieval and the default network.* In studies of recognition, the network of regions activated during episodic memory retrieval has been shown to overlap with the network of regions defined as the default network (Buckner, et al., 2005; Greicius, Srivastava, Reiss, & Menon, 2004; Vincent, et al., 2006). Hippocampus and adjacent MTL regions are known to be part of the default network (Greicius, et al., 2004), and seeding hippocampus in a functional connectivity analysis reveals connectivity with precuneus, posterior cingulate, and ventromedial frontal lobe, which are regions commonly identified as default network (Vincent, et al., 2006). While suppression of the default network has been attributed to many different cognitive functions, in this study we observe deactivation of the default network, including anterior hippocampus, during a difficult episodic recall task requiring post-retrieval processing. Although this task might be expected to activate the retrieval network/default network, the opposite was seen. This suggests that task difficulty may be a more important modulator of this network than memory retrieval or internal focus of attention.
In Experiment 2, a trend toward hippocampal deactivation was seen during simple classification, which was not seen in the block-design experiment. It is possible that during the fixation task following a ‘classify’ trial, inadvertent pair retrieval and processing occurred, since all items had been studied as paired associates. This could explain the difference between the results obtained using a block-design (where there was little time to further consider the stimuli before the next trial) and an event-related design with fixation (where there may have been time during fixation to further consider the preceding stimulus).

The MTL regions suppressed by the EO task differed from those suppressed by the ‘recall-classify’ task, though both tasks led to suppression of non-MTL default regions. This suggests that the task employed may influence which components of the default network are modulated. In a review of default network literature, Buckner, Andrews-Hanna, & Schacter (2008) discuss the default network in terms of a core set of regions with high region-to-region correlations. MTL regions, including the parahippocampus and hippocampus, comprise a subnetwork with variable correlation with other regions in the default network. Regions such as the posterior cingulate / retrosplenial cortex and ventromedial prefrontal cortex show high correlation with the MTL subnetwork, while the dorsomedial prefrontal cortex shows negative correlation with the MTL subnetwork. These findings suggest that the default network is not consistently activated as a unit, but rather that subcomponents may be more or less activated at different times. The present findings support such a notion. For example, the convergent findings between the present study and those of Stark and Squire...
(2001) would suggest that even-odd task performance results in suppression of posterior parahippocampal regions, performance of the ‘recall-classify’ task results in suppression of anterior hippocampus, and performance of the ‘classify’ task does not result in significant suppression of MTL regions. Each of these tasks, however, does result in suppression of the core set of default regions - the posterior cingulate / retrosplenial cortex and ventromedial prefrontal cortex.

Task difficulty and the default network. Event related fMRI allows examination of trial to trial differences in reaction time, which may provide insight into the relationships between frontal lobe activation, default network suppression, MTL suppression, and task difficulty. Reaction time is often used as a marker of task difficulty and it has specifically been employed to examine difficulty in categorization of items (Demb, et al., 1995; Kounios & Holcomb, 1994; Rajah, Ames, & D'Esposito, 2008; Taylor & Thoroughman, 2008; West & Holcomb, 2002). When such a construct is applied to the current data and activation is examined in relation to reaction time, differing levels of activation in DLPFC and anterior hippocampus were observed. As seen in prior studies, DLPFC activity was highly related to reaction time, with longer reaction time associated with greater DLPFC activity in the ‘recall-classify’ and ‘classify’ conditions. Interestingly, anterior hippocampal activity showed the reverse pattern, where longer reaction times were associated with more suppressed hippocampal activity in the ‘recall-classify’ condition only. So while in the DLPFC it is possible that the activity difference is due to classification difficulty, in the
hippocampus it would appear that there is an interaction between recollection and task difficulty.

Conclusion

The present study demonstrates that DLPFC and hippocampal activity are dissociated during difficult episodic retrieval tasks and that the default network/hippocampus is suppressed during episodic memory retrieval and post-retrieval processing. Default network regions outside the MTL were suppressed by all tasks relative to passive fixation, but anterior hippocampus was suppressed only during episodic retrieval with post-retrieval processing. These findings were replicated and extended in a second group of subjects demonstrating greater dissociation of DLPFC and hippocampal activity in memory-recall trials with longer reaction times. These studies demonstrate that DLPFC and hippocampal regions, often diverging when default network is activated, also may diverge during episodic retrieval. This suggests a more complex relationship during retrieval and post-retrieval processing. Exploring difficulty of memory retrieval judgments in relation to the default network could extend our understanding of the brain bases of retrieval and shed light on memory recall studies showing an overlap of the retrieval and default networks. Directed study of the circumstances leading to divergence of hippocampal activity from frontal, retrieval network, and default network activity may help identify the role of cooperation and competition between memory systems in everyday function.
Acknowledgments

Chapter 2, in full, is a reprint of the material as it appears in Journal of Cognitive Neuroscience, 2010.


The dissertation author was the primary investigator and author of this paper.
CHAPTER 3:
ELABORATION VERSUS SUPPRESSION OF CUED MEMORIES: INFLUENCE OF MEMORY RECALL INSTRUCTION ON DEFAULT NETWORK, RETRIEVAL NETWORK, AND HIPPOCAMPAL ACTIVITY

Abstract

While studies of memory retrieval usually focus on the medial temporal lobe, many studies find modulated blood oxygen level dependent (BOLD) activity in default network and subregions of the parietal lobe during tasks involving memory. This study explores the effects of task instruction and recall success on BOLD activity in these regions using functional magnetic resonance imaging. Specifically, brain activity was examined during suppression of memory retrieval, simple retrieval, and elaborative retrieval of paired associates. There was greater negatively-deflected activation in default network for poorly-remembered pairs, regardless of task instruction. Dorsal parietal cortex (BA 7) showed the greatest amount of increased activation during elaborative recall, with no difference in recall and suppress strongly-remembered conditions. Posterior ventral parietal cortex (BA 39) showed no difference in activity for strongly-remembered pairs of any trial type, and a decrease in activity for poorly-remembered pairs in the recall conditions. For strongly-remembered pairs, anterior ventrolateral parietal cortex (BA 40) shows the greatest amount of activity for elaborative recall, followed by recall then suppress. Hippocampus showed distinct activity from the parietal cortex and default network, and showed a positively-
deflected activation with successful recall. This study has shown that default network, parietal lobe subregions and hippocampus respond differently to strongly- and poorly-remembered trials when subjects are instructed to suppress, recall, or recall with elaboration.
Introduction

Several imaging and electrophysiological studies have found that activity in the human hippocampus is modulated during encoding and retrieval of memories (for review, see Squire, 2009), but how memory task instruction and success affect medial temporal lobe, parietal lobe and default network regions remains unknown. While top-down modulation of hippocampal activity has been observed during memory retrieval and memory suppression using functional magnetic resonance imaging, these two memory processes have not been explored together. This study explores the effects of top-down modulation on memory retrieval in order to determine the effects of task instruction and recall success on blood oxygen level dependent (BOLD) activity in these regions.

While studies of memory retrieval usually focus on the medial temporal lobe, many studies find increased BOLD activity in subregions of the parietal lobe during tasks involving memory (Cabeza, 2008; Ciaramelli, Grady, & Moscovitch, 2008; Dobbins, et al., 2003; Eldridge, et al., 2000; Henson, Rugg, et al., 1999; Vilberg & Rugg, 2008; Wheeler & Buckner, 2004). In general, stronger memories tend to elicit positive activation in the precuneus, lateral parietal cortex, retrosplenial cortex, posterior cingulate, and intraparietal sulcus (Dobbins, et al., 2003; Eldridge, et al., 2000; Henson, Rugg, et al., 1999; Vilberg & Rugg, 2008, 2009; see Wagner et al. 2005 for review). There are many competing hypotheses surrounding the exact role of the parietal cortex in episodic memory retrieval. One hypothesis supports these
regions acting as a mnemonic accumulator, holding information until a critical threshold is reached for memory recognition (Shadlen & Newsome, 2001). Another supports the role of the parietal lobe for the subjective experience of recollection (Ally, Simons, McKeever, Peers, & Budson, 2008; Olson & Berryhill, 2009). A third hypothesis supports the lateral parietal cortex involvement in internal attention to memory (Cabeza, 2008; Ciaramelli, et al., 2008; Wagner, et al., 2005), and a final hypothesis, supported by many studies, implicates the parietal cortex in holding retrieved information and acting as a buffer during episodic memory retrieval (Baddeley, 2000; Vilberg & Rugg, 2008; see Wagner et al. 2005 for review).

The parietal cortex is often subdivided into dorsal parietal cortex and ventral parietal cortex, with theories differing on the exact contributions of each subregion. One view suggests that the dorsal parietal cortex reflects top-down direction of attention to retrieval, or goal-driven attention (Cabeza, 2008; Ciaramelli, et al., 2008). This region shows increased activation for low-confidence memory judgments, where subjects need greater attention to memory retrieval (Daselaar, et al., 2006; Fleck, et al., 2006; Kim & Cabeza, 2009). Additionally, judgments of recollection where greater top-down retrieval effort is needed for source memory retrieval elicit greater activation in this region that judgments of familiarity, which do not require these extra details (Ciaramelli, et al., 2008). Unlike the dorsal parietal cortex, the ventral parietal cortex is thought to play a more direct role in memory retrieval. Greater activation has been noted for recollection relative to familiarity, with sensitivity for the frequencies of old and new items (Herron & Wilding, 2004; Vilberg & Rugg, 2008). It has also been
hypothesized that the ventral parietal cortex is implicated in bottom-up attention due to the capture of attention due to the oldness of an item (Cabeza, 2008; Ciaramelli, et al., 2008). Parts of the ventral parietal cortex fall in the network of regions commonly identified as the default network, and therefore default network activity should be taken into consideration when examining ventral parietal cortex activation (see Buckner & Vincent, 2007 for review).

The idea of a default network was taken from the idea that a set of regions in the cortex is more active in the resting state than during the performance of tasks requiring external focus of attention (Raichle, et al., 2001). Default network activity has been attributed to mind wandering (Mason, et al., 2007) as well as internally directed thought (Esposito, et al., 2006; Fransson, 2006; Gusnard, et al., 2001; McKiernan, et al., 2003; Raichle, et al., 2001). Many studies have shown that default network activity decreases during attention-demanding cognitive tasks (Raichle, et al., 2001). A common interpretation is that default network activity is related to spontaneous, task-related self-referential, or introspective mental activity (Gusnard, et al., 2001) and general information gathering and evaluation (Raichle, et al., 2001). Paradoxically, the default network is deactivated both during more difficult tasks requiring external focus of attention (Stark & Squire, 2001) and tasks of memory recognition, which require more internally directed thought (Buckner & Vincent, 2007). Some studies have focused on task-induced deactivation and the how this relates to task difficulty (McKiernan, et al., 2003).
By including tasks involving both memory retrieval and memory suppression, one may be able to determine how task instruction and recall success contribute to BOLD activity in the retrieval and default networks. Examining suppression, retrieval, and elaborative retrieval of episodic memory might help disentangle the aspects of task difficulty, memory strength, and introspection inherent in memory retrieval in order to better separate mnemonic from non-mnemonic networks in task-related fMRI activity.

Methods

Twelve healthy right-handed subjects were recruited from the University of California, San Diego community and the surrounding area (mean age = 27 ± 3 years, 8 male). Subjects were paid $40 for their participation and gave informed consent approved by the Institutional Review Board of the University of California, San Diego.

Stimuli were 120 color drawings of common objects selected from Rossion and Pourtois color Snodgrass images (Rossion & Pourtois, 2004) randomly paired into 60 pairs and were studied to criterion. During scanning, subjects were presented with two adjacent noise-mask-filled boxes on the viewing screen, one outlined in black and one outlined in either red, blue, or green (Figure 7). After 1 second, an image from the studied pairs appeared in the black box for 0.5 seconds. Subjects were asked to either (1) suppress the item that had been paired with the item seen (suppress, red box), (2)
recall the pair of the item seen (recall, blue box), or (3) recall the pair of the item seen and answer a question about it that appeared on the screen (elaborative recall, green box). Trials were jittered with 0, 1.5, 3, or 4.5 seconds of fixation baseline to optimize the study design (Dale, 1999). Each subject underwent a single scan session that included five 428 second scans. Since verbal recollection could not be confirmed during scanning, following the scan, subjects saw one item from each pair of images and verbally recollected the item paired with the presented item. Pairs correctly recalled were used in subsequent analyses as ‘strongly-remembered’ and pairs not correctly recalled were deemed ‘poorly-remembered.’

Data from each run were reconstructed. Slices were temporally aligned and co-registered with a 3D registration algorithm. Voxels outside the brain were removed using a threshold mask of the functional data. Functional runs were corrected for motion. A general linear model was constructed using multiple regression analysis, and included six motion regressors from the registration process and regressors for ‘suppress,’ ‘recall,’ and ‘elaborative recall’ condition ‘strong’ and ‘poor’ memory responses. The time-course was also examined to reveal regions influenced by the presence and absence of an active task. Standard landmarks were defined manually on the anatomical scans, and then the anatomical and functional scans were transformed into Talairach space (Talairach & Tournoux, 1998) using AFNI nearest neighbor interpolation (Cox, 1996). In order to improve alignment of MTL structures, the region of interest large deformation diffeomorphic metric mapping alignment technique (Miller, Beg, Ceritoglu, & Stark, 2005) was used.
A hemodynamic response was estimated for the 15 seconds following the onset of the stimulus using signal deconvolution. Voxel-wise t-tests (two-tailed) were performed to compare average BOLD signal between conditions. Because of the small volume of our area of interest (hippocampus), clusters were defined with a connectivity of 4mm between voxel centers and including at least 5 voxels. These clusters, significant at p<.05 (two-tailed and corrected for multiple comparisons) were displayed on a statistical map overlaid onto an average structural image, and the average hemodynamic response function was then extracted for each cluster of interest. Broadmann areas were defined anatomically based on the Talairach atlas, and BA 7, 39, and 40 were used to extract the average hemodynamic response function for parietal lobe subregions.

Imaging was done in a 3T 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 s, one shot per repetition, echo time = 30, flip angle = 90, bandwidth = 31.25 MHz). Twenty-two slices covering the entire brain were acquired perpendicular to the long axis of the hippocampus with 4 x 4 x 7 mm voxels, allowing greater summation of activity along the hippocampal axial plane (Brewer & Moghekar, 2002). A T1-weighted high resolution (1 x 1 x 1 mm), three-dimensional magnetization-prepared rapid gradient echo or fast spoiled gradient recalled anatomical dataset was collected. A structural scan was acquired in the same slice locations as the functional images for use in confirming alignment of functional data to the high-resolution anatomical scan.
Results

*Behavioral Results.* In the ‘elaborative recall’ trials, subjects responded in 96% of trials (average reaction time: 1.94 ± .45 seconds). Of the trials in which there was a response, subjects made a correct classification in 75 ± 1% of trials, an incorrect classification in 9 ± 1% of trials, and were “unsure” in 16 ± 1% of trials. In the post-scan memory test, subjects correctly identified the pair of the presented image 71 ± 3% of the time for pairs that had been suppressed, 74 ± 4% for pairs that had been recalled, and 75 ± 3% for pairs that had been recalled with elaboration. There is a lower amount of trials for the ‘poor memory’ condition across all three trial types, and while it should not affect the magnitude of the response, it does suggest a possible noisy estimate of the mean for this activity. While there was a trend toward better subsequent memory for the pairs that had been recalled during scanning, there was not a significant difference in subsequent memory for suppressed or recalled pairs.

*Parietal Lobe Response.* Dorsal parietal cortex (BA 7, Figure 8, orange) shows the greatest amount of increased activation during elaborative recall, with no difference in recall and suppress strongly-remembered conditions (Figure 8A). In this region, there is a top-down modulation of task instruction, where there is a greater difference in activity between strongly- and poorly-remembered trials in the recall and elaborative recall conditions, but no different in the suppress condition (Figure 8D). Posterior ventrolateral parietal cortex (BA 39, Figure 8, magenta) does not show a top-down effect based on task type, but does show modulation based on recall success.
Recall and elaborative recall poorly-remembered trials drive down activation in this region below baseline and below strongly-remembered trials (Figure 8B). Additionally, there was a greater difference in strongly-remembered and poorly-remembered responses for recall trials than for elaborative recall trials, and no difference for suppress trials (Figure 8E). For strongly-remembered pairs, anterior ventrolateral parietal cortex (BA 40, Figure 8, yellow) shows the greatest amount of activity for elaborative recall pairs, followed by recall and then suppress. There is less activity within elaborative recall and recall trials for poorly-remembered pairs, but no difference for suppress pairs (Figure 8C). Like in posterior ventrolateral parietal cortex, there was no difference in activation for poorly- and strongly-remembered suppress items, and there was a greater difference in activation for recall than for elaborative recall pairs (Figure 8F).

**Default Network.** Examining the comparison between task and no task, sixteen clusters of activity were found in ten regions of the brain (superior frontal gyrus, medial frontal gyrus, insula, precentral gyrus, middle temporal gyrus, cingulate gyrus, precuneus, cuneus, inferior parietal gyrus, and superior temporal gyrus) that had less activity during the performance of a task compared with the fixation baseline (Figure 9). These regions, identified as part of the default network, commonly show a decrease in BOLD activity during an active task. Further analysis of the activity in this network of regions showed a greater decrease in activity for poorly-remembered pair trials than for strongly-remembered pair trials (p<.05, p<.001; Figure 9).


**Hippocampal Response.** The hippocampus, which traditionally is identified as part of the default network, is influenced by the explicit instruction to recall and by recall success. In a comparison of strongly-remembered trials where subjects were instructed to recall and poorly-remembered trials of the same types, right posterior hippocampus was the only region of significance (p<.01). Right hippocampus showed greater BOLD activity for trials were subjects were instructed to recall. Additionally, this increased activity was only seen for strongly-rememberd trials (Figure 10). Therefore, in the hippocampus, there is an interaction of instruction and success, since there was only an increased response for the trials in which subjects were instructed to recall and successfully did so.

Discussion

This study has shown that parietal lobe and default network regions respond differently to strongly- and poorly-remembered trials when subjects are instructed to suppress, recall, or recall with elaboration. Hippocampus responds unlike the parietal lobe or the default network during strong and poor memory recall and suppression. Parietal lobe activation is implicated in tasks of memory retrieval, but the exact contributions of subregions of the parietal lobe remained poorly understood. While the default network has been the source of much discussion in the literature, it remains unclear what causes the stereotypical decrease in activity seen in this network of regions. While some studies attribute this decrease to task difficulty and others to
exogenously directed thought, this study employed a task where the more difficult component of the task also required an external focus of attention to do a classification. In this study, the largest deviation from baseline was during the tasks that required internal focus for recollection, but the deactivation of the default network was driven down further by poor-memory responses, which were also the responses requiring more search and mental effort. Other studies have shown that there is more deactivation for tasks that require an external focus of attention as compared with a fixation cross baseline (Stark & Squire, 2001); however, it seems that this could be related to something other than an exogenous focus of attention since a task requiring internal focus of attention along with increased difficulty resulted in increased suppression of the default network during the poor-memory recall and suppression trials.

Examining dorsal and ventral parietal cortex activation during memory suppression, recall, and elaborative recall shows regional differences in activation. Dorsal parietal cortex (BA 7) shows a top-down modulation of activation based on task instruction. Elaborative recall shows the greatest amount of activity, with no difference in recall and suppress trials. The larger difference in poorly- and strongly-remembered responses for recall and elaborative recall tasks and no difference for the suppress task supports the idea of top-down modulation in this region based on instruction. Posterior ventral parietal cortex (BA 39) shows increased negatively-deflecting activation for poorly-remembered recall and elaborative recall trials. This region’s activity appears similar to default network, where there is an effect of task
difficulty that modulates activity. Anterior ventral parietal cortex (BA 40) shows a double dissociation of the bottom-up capture of attention and the ability to keep attention from being captured by previously-seen stimuli. This region shows a step-wise increase in activation for strongly-remembered suppress, recall, and elaborative recall trials. Recall and elaborative recall trials show a difference between strongly- and poorly-remembered pairs, with a larger difference in recall trials than in elaborative recall trials. Suppress trials show no difference between strongly- and poorly-remembered trials, perhaps exemplifying the ability of subjects to keep attention from being captured by previously-seen stimuli when instructed not to recall. These results support the idea that the parietal cortex is subdivided into distinct regions that diverge in their recall-based activity with dorsal parietal cortex supporting a top-down modulation and ventral parietal cortex supporting bottom-up affects of memory recall itself.

Many studies use the difference between strong and weak memory to examine recall-related activity in regions of the brain. Examining ventral parietal cortex, it is noted that there is a large difference between strongly- and poorly-remembered recall and elaborative trials, but no difference for suppress trials (Figure 8E, F). Looking at the difference graphs for these regions it would seem as if they are behaving in a similar way, however a closer examination of the impulse response curves illuminates positively-deflected activity in BA 40 above baseline for strongly-remembered trials while BA 39 shows negatively-deflected activity for poorly-remembered trials. These regions demonstrate the importance of examining impulse response functions and the
direction of deflection of activity in addition to the comparison of memories of different strengths.

Recent work has examined task induced deactivation, defined as areas showing higher levels of blood flow during rest than during an active task (McKiernan, et al., 2003). Their results suggested that task induced deactivation may represent a reallocation of resources to regions involved in the performance of the task. In addition, they found that the magnitude of task induced deactivation increased with increased task difficulty. Consistent with this finding, the present study showed that within the default network, the poorly-remembered trials, which were also the more difficult trials, showed a decrease in activation beyond the decrease seen in strongly-remembered trials. Activity in this network of regions included task-induced deactivation for the active task; additionally, there was more deactivation for the poorly-remembered trials compared to the strongly-remembered trials within one task type. These results suggest that taking the relationship of BOLD activity to baseline into account when looking at a subtraction of two conditions will aid in a more thorough understanding of areas of significantly different activation.

The default network consists of two subsystems of regions that are more correlated with each other than with other portions of the default network. The parahippocampal cortex and hippocampal formation are more closely correlated with each other than with other structures in the network, although the medial temporal lobe subsystem is correlated with main hubs of the network like the posterior cingulate
/ retrosplenial cortex, the ventromedial prefrontal cortex, and the inferior parietal lobule (Buckner, et al., 2008). While medial temporal lobe structures are known to correlate with activity in the default network, it was previously unknown how the hippocampus and parahippocampus modulate based on task type or if they can show activity distinct from the rest of the default network. These results suggest that during memory recall, the regions of the hippocampus are functionally distinct from the default network, and in fact diverge in the deflection of their activity from baseline.

Comparing the activation seen in the parietal lobe (Figure 8), the default network (Figure 9) and the hippocampus (Figure 10) during strong and poor memory suppression and retrieval, distinct patterns of activation are observed. While in traditional resting state correlation analyses the hippocampus tends to be functionally connected to the default network, including portions of the parietal cortex, further exploration of the activity in relation to baseline exposes fundamental differences in the patterns of activation. Dorsal parietal cortex shows a top-down modulation of attention and ventral parietal cortex shows bottom-up modulation in the anterior regions and default network-like activity in posterior regions. Default network showed negatively-deflecting activation, with greater decrease for poorly-remembered responses. In the hippocampus, strong memory retrieval caused an increase in activity compared to baseline, while poor memory retrieval did not elicit as large of a response. While the parietal lobe, default network, and hippocampus are all implicated in memory recall, their individual patterns of activity in relation to baseline confirmed that even though they may sometimes be functionally correlated, they are
differentially affected by top-down and bottom-up modulation of attention, and there is a difference in the pattern of activity that makes the hippocampus functionally distinct from these regions and networks.

Probing activation separately for the hippocampus and the parietal lobe and default network reveals a top-down effect of instruction on activation in subregions of the parietal lobe and in the hippocampus, but not in the default network. While there was an increase in hippocampal activity only for strong memory recall, the parietal lobe showed regional differences based on top-down and bottom-up modulation, and the default network showed greater decrease in activity for all poorly-remembered responses, regardless of the instruction to recall or suppress. Although hippocampus and default network sometimes show functional correlation of activation, during studies of memory they respond differently to task instruction and memory recall success. The default network and BA 39 show a deflection from baseline in the opposite direction of BA 7, BA 40, and the hippocampus. Subregions of the parietal cortex respond differently to memory suppression, recall, and elaborative recall. While the hippocampus shows positive deflections from baseline, hippocampus shows more increase for strongly-remembered trials where the subject was instructed to recall while the default network shows differences within each trial type for strongly- and poorly-remembered trials.
Acknowledgments

Chapter 3, in part, is a reprint of the material as it was submitted by

Gimbel, Sarah I. and Brewer, James, B.

The dissertation author was the primary investigator and author of this paper.
CHAPTER 4:

REACTION TIME, MEMORY STRENGTH, AND FMRI ACTIVITY DURING MEMORY RETRIEVAL: HIPPOCAMPUS AND DEFAULT-MODE NETWORK ARE DIFFERENTIALLY RESPONSIVE DURING RECOLLECTION AND FAMILIARITY JUDGMENTS

Abstract

Retrieval is often subdivided into recollection and familiarity. Memory strength and reaction time (RT) differ for each, complicating fMRI studies of these processes. Recollection leads to greater activity in the hippocampus and default-mode network (DN), components of the “retrieval network” identified for strong relative to weak or absent memory retrieval. Increased DN activity with recollection is thought to reflect self-referential processes, but prior studies have not accounted for varying RT, which modulates DN activity and is consistently faster for recollection than familiarity. We examined the influence of RT and memory strength on recollection and familiarity activity. Surprisingly, the hippocampus functionally dissociates from DN during retrieval. DN is generally influenced by RT and signal is suppressed when subjects are task-engaged in either recollection or familiarity; suppression is greater for slower trials. The hippocampus activates only for recollection trials; activation is greater for slower recollection trials, but not for slower familiarity trials.
Introduction

Retrieved episodic memories can be classified as ‘remembered’ or ‘known’ (Mandler, 1980; Rajaram, 1996). ‘Remember’ is a judgment of recollection, defined as not only remembering an event, but also remembering specific details about the encoding event. ‘Know’ is a judgment that an item is familiar, but without the retrieval of specific details about the encoding event. Studies of recollection and familiarity have focused on the medial temporal lobe (MTL), specifically the hippocampus, since its involvement in memory encoding, consolidation, and retrieval is well known (Bayley & Squire, 2005; Cohen & Squire, 1980; Scoville & Milner, 1957).

Functional imaging has been used to explore the neural bases of recollection and familiarity in humans. Consistent with findings from hippocampal lesion literature, imaging studies show increased hippocampal activity during episodic recollection (Henson, 2005; Schacter, et al., 1996) and for recollection relative to familiarity (Cabeza, et al., 2001; Cansino, et al., 2002; Eldridge, et al., 2000; Schacter, et al., 1996). This recollection/familiarity dissociation is also seen in the parietal and temporal lobes, where precuneus shows activation for both recollection and familiarity (Henson, Shallice, et al., 1999; Sharot, et al., 2004), while inferior, posterior, and lateral parietal regions and lateral temporal regions show activation for either recollection (Henson, Rugg, et al., 1999; Montaldi, et al., 2006; Wheeler & Buckner, 2004) or familiarity (Yonelinas, et al., 2005). Posterior parietal regions show a ‘retrieval-success’ effect, seen for deeply encoded words versus shallowly encoded
words (Shannon & Buckner, 2004) and old versus new items (for review see Rugg & Henson, 2002). Recollection is associated with increased activity in both superior- and inferior-posterior parietal cortex while familiarity is associated with activity in superior-posterior parietal cortex (Henson, Rugg, et al., 1999; Vilberg & Rugg, 2008).

Brain regions with greater activity during confident memory retrieval have been termed the ‘retrieval-network.’ In a meta-analysis of memory tasks and the parietal lobe, Wagner, Shannon, Kahn, & Buckner (2005) report greater blood oxygen level dependent (BOLD) signal in parietal-lobe subregions across multiple memory experiments with comparisons of recollection/familiarity, correct rejections, false alarms, and misses (Dobbins, et al., 2003; Eldridge, et al., 2000; Henson, Rugg, et al., 1999; Wheeler & Buckner, 2004). Whether the comparison is old versus new judgments, hits versus correct rejections, hits versus misses, source hits versus source misses, or any other “stronger” vs. “weaker” memory comparison, positive activation is seen in precuneus, lateral parietal cortex, posterior cingulate, retrosplenial cortex, and intraparietal sulcus. These regions, most active for stronger memories, overlap with the posterior portion of the set of regions commonly identified as the default-mode network (DN) of brain function (Cavanna, 2007).

The DN is a set of brain regions less active during task performance than during rest or fixation (Raichle, et al., 2001). It includes ventromedial prefrontal cortex, posterior cingulate/retrosplenial cortex, inferior parietal lobule, lateral temporal cortex, dorsomedial prefrontal cortex, and hippocampus (for review see Buckner, et
Elevated DN activity during fixation suggests that, in the presence of a task, DN would show a negative deflection from baseline with greater deflection for longer time spent ‘on-task.’ Indeed, prior studies have shown an association between reaction time (RT) and DN suppression (McKiernan, et al., 2003; Park, Polk, Hebrank, & Jenkins; Weissman, Roberts, Visscher, & Woldorff, 2006). While not all retrieval-network regions are part of the DN, a subset appears to be modulated by the simple performance of any of a wide variety of tasks. Since the retrieval-network shows increased activity during confident memory retrieval, it is likely that some activity that has been attributed to retrieval might in fact be a general modulation of DN activity.

Many studies have noted that confident memory retrieval is performed faster than judgments of familiarity or retrieval with lower confidence (Dewhurst, et al., 2006; Rotello & Zeng, 2008; Wixted, 2009; Wixted & Stretch, 2004). Increased RT for familiarity relative to recollection could be due to amount of search needed to bring up a memory, post-retrieval processing required for memory judgment, or other components of retrieval. RT is a confounding component uncontrolled in most studies that use the ‘remember/know’ paradigm. In fact, it is plausible that increased activity commonly observed in the retrieval-network could simply reflect decreased suppression of the DN for tasks performed more quickly and easily. Thus, an analysis of ‘remember/know’ judgments constrained by RT may help disentangle DN from retrieval-network and determine which activity in retrieval-network structures specifically relates to recollection versus familiarity.
This study examined how RT influences BOLD activity in the hippocampus and DN during correct ‘remember/know’ responses. Since the hippocampus is often functionally connected with the rest of the DN, the goal of this study was to determine if RT may account for the common default/retrieval-network and hippocampal activations identified in memory studies that use the ‘remember/know’ paradigm. We expect that if the DN and hippocampus are part of the same network during memory retrieval, RT should similarly influence their activity. Conversely, if the DN and hippocampus comprise separate networks in the brain that are dissociable during memory retrieval, slower RT would yield differential and possibly divergent hippocampal activity from DN activity during recollection, and possibly familiarity.

Methods

Twelve healthy right-handed subjects were recruited from the University of California, San Diego community and surrounding area (mean age = 23 ± 3 years, 2 male). Subjects received $40 for their participation and gave informed consent approved by the Institutional Review Board of the University of California, San Diego. Stimuli were 384 color pictures of common, namable objects (Bakker, Kirwan, Miller, & Stark, 2008), separated into 256 shown in a pre-scan test and 128 novel used during the scan.

Prior to scanning, subjects studied 256 objects, each for 3 seconds, and made a living/non-living judgment. During scanning, subjects saw either a studied or novel
object and were asked to judge each with ‘remember,’ ‘know,’ or ‘novel.’ Subjects were instructed to respond “remember” if they remember seeing the image during the study task and remember specific details about its presentation, “know” if the image was familiar but they do not recall specific details about seeing it before, or “new” if the image was not presented during the study session (Yonelinas, 2001). Each image was presented for 3 seconds. Trials were jittered with 0, 1.5, 3, or 4.5 seconds of fixation-cross baseline to optimize the study design (Dale, 1999). Each subject underwent a single session of four 530-second runs.

Using AFNI (Cox 1996), data from each run were field-map corrected to account for inhomogeneities in the magnetic field, and slices were reconstructed to a 3-dimensional volume, temporally aligned, co-registered, and motion corrected. A general linear model was constructed using multiple regression analysis and included six motion regressors and regressors for ‘remember,’ ‘know,’ and ‘novel’ correct and incorrect responses. A second and third general linear model were constructed to examine trials of different RTs and task versus no task activity (used to mask the ‘remember’ minus ‘know’ activation map in Figure 11). Standard landmarks were defined manually, and the anatomical and functional scans were transformed into Talairach space (Talairach & Tournoux, 1998). For each condition, a hemodynamic-response function was estimated for 15 seconds following the onset of the stimulus using signal deconvolution. Amplitude-modulated regression was used to determine regions correlated with RT for the ‘remember’ and ‘know’ correct trials. Cluster maps were displayed using SUMA (Saad, Reynolds, Argall, Japee, & Cox, 2004) on the pial
surface of the Talairach and Tournoux N27 average brain from Freesurfer (http://surfer.nmr.mgh.harvard.edu). In order to improve alignment of MTL structures, the region of interest large deformation diffeomorphic metric mapping alignment technique (Miller, et al., 2005) was used.

After individual deconvolution analysis, single-subject parameter estimates were entered into group level analyses. Voxel-wise $t$-tests (two-tailed) and regression analyses were performed to compare average signal between conditions and between the presence and absence of a task. Clusters were defined with a connectivity of 4mm between voxel centers and including at least 5 voxels for a whole brain significance of $p<.05$ and a voxel-wise significance of $p<.001$ when corrected for multiple comparisons. Clusters were extracted at $p<.01$ (two-tailed, corrected for multiple comparisons) and were displayed as a statistical map overlaid onto an average structural image. The average hemodynamic response function was extracted for each cluster of interest.

Imaging was done in a 3T 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 s, one shot per repetition, echo time = 30, flip angle = 90, bandwidth = 31.25 MHz). Twenty-two slices covering the brain were acquired perpendicular to the long axis of the hippocampus with 3.4 x 3.4 x 7 mm voxels, allowing greater summation of activity along the hippocampal axial plane (Brewer & Moghekar, 2002). A T1-weighted high
resolution (1 x 1 x 1 mm), three-dimensional fast spoiled gradient recalled anatomical dataset was collected.

Results

In this study of memory retrieval, more BOLD activation was observed in the DN and hippocampus during ‘remember’ responses than during ‘know’ responses. However, activity in these regions was dissociated; the hippocampus showed a response-curve with a positive deflection from baseline for ‘remember’ items, while the DN showed negatively-deflecting response-curves that dipped more negatively for ‘know’ items than for ‘remember’ items.

*Regions more active for ‘Remember’ than ‘Know:’* Old items were judged as ‘remember’ 60.1 ± 6.2% of the time and as ‘know’ 17.8 ± 3.2% of the time. Novel items were judged as ‘new’ 84.2 ± 2.4% of the time. Brain regions showing greater BOLD activity during ‘remember’ trials than during ‘know’ trials ($p<0.01$, corrected for multiple comparisons) are identified in Figure 11. There were no voxels showing the opposite relationship. Regions identified in this contrast include typical DN regions (bilateral postcentral gyrus, medial parietal lobe, precuneus, insula, and hippocampus). In order to more closely examine the BOLD dynamics in the DN and hippocampus separately, all regions of differential activity in the ‘remember minus know’ contrast were masked by the anatomically defined hippocampus and functionally defined DN for use in further analyses. Activity that was modulated by
the remember-know contrast and that fell within the DN (Figure 12, green) or hippocampus (Figure 12, blue) was explored for differences between ‘remember’ and ‘know’ responses and for relationships with RT.

Inspection of impulse-response functions in the DN and hippocampus confirm greater activity during ‘remember’ than during ‘know’ trials (Figure 12); however, the impulse responses were in opposite directions and were differentially influenced by ‘remember’ and ‘know’ judgments. The DN showed a negative deflection of activity that was of greater amplitude during ‘know’ trials than during ‘remember’ trials. Hippocampus showed a positive deflection of activity during ‘remember’ responses and no change in activity during ‘know’ responses, both compared to a fixation-cross baseline (Figure 12).

*Reaction time Analysis*: ‘Remember,’ ‘know,’ and ‘novel’ responses had significantly different RTs \(F(2,33) = 23.762, p<.001;\) R-K: \(t(11)=-4.981, p<.001;\) R-N: \(t(11)=-2.220, p<.05;\) K-N: \(t(11)=6.199, p<.001.\) ‘Remember’ responses were fastest (1199±57 msec), followed by ‘novel’ (1365±41 msec), then ‘know’ (1676±50 msec) (distributions displayed in Figures 13A-C). Figure 13E displays average activity extracted for the six largest clusters in the DN (Figure 13D), plotted against the average RT across all 12 subjects for correct ‘remember,’ ‘know,’ and ‘novel’ trials. Since average activity linearly decreased with longer RT, activity from these six clusters is displayed to demonstrate the potential association between neural activity and RT in the DN.
DN and Hippocampal Activity: Amplitude regression analysis identified brain regions whose activity correlated with RT for ‘remember’ and ‘know’ trials (Figure 14). There was an inverse correlation of both ‘remember’ and ‘know’ trials with RT in DN (p<.01, Figure 14A,B). Hippocampus, however, showed a positive correlation for ‘remember’ (p<.01, Figure 14C) and no correlation for ‘know’ (p>.01, Figure 14D).

To examine the effects of RT and memory strength, correct ‘remember’ and ‘know’ trials were split into those with RT slower than and faster than 1500 msec. Fast ‘know’ trials were compared with slow ‘remember’ trials, allowing a near-optimal balance in trial number for the two conditions while reversing the direction of RT and memory-strength confounds present in unconstrained analyses. Typically, RT and false-alarm rates are higher for ‘know’ than for ‘remember.’ In this analysis, RT and false-alarm rates (Table 4) were higher for slow ‘remember’ items (trials: 259, Average RT: 1852 msec, FA rate: 1%) than for fast ‘know’ items (trials: 233, Average RT: 1224 msec, FA rate: 0%), providing a test of whether hippocampal and DN activity remains higher for ‘remember’ than for ‘know’ despite lower memory-strength and slower RT.

Despite this, activity was still greater in DN (Figure 15A) and hippocampus (Figure 15B) for slow ‘remember’ trials than fast ‘know’ trials, and the hippocampus still showed a significant increase during ‘remember’ trials compared with baseline (Slow remember: t(11) = 2.387, p<.05; Fast know: t(10) = -.043, p=1) while the rest of the DN showed a decrease for both ‘remember’ and ‘know’ trials (Slow remember: t(11) = -2.718, p<.05; Fast know: t(10) = -5.772, p<.001).
Discussion

During episodic retrieval, more activity was elicited for ‘remember’ than for ‘know’ responses in areas commonly identified as the “retrieval-network.” In a meta-analysis of DN activity by Buckner et al. (2008), activation from the ‘remember-know’ contrast and hippocampal-correlated DN activation overlapped in the hippocampus and posterior DN regions (Cavanna, 2007; Vincent, et al., 2006; Wagner, et al., 2005). By examining the time-course of this activity, the present study demonstrates that the hippocampus dissociates from the DN during ‘remember’ and ‘know’ judgments and also demonstrates why these regions are co-identified using subtraction analyses. The hippocampus responds to ‘remember’ trials with a positive deflection from baseline that is of greater amplitude with slower RT, while the DN shows a negative deflection from baseline that is of greater amplitude with slower RT. The DN responds to ‘know’ trials with an even deeper negative deflection from baseline that is also of greater amplitude with slower RT, while the hippocampus does not have a change in response during these trials. Though the hippocampus is considered to be part of and is typically functionally correlated with the DN, during episodic retrieval, hippocampal activity dissociates from DN activity.

The present study demonstrates that even though RT is correlated with hippocampal activity during recollection, selective hippocampal involvement during ‘remember’ trials remains even after controlling RT. This activation, unseen during correct ‘know’ trials, lends support to the dual process model of memory recall, where
hippocampus supports recollection but not familiarity. Even in ‘remember’ trials with a slower RT and lower confidence, the hippocampus still showed a positive deflection from baseline only for ‘remember’ responses and no deflection for ‘know’ responses.

Prior studies noted increased hippocampal activity for recollection-based but not for familiarity-based responses (Eldridge, et al., 2000); however, it was unknown whether these effects were due to the brain bases of the recollection/familiarity dissociation, due to differences in memory strength, or primarily driven by differences in DN, since MTL regions are functionally linked to the DN. If ‘remember’ judgments yield elevated hippocampal activity even when ‘remember’ and ‘know’ judgments are equated for memory strength and RT, it would support selective hippocampal involvement in recollection. The present study did not additionally obtain subjects’ subjective ratings of memory strength, given potential influences of such metamemory judgments, themselves, on hippocampal and DN activity and a desire to maintain consistency with prior imaging studies of recollection and familiarity. Nevertheless, such ratings of retrieval confidence might allow greater flexibility in examining the confound of memory-strength present in prior studies.

Hippocampal activity diverges from other DN activity during memory-related tasks and is differentially influenced by RT during recollection- and familiarity-based memory retrieval. Task-related activity differences in these regions survive correction for differences in RT and memory strength. ‘Remember’ and ‘know’ judgments might require different amounts of search or might rely on different metamemory processes
to make the judgments themselves. Despite the wealth of imaging studies on memory, these additional components of memory retrieval are poorly understood, calling for further research to determine how regional brain activity might be affected by the interactive components of memory strength and RT.

Acknowledgments

Chapter 4, in full, is a reprint of the material as it was submitted to Cognitive Neuroscience, 2010. Gimbel, Sarah I. and Brewer, James, B.

The dissertation author was the primary investigator and author of this paper.
CHAPTER 5:

CONCLUSIONS

In this dissertation, I have addressed the role of hippocampus and dorsolateral prefrontal cortex (DLPFC), default network, and retrieval network in memory recall. Specifically, hippocampus is dissociated from each of these regions and networks during confident memory recall and recall with post-retrieval processing. Further, I looked at the effects of memory strength and reaction time in order to disentangle these confounding factors from activity due purely to memory recall. Taken together, these studies address network-level modulations in activation during memory retrieval, and how hippocampus modulates in lock-step or in anti-correlation with other regions of the brain when post-retrieval processing, task instruction, success, reaction time, and confidence are taken into account.

In Chapter 2, block and event-related tasks were employed to examine hippocampal and cortical activity for recollection with post-retrieval processing versus processing of a stimulus without the element of recollection. A novel non-verbal task was employed to allow for the scoring of memory recollection accuracy without having the subjects speak. These studies demonstrate that DLPFC and hippocampus have dissociated activity during difficult episodic retrieval, with increased dissociation in longer trials. Additionally, default network and anterior hippocampus show negatively-deflecting activation from baseline during episodic retrieval with post-
retrieval processing; non-hippocampal default network regions also show negative-deflecting activation during a simple classification task.

These studies start to examine the effects of post-retrieval processing, reaction time and task difficulty on hippocampal activity. While it has long been known that task difficulty affects activity in DLPFC, these studies show that the divergence of DLPFC and hippocampal activity during retrieval with post-retrieval processing is increased with longer reaction time and greater task difficulty. The exact direction of modulation is not known from these studies, but prefrontal cortex may have a top-down modulation effect on hippocampus where increased difficulty in memory recall and post-retrieval processing causes increased activation in DLPFC, followed by decreased activation in hippocampus. While additional studies are needed to determine the direction of activity modulation, preliminary evidence from the examination of the time-course of activity suggests that hippocampal activity decreases slightly later following the onset of the stimulus, allowing for the possibility that DLPFC has a top-down modulatory effect on hippocampus.

In Chapter 3, strong and poor memories were examined during tasks involving suppression, recall, and elaborative recall. Subjects were asked to suppress or recall a second item from a previously-studied pair, and in half of the recall trials, subjects were asked to elaborate on their memory. Default network and retrieval network showed divergent activity during all three conditions, with greater suppression for poorly-remembered than strongly-remembered pairs in the default network only. The
hippocampus, however, showed an interaction of task instruction and success and only had increased activity when subjects were asked to recall and successfully did so.

This study examined the default network and retrieval network separately, and did not find overlap between regions that showed decreased activity for task versus fixation baseline and regions that showed increased activity for stronger memory retrieval. The hippocampus has been considered part of each of these networks, and examining the networks separately introduces the idea that hippocampus might be selectively involved in the retrieval and default networks depending on the task being performed. It is possible that in the absence of a memory task, hippocampus modulates with default network whereas in the presence of a memory task, hippocampus modulates more like the retrieval network. Examining the hemodynamics of the hippocampus in relation to those of the default and retrieval networks helps to bring into focus how a structure so central to memory processes is integrated into other networks of regions also important for memory recall.

In Chapter 4, the remember / know paradigm was employed to more closely examine hippocampal and default network activity with attention to the often confounding factors of reaction time and memory strength. While hippocampus and default network seem to have convergent activation when comparing recollection and familiarity, closer examination of the time-course of activity reveals divergent activation. While the hippocampus shows positively-deflecting activity for recollection and no change from baseline for familiarity, the default network shows greater negatively-deflecting activity for recollection relative to familiarity (both
decreased from baseline). Reversing the normal distribution of reaction time and false alarm rate maintains the same pattern of activity, supporting the dual-process model of memory recall.

For decades there has been a debate about whether recollection and familiarity are both supported in the hippocampus and whether they are gradients of one memory process or separate recall processes. Very recently, studies have started to take confounding components of memory recall into account when examining the brain regions supporting recollection and familiarity. By focusing on reaction time and false alarm rate, this study reverses the normal distribution and allows examination of these processes in a more pure manner. This study finds maintained increase in activity in hippocampus for recollection relative to familiarity and baseline, even when reaction time and false alarm rate are controlled. While this supports the dual process model of memory recall, it brings to light the importance of considering confounding aspects of the task unrelated to the memory recall itself.

While hippocampus is often functionally correlated with the retrieval and default networks, these studies, taken together, show that hippocampal activity can be modulated by task type and is dissociable from these networks during tasks of memory retrieval. Here, I have described experiments showing that 1) DLPFC and hippocampal regions, often diverging when default network is activated, also diverge during episodic retrieval; 2) there is a top-down effect of instruction and success on activation in the hippocampus, but not the default network or retrieval network; and 3) hippocampal activity diverges from other default network activity during memory-
related tasks and is differentially influenced by reaction time during recollection- and familiarity-based memory retrieval. Even though the hippocampus is functionally correlated with the default network in the absence of a task, during tasks involving memory retrieval the hippocampus acts independently of other memory-related regions of the brain. This directed study of the circumstances leading to divergence of hippocampal activity from frontal, retrieval network, and default network activity helps identify the role of cooperation and competition between memory systems in everyday function.
Table 1: Mean reaction time (RT), average of RT standard deviations (SD), min RT, and max RT for ‘recollect-classify’ (RC) and ‘classify’ (C) conditions for each subject. These average RT SDs were used to classify each trial as 0, 1, 2, 3, -1, -2, or -3 SDs from the mean RT for each subject individually.

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>RC Mean RT</td>
<td>1475</td>
<td>1311</td>
<td>1679</td>
<td>1881</td>
<td>1327</td>
<td>1466</td>
<td>1669</td>
<td>1839</td>
</tr>
<tr>
<td>RC Average SD</td>
<td>267</td>
<td>297</td>
<td>410</td>
<td>355</td>
<td>296</td>
<td>384</td>
<td>447</td>
<td>430</td>
</tr>
<tr>
<td>RC Min</td>
<td>1006</td>
<td>934</td>
<td>1015</td>
<td>1205</td>
<td>773</td>
<td>934</td>
<td>884</td>
<td>787</td>
</tr>
<tr>
<td>RC Max</td>
<td>2147</td>
<td>2070</td>
<td>2416</td>
<td>2463</td>
<td>2063</td>
<td>2293</td>
<td>2423</td>
<td>2449</td>
</tr>
<tr>
<td>C Mean RT</td>
<td>937</td>
<td>964</td>
<td>986</td>
<td>1378</td>
<td>922</td>
<td>1107</td>
<td>950</td>
<td>1278</td>
</tr>
<tr>
<td>C Average SD</td>
<td>157</td>
<td>245</td>
<td>233</td>
<td>413</td>
<td>334</td>
<td>391</td>
<td>348</td>
<td>436</td>
</tr>
<tr>
<td>C Min</td>
<td>743</td>
<td>660</td>
<td>689</td>
<td>604</td>
<td>497</td>
<td>553</td>
<td>466</td>
<td>472</td>
</tr>
<tr>
<td>C Max</td>
<td>1442</td>
<td>1908</td>
<td>1769</td>
<td>2291</td>
<td>1880</td>
<td>2087</td>
<td>1899</td>
<td>2219</td>
</tr>
</tbody>
</table>
Table 2: Clusters significant for ‘recall-classify’ versus ‘classify’ conditions (p<.001). BA = Brodmann Area.

| Table 2: Clusters significant for ‘recall-classify’ versus ‘classify’ conditions (p<.001). BA = Brodmann Area. |
|---|---|---|---|---|
| x | y | z | Volume | T-value |
| A) RC > C (p<.001) | | | | |
| R. Cingulate gyrus (BA 32) | 0.7 | 20.6 | 39.8 | 2624 | 7.20 |
| L. DLPFC (middle frontal gyrus) (BA 9) | -43.9 | 13.4 | 32.1 | 1728 | 7.57 |
| L. Inferior parietal lobule (BA 39) | -33.1 | -59.6 | 38.9 | 1664 | 7.35 |
| R. Anterior Insula (BA 13) | 27.7 | 19.5 | 5.4 | 960 | 7.49 |
| R. DLPFC (middle frontal gyrus) (BA 9) | 37.4 | 26.1 | 30.3 | 768 | 6.31 |
| L. Anterior Insula (BA 13) | -29.4 | 20.8 | 3.7 | 640 | 7.74 |
| R. Precuneus (BA 7) | 7.8 | -67.5 | 40.5 | 512 | 5.01 |
| R. Precuneus (BA 7) | 24.7 | -61.7 | 33.9 | 320 | 5.11 |
| L. Cingulate gyrus (BA 32) | -10 | 24.9 | 30 | 256 | 4.86 |
| L. Precuneus (BA 7) | -14.6 | -66.8 | 30.8 | 256 | 5.71 |
| B) C > RC (p<.001) | | | | |
| R. Insula (BA 13) | 45.7 | -14 | 16.7 | 9728 | -8.74 |
| L. Insula (BA 13) | -43.4 | -11.1 | 4.9 | 5568 | -8.88 |
| R. Precentral gyrus (BA 4) | 32.7 | -27.9 | 50.4 | 2112 | -10.06 |
| L. Postcentral gyrus (BA 5) | -27.2 | -39.7 | 61.2 | 1472 | -8.28 |
| L. Paracentral lobule (BA 6) | -2.2 | -25.6 | 50.8 | 1280 | -6.98 |
| R. Superior parietal lobule (BA 5) | 19.7 | -39.6 | 58.6 | 832 | -5.67 |
| L. Postcentral gyrus (BA 40) | -50.2 | -25 | 13.7 | 768 | -7.91 |
| R/L. Paracentral lobule (BA 31) | -2.7 | -16.7 | 43 | 640 | -7.60 |
| L. Hippocampus (BA 34) | -25.4 | -6.6 | -12.3 | 576 | -9.91 |
| R. Postcentral gyrus (BA 2) | 25.3 | -36 | 66.9 | 512 | -6.18 |
| L. Precentral gyrus (BA 4) | -55.7 | -12.8 | 33.1 | 448 | -6.27 |
| R. Hippocampus (BA 34) | 20.3 | -9 | -10.9 | 256 | -5.55 |
Table 3: Clusters significant for even/odd discrimination versus fixation conditions (p<.001). BA = Brodmann Area.

<table>
<thead>
<tr>
<th>Talairach x</th>
<th>y</th>
<th>z</th>
<th>Volume</th>
<th>T-value</th>
</tr>
</thead>
</table>

**A) Even/Odd > Fixation (p<.001)**
- L. Inferior parietal lobule (BA 40) -44.1 -32.9 43.1 1536 8.33
- R. Fusiform (BA 19) 38.1 -66.6 -6.4 768 6.21
- L. Medial frontal gyrus (BA 6) -6.8 -1.9 50.7 576 6.39
- R. Declive 2 -56.5 -14.2 512 6.45
- L. Inferior occipital gyrus (BA 18) -32.8 -82.2 -2.2 448 5.25
- R. Middle occipital gyrus (BA 18) 27.6 -87.2 -1.6 448 6.98
- L. Thalamus -13.2 -17.4 11.5 320 5.45
- L. Inferior parietal lobule (BA 40) -31.2 -49.5 40.8 320 6.45
- L. Postcentral gyrus (BA 2) -48.6 -29.8 52.5 320 6.41

**B) Fixation > Even/Odd (p<.001)**
- R. Precuneus (BA 7) 3.6 -33.9 44.4 2688 -8.35
- L. Posterior cingulate gyrus (BA 31) -9.1 -38.6 38 960 -6.94
- R. Sub-gyral (BA 40) 22.5 -36.1 56.6 960 -5.79
- L. Cuneus (BA 7) -11.5 -72.5 32.3 832 -8.50
- L. Middle frontal gyrus (BA 46) -40.1 43 3.5 448 -5.89
- R. Parahippocampal gyrus (BA 36) 23.1 -39.3 -3.7 448 -7.71
- L. Middle temporal gyrus (BA 39) -48.2 -63.2 27.2 384 -7.24
- R. Precuneus (BA 7) 16.5 -75.4 39.6 384 -6.90
- L. Precuneus (BA 19) -22.4 -77.3 41 384 -6.56
- L. Inferior frontal gyrus (BA 45) -46 38.3 1.4 320 -7.27
- L. Precuneus (BA 31) -7.4 -48.4 28 320 -4.80
- R. Parahippocampal gyrus (BA 27) 24 -31.4 -8 256 -6.00
- R. Insula (BA 13) 39.9 -23.1 16 256 -6.22
- R. Posterior cingulate gyrus (BA 30) 9.2 -52.3 17.8 256 -5.61
- R. Cuneus (BA 18) 8 -75.1 28 256 -4.92
- L. Angular gyrus (BA 39) -44.1 -67.4 36 256 -5.88
Table 4: Hit rates and False Alarm rates for ‘Remember’ and ‘Know’ trials separated by reaction time.

<table>
<thead>
<tr>
<th></th>
<th>Hit Rate</th>
<th>False Alarm Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>.78</td>
<td>.10</td>
</tr>
<tr>
<td>Remember</td>
<td>.60</td>
<td>.03</td>
</tr>
<tr>
<td>Remember Fast</td>
<td>.52</td>
<td>.02</td>
</tr>
<tr>
<td>Remember Slow</td>
<td>.08</td>
<td>.01</td>
</tr>
<tr>
<td>Know</td>
<td>.18</td>
<td>.07</td>
</tr>
<tr>
<td>Know Fast</td>
<td>.08</td>
<td>0</td>
</tr>
<tr>
<td>Know Slow</td>
<td>.10</td>
<td>.07</td>
</tr>
</tbody>
</table>
Figure 1: Study design. Each subject viewed the study phase outside of the scanner. Subjects were asked to memorize 128 pairs of images that were shown 3 times each. During scanning, subjects performed the block task in which ‘recall-classify,’ ‘classify,’ even/odd, and fixation cross trials were presented in blocks lasting 24 seconds each. In Experiment 3, subjects performed the event-related task in which ‘recall-classify’, ‘classify’, and even/odd discrimination trials were interleaved.
Figure 2: Experiment 1 BOLD activation. Difference in BOLD activation for significant clusters in the ‘recall-classify versus ‘classify’ condition (p < .001). A, Activation in right DLPFC (37.4, 26.1, 30.3) for each condition. B, Activation in left anterior hippocampus (-25.4, -6.6, -12.3) and C, right anterior hippocampus (20.3, -9, -10.9) for each condition. RC = recall-classify, C = classify, EO = even/odd discrimination, FIX = fixation. Error bars represent SEM. Interior clusters up to 29mm deep are projected onto the surface and the color scale bar represents percent-signal change. *p < .05, **p < .01 ***p < .001.
Figure 3: Experiment 1: Correlation between hippocampal suppression and DLPFC activation. In a contrast of ‘recall-classify’ and ‘classify’ conditions, hippocampal activity is negatively correlated with DLPFC (BA 9) activity. Left hippocampus was used as the seed region. Only HC and DLPFC clusters are shown.
**Figure 4:** Experiment 1: Default network activation. *A,* Activation for the even/odd-fixture condition modified from Stark and Squire (6). *B,* Activation for the even/odd-fixture condition in the block-design study. Clusters with greater activation in the even/odd condition are shown in red and clusters with greater activation in the fixation condition are shown in blue.
Figure 5: Experiment 1: Comparison of activation in ‘recall-classify’ versus ‘classify’ and even/odd versus fixation conditions. Top row: cut through the anterior hippocampus and Bottom row: cut through the posterior parahippocampus for conditions A, ‘recall-classify’ versus ‘classify’ and B, even/odd versus fixation. BOLD activation for clusters significant in each condition at p < .01. RC = recall-classify, C = classify, EO = even/odd discrimination, FIX = fixation. Interior clusters up to 9mm deep are projected onto the surface and color scale bar represents percent-signal change.
Figure 6: Experiment 2: Event-related DLPFC and hippocampal activation. Impulse-response curves for A, left DLPFC (45, 15, 34), and B, right hippocampus (21, -15, -15) for ‘recall-classify’ and ‘classify’ conditions (left), separated into trials with a reaction time 1-3 SDs above (+) or below (-) the mean (right). Error bars represent SEM. Clusters used to extract impulse-response curves were from the ‘recall-classify’ versus ‘classify’ contrast at p<.05, shown on the image. RC = recall-classify, C = classify. Interior clusters up to 9mm deep are projected into the surface and the color scale bar represent percent signal change.
Figure 7: Study design. Each subject viewed the study phase outside of the scanner. Subjects were asked to memorize 60 pairs of images that were learned to criterion. During scanning, subjects performed the event-related task in which ‘suppress,’ ‘recall,’ and ‘elaborative recall’ trials were interleaved with jittered fixation cross baseline.
Figure 8: Activation during suppression, recall, and elaborative recall differs for subregions of the parietal lobe. Activation in Broadmann Areas 7 (orange), 39 (magenta), and 40 (yellow). A-C) Impulse response curves for suppress, recall, and elaborative recall strongly-remembered and poorly-remembered trials. D-F) Difference scores for suppress (red), recall (blue), and elaborative recall (green) trials. Difference scores were calculated by subtracting the poorly-remembered trial activation from the strongly-remembered trial activation.
Figure 9. Task instruction and recall success influence the default network. Activity identified in the default network (blue). Default network activity revealed by task-fixation contrast. Significant clusters (p<.01) used to extract average activity for each task condition, for both correct and incorrect responses. * p<.05, *** p<.001 for remembered versus forgotten trials within each trial type. Activity presented on an average anatomical brain of all study participants. Error bars represent standard error of the mean.
Figure 10: Hippocampal activity during ‘suppress,’ ‘recall,’ and ‘elaborative recall’ strongly-recalled and poorly-recalled trials. A cluster map of strong memory minus poor incorrect (p<.01) was overlaid on an average anatomical brain from all twelve subjects. BOLD activity was increased in the hippocampus for trials where the subject was instructed to recall the previously studied pair and successfully did so, but not when there was no instruction to recall or when there was poor recall. Right hippocampal cluster centered at (30, -26, -4). Error bars represent standard error of the mean.
Figure 11: Cluster map of ‘remember minus know’ ($p<.01$, corrected for multiple comparisons). Clusters overlaid on an average anatomical brain of the 12 study participants.
Figure 12: Default network and hippocampus activity in the ‘remember minus know’ contrast ($p<.01$). Cluster map (below) shows regions of overlap between the default network (defined as regions of deactivation in task minus no task contrast, green) and hippocampus (defined anatomically, blue) and the ‘remember minus know’ contrast ($p<.01$). Clusters overlaid on an average anatomical brain of all 12 study participants. Impulse response curves in the default network (top left) and hippocampus (top right) for ‘remember’ (purple) and ‘know’ (orange) judgment trials. Y-axis is percent signal change; X-axis is time (seconds) after the onset of the stimulus.
Figure 13: Reaction time distribution varies for ‘remember,’ ‘novel’ and ‘know’ trials. Reaction time distribution for A) ‘remember,’ B) ‘novel,’ and C) ‘know’ trials. E) Percent signal change of activity for the six largest clusters in ‘remember minus know’ (D) for ‘remember,’ ‘novel,’ and ‘know’ correct judgments plotted against average reaction time for that trial condition across all twelve subjects. Clusters overlaid on an average anatomical brain of all 12 subjects. A-C) X-axis is reaction time (msec); Y-axis is number of trials, summed across all 12 subjects. E) X-axis is percent signal change; Y-axis is average reaction time (msec) for each trial type across all 12 study participants.
Figure 14: Regions correlated with reaction time. Map of regions positively and negatively correlated with reaction time for ‘remember’ trials (A, C) and ‘know’ trials (B, D). Cluster maps for ‘remember’ and ‘know’ are presented on the pial surface of the Talaraich and Tournoux N27 average brain (A, B), and on an average anatomical brain of the 12 study participants (C, D). (p<.01, warm colors = positive correlation, cool colors = negative correlation)
Figure 15: Reaction time does not account for all task-related differences in ‘remember’ and ‘know’ trial activity in the default-mode network and hippocampus. Impulse response curves for the A) default-mode network and B) hippocampus for ‘remember’ trials with reaction time slower than 1500 msec (‘slow remember,’ blue) and ‘know’ trials with reaction time faster than 1500 msec (‘fast know,’ green). Masks used to extract impulse response curves are the same as those in Figure 2C. Y-axis is percent signal change; X-axis is time (seconds) after the onset of the stimulus.
REFERENCES


Park, D. C., Polk, T. A., Hebrank, A. C., & Jenkins, L. J. Age differences in default mode activity on easy and difficult spatial judgment tasks. *Front Hum Neurosci, 3*, 75.


