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BOLD signals of episodic memory retrieval in the hippocampus and neocortex

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

Neurosciences

by

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The dissertation of Emilie Topinka Reas is approved, and is acceptable in quality and form for publication on microfilm and electronically:

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DEDICATION

While this dissertation may have but one official author, it has in truth been authored by my family, friends and colleagues who have supported me along my doctoral journey.

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ABSTRACT OF THE DISSERTATION

BOLD signals of episodic memory retrieval in the hippocampus and neocortex

by

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Functional neuroimaging studies have demonstrated activation of the brain's medial temporal lobe during episodic memory retrieval. However, inconsistent evidence from lesion studies indicate that, although the medial temporal lobe is essential for acquiring new declarative memories, it may not be critical for all forms of retrieval. Given the multitude of mnemonic and non-mnemonic processes invoked during a guided retrieval episode, including attending to memory cues, searching through a memory store, reactivating the target memory, monitoring the ongoing experience and reflecting on a recovered memory, it can be challenging to disentangle the functional drivers of retrieval-related brain responses. This dissertation presents a series of studies that use functional

magnetic resonance imaging to more thoroughly characterize the role of the medial temporal lobe, and surrounding frontal and parietal regions, in effortful memory retrieval. Three investigations examine the influence of memory search on activity in the hippocampus and neocortex. Results implicate a widespread hippocampal-cortical system that is modulated by task difficulty and covaries with hippocampal signals that track incidental encoding of the background environment. This evidence is discussed in light of a primary hippocampal function for memory encoding that is regulated by dynamic task demands. A final study examined how the contextual information of a retrieved memory is coded in the medial temporal lobe. Applying both univariate and multivariate analyses, this investigation identified medial temporal activation patterns representing distinct memory features. It further characterized these signals in terms of their mean regional or spatially distributed activity, as well their behavioral correlates to task difficulty. Together, these studies provide further insight into the delicate interplay between mnemonic and attentional brain functions supporting guided memory retrieval.

CHAPTER 1:

INTRODUCTION

If any one faculty of our nature may be called more wonderful than the rest, I do think it is memory. There seems something more speakingly incomprehensible in the powers, the failures, the inequalities of memory, than in any other of our intelligences. The memory is sometimes so retentive, so serviceable, so obedient; at others, so bewildered and so weak; and at others again, so tyrannic, so beyond control! We are, to be sure, a miracle every way; but our powers of recollecting and of forgetting do seem peculiarly past finding out.

- Jane Austen

What is life without the ability to revisit the past? The quality of the present moment is enriched by reviving the wonders, joys and even pains of prior experiences, pondering the consequences of previous actions or mentally connecting with friends from the past. Memory establishes a seed from which flourish our personal relationships, future decisions and understanding of our surrounding world. Without this precious function, a human may be absent their identity and their life devoid of meaning.

This invaluable form of memory for prior experiences - episodic memory - relies on the coordinated interaction of multiple processes, including encoding novel information, consolidating it into storage and its subsequent retrieval. A memory is born when contextual details of an experience are bound into a unique representation, but what purpose does that memory trace serve if the brain cannot later access it? In the

chapters that follow, I will present a series of investigations that aim to characterize the neural framework underlying this critical process - recovering a memory representation from storage.

The role of the medial temporal lobe in memory retrieval

Despite the indispensability of a functional memory system, the mechanisms by which the brain performs these operations remains incompletely understood. Our most definitive understanding of the brain structures essential to episodic memory comes from individuals with selective brain lesions. Behavioral observations from patients such as the celebrated Henry Molaison (Scoville and Milner, 1957) and E.P. (Bayley and Squire, 2002) have revealed the critical role that the medial temporal lobe (MTL), and particularly the hippocampus, serves in acquiring new declarative memories. Without an intact hippocampus, one can still recall very old memories, but is unable to establish new, or recall recently created, memories. Given the inherent interdependence of memory encoding and retrieval (i.e. an encoding deficit will preclude subsequent retrieval), it is challenging to dissociate the role of the MTL in forming and retrieving memories from lesion studies alone. Furthermore, while such approaches can inform about the functional necessity of a given region, additional approaches are needed to inform about *how* these structures perform their respective operations.

Studies employing an array of neuroimaging techniques, such as electrophysiological recordings, functional magnetic resonance imaging (fMRI) and positron emission tomography, in humans and animals have offered further insight into

neuronal, hemodynamic and metabolic activity subserving memory. Consistent with the lesion literature, these studies confirm the involvement of the MTL in memory retrieval, and suggest that distinct memory functions may be distributed across MTL subregions (Squire et al., 2004; Squire and Zola-Morgan, 1991). However, these studies indicate that the MTL does not work in isolation, but rather communicates with the surrounding neocortex to execute a multi-stage cascade of retrieval processes. In particular, multiple brain networks comprising frontal and parietal regions are thought to support retrieval components such as guiding directed retrieval, attending to internally or externally generated memory cues, monitoring memory accuracy, or elaborating upon recovered memory content (Buckner, 2003; Cabeza et al., 2008; Kim, 2010; Spreng et al., 2010).

Dissociating retrieval-related from non-mnemonic activity

An outstanding and central question is how these neocortical networks coordinate with the MTL memory system to allow the reconstruction of, and access to, a stored memory. Of particular consideration for unraveling this mystery is dissociating neural activity directly involved in mnemonic recovery, from that involved in the sequence of accessory memory processes that indirectly support retrieval. For instance, a logical interpretation for regional brain activation during successful retrieval might be that the given area is involved in retrieval; yet might it alternatively support attentional, cognitive control or non-retrieval memory functions involved in the broader retrieval episode?

Retrieval-related responses in the hippocampus may be particularly vulnerable to such ambiguous interpretations, as the hippocampus is thought to lie at the intersection of the medial temporal memory and "default mode" networks (Buckner et al., 2008; Huijbers et al., 2011). This latter brain system is most active during passive, resting states, and can be modulated task demands, generally deactivating with elevated cognitive load. Thus, an extant challenge to understanding the role of the hippocampus in memory retrieval is distinguishing activity related directly to memory recovery from that which may covary with retrieval performance, but is indirectly modulated by non-mnemonic processes.

In the following chapters I will present three fMRI investigations that address this issue, including studies that examine reduced hippocampal and default network activity during retrieval search (Chapter 2; Reas et al., 2011); dissociable cortical systems that differentially subserve retrieval search and memory strength (Chapter 3; Reas and Brewer, 2013c); and hippocampal responses during effortful retrieval that track both incidental encoding and retrieval search (Chapter 4; Reas and Brewer, 2013a). Chapter 5 reviews findings from these and prior investigations, to provide a cohesive theory that may reconcile many of the ambiguous reports of non-memory-related hippocampal activity (Reas and Brewer, 2013b). This evidence argues strongly that the hippocampus is reliably and persistently engaged in fundamental mnemonic operations that may covary with, and are hence attributed to, non-mnemonic processes.

Multivoxel MTL representations of memory context

While the MTL is known to be important for associative memory, there is uncertainty over how the region collectively binds the contextual details of an experience into a unified memory. Broadly, an episodic memory comprises three primary features - information about what happened, where and when. Electrophysiology studies have demonstrated that such features may be represented by sparse populations of neurons tuned to particular information (Eichenbaum, 2013; Moser et al., 2008; Naya and Suzuki, 2011). This information may be diffusely represented throughout the MTL or may be integrated by subregions specialized for distinct memory features. The recruitment of a unique neural population during a retrieval event would thus manifest as a spatially distributed activity pattern throughout the involved region.

Although fMRI can only infer the location of neural activity to a rough approximation, it is still sensitive to spatial variations in brain activity which may arise from the engagement of distinct neural populations. Multivoxel pattern analysis has recently become a popular method to detect spatially distributed activity associated with specific cognitive states (Serences and Saproo, 2012). In Chapter 6, I present a final investigation into how MTL subregion activity patterns represent recalled episodic memory context (Reas and Brewer, submitted). This study characterizes both the spatial pattern and behavioral correlates of the multivoxel fMRI signal, in order to dissociate 1) finely distributed activity patterns from large-scale regional recruitment, as well as 2) activity related to memory content from that related to time-on-task. Findings from this experiment support the notion that recalled memory features can be uniquely

represented by medial temporal subregions, while highlighting important distinctions about how this contextual information is coded.

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CHAPTER 2:

SEARCH-RELATED SUPPRESSION OF HIPPOCAMPUS AND DEFAULT NETWORK ACTIVITY DURING ASOCIATIVE MEMORY RETRIEVAL

Abstract

Episodic memory retrieval involves the coordinated interaction of several cognitive processing stages such as mental search, access to a memory store, associative re-encoding and post-retrieval monitoring. The neural response during memory retrieval is an integration of signals from multiple regions that may subserve supportive cognitive control, attention, sensory association, encoding or working memory functions. It is particularly challenging to dissociate contributions of these distinct components to brain responses in regions such as the hippocampus, which lies at the interface between overlapping memory encoding and retrieval, and "default" networks. In the present study, event-related functional magnetic resonance imaging and measures of memory performance were used to differentiate brain responses to memory search from sub-components of episodic memory retrieval associated with successful recall. During the attempted retrieval of both poorly and strongly remembered word pair associates, the hemodynamic response was negatively deflected below baseline in anterior hippocampus and regions of the default network. Activations in anterior hippocampus were functionally distinct from those in posterior hippocampus and negatively correlated with response times. Thus, relative to the pre-stimulus period, the hippocampus shows reduced activity during intensive engagement in episodic memory search. Such deactivation was most salient during trials that engaged only pre-retrieval search processes in the absence

of successful recollection or post-retrieval processing. Implications for interpretation of hippocampal fMRI responses during retrieval are discussed. A model is presented to interpret such activations as representing modulation of encoding-related activity, rather than retrieval-related activity. Engagement in intensive mental search may reduce neural and attentional resources that are otherwise tonically devoted to encoding an individual's stream of experience into episodic memory.

Introduction

Functional imaging has the potential to dissect the influences of integrated, but separable, neural processes contributing to successful recall; however, the challenge remains to identify and isolate such components and then dissociate these rapid, transient processes. Human and animal studies implicate the hippocampus in the encoding and retrieval of episodic memories (Lepage et al., 1998;Tulving and Markowitsch, 1998;Eichenbaum, 2004;Ranganath et al., 2004a;Squire et al., 2007). In functional imaging studies, multiple factors, including the strength of the memory and the extent to which associated source details are recalled, influence hippocampal activity during episodic memory retrieval (Eldridge et al., 2000;Fortin et al., 2004;Ranganath et al., 2004b;Squire et al., 2007;Wais et al., 2010). Still, retrieval involves several sub-processes subserved by interacting cognitive modules (Moscovitch, 1992) and the specific contributions of these components to retrieval-related neural responses are not fully understood. For example, brain activity during retrieval may be modulated by the extent of task engagement, mental search, depth of processing, or post-retrieval monitoring. Regions activated during encoding can be engaged during retrieval of the original memory, suggesting that reactivation of the memory trace and associative re-encoding are additional retrieval sub-processes (Nyberg et al., 2000;Buckner et al., 2001;Woodruff et al., 2005). Distinct elements, such as memory strength and degree of search during memory retrieval attempts, may be highly correlated; studies intending to examine an isolated process may be confounded by these uncontrolled components. Additional investigation is necessary to better identify and understand the neural bases underlying subcomponents of memory retrieval.

Reports of relative signal differences between conditions, including increased activity with greater retrieval success, higher confidence or more accurate source recollection (Yonelinas et al., 2005;Daselaar et al., 2006;Montaldi et al., 2006), have contributed significantly to our current understanding of hippocampal function during retrieval. While such comparisons are useful for distinguishing separable neural processes, they assume isolated insertion of independent components without accounting for interactions between sub-processes (Friston et al., 1996). For example, contrasting remembered with forgotten items during attempted recall yields functional responses often attributed to retrieval success. However, within this contrast are differences in attention or search, and associated task difficulty, that also vary with recall success or failure.

Examining the direction of blood oxygen level dependent (BOLD) signal deflection from baseline may help reveal functionally relevant deactivations otherwise masked by relative between-condition differences. Interpreting a change from baseline carries certain challenges, such as determining which processes are active during the baseline state (Gusnard and Raichle, 2001) or whether deflection represents engagement of task-relevant or gating of task-irrelevant activity. However, information about the magnitude of signal deflection can provide additional insight into task-dependent responses. For example, the magnitude of deactivation from baseline may correlate with the degree of task engagement, task difficulty, or response time, relationships largely hidden when cognitive subtraction is used exclusively. Examining such characteristics of the task–evoked response, in conjunction with the signal difference from an optimally

controlled condition, may therefore permit a more powerful interpretation of a BOLD effect.

Emerging evidence suggests a role for the hippocampus in multiple cortical networks that support encoding and retrieval. Several studies have found correlated activity between the hippocampus and regions involved in the default activation mode (Greicius et al., 2004;Buckner et al., 2008). This "default network" is commonly defined as a set of regions in medial prefrontal and posterior, lateral temporal and inferior parietal cortex that are most active during passive resting states but can also be engaged by internally-directed or personally relevant thought. Evidence that these regions are active during autobiographical memory (Andreasen et al., 1995;Maguire, 2001;Addis et al., 2004a;Addis et al., 2004b;Spreng and Grady, 2010) suggests an overlap between neural systems underlying resting state activity and memory consolidation or retrieval. This possibility is supported by studies showing that default network regions are modulated by the degree of encoding success or recall confidence (Daselaar et al., 2004;Daselaar et al., 2009;Kim, 2010), and that disrupted default network connectivity corresponds with aging-related memory deficits (Andrews-Hanna et al., 2007). Although activation of these regions may support some aspects of memory consolidation or recall, successful execution of many demanding cognitive tasks correlates with default network deactivation (McKiernan et al., 2003;Fox et al., 2005;Buckner et al., 2008).

Functional magnetic resonance imaging (fMRI) measurements during successful retrieval likely reflect an integrated response to a series of interacting processes rather than activity during an isolated moment of memory access. Recall involves multiple stages including, for example, directed search for the memory from storage, successful

retrieval, and working memory processes necessary to hold an item online while performing post-retrieval processing, such as making a judgment about the recalled item. Cognitive control and selective attention may contribute to top-down modulation of memory retrieval or to post-retrieval monitoring (Moscovitch, 1992;Buckner, 2003;Daselaar et al., 2008). Given the position of the hippocampus at the intersection of overlapping networks, hippocampal activity during memory retrieval may be concurrently regulated by any of these stages of memory processing. Task-related deactivation, such as that seen in default network regions, might also explain relative signal differences in the hippocampus. A prior study demonstrated robust hippocampal deactivation during cued recall and post-retrieval processing of visual paired associates (Israel et al., 2010), described as 'elaborative associative recall'. Externally directed thought and task difficulty are known to deactivate the default network (Greicius et al., 2003b;McKiernan et al., 2003;Vincent et al., 2008), and maintenance of an item in working memory can suppress hippocampal activity (Axmacher et al., 2007). It is therefore possible that either directed search effort prior to retrieval or post-retrieval working memory processing is a primary mediator of hippocampal activity during memory retrieval, rather than the retrieval event, itself.

The present study sought to isolate the mechanisms underlying hippocampal deactivation during elaborative associative recall. Event-related fMRI was used to investigate BOLD responses during cued recall and post-retrieval processing of previously studied word pairs relative to a non-memory classification task. Consistent with prior evidence of hippocampal deactivation during elaborative associative recall of paired visual objects (Israel et al., 2010), results confirmed that hippocampal deactivation

occurs during elaborative associative recall of paired words, allowing further isolation and examination of the factors that modulate this suppression. To investigate the neural correlates underlying retrieval-related components of memory search, successful retrieval and post-retrieval processing, we examined task conditions that had different levels of each. Contrasts between conditions were first performed to reveal relative signal differences afforded by traditional subtraction methods. Impulse response curves were then examined to evaluate the temporal dynamics of the BOLD response and signal deflection relative to baseline, and relationships with task performance and reaction times. By isolating activations associated with attempted retrieval, this study was able to dissociate a hippocampal response linked to memory search from those linked to retrieval success or post-retrieval processing.

Methods

Subjects

Fifteen healthy, right-handed, English-speaking volunteers with normal or corrected vision from the University of California, San Diego (UCSD) community and surrounding areas participated in this study. All subjects gave informed written consent in accordance with criteria of the UCSD Institutional Review Board. Five subjects were excluded from further analysis due to an insufficient number of poorly remembered trials; data from the remaining ten participants (seven male, mean age 27.2 ± 3.0 years) are reported.

Stimuli

Stimuli were 128 English nouns ranging from one to four syllables. Half of the words represented living and half represented non-living items. Words were combined into 64 pairs pseudorandomly to prevent unintentional semantic associations between words.

Experimental design

During a pre-scan learn-to-criterion study task, 64 word pairs were presented one at a time on a laptop. Subjects were instructed to remember each word pair. Each pair appeared for three seconds, followed by a fixation cross for one second (Figure 2.1A). After study, subjects were given a self-paced cued recall test in which one word from each pair appeared and subjects verbally responded with the pair of the presented word. Forgotten pairs were repeated in subsequent study-test sequences until all pairs were correctly identified.

After a delay of approximately 20 minutes, subjects completed a modified version of previously described recall and classify tasks (Israel et al., 2010;Seibert et al., 2011) during event-related fMRI data acquisition (Figure 2.1B). In each trial a black box and a colored box were presented for one second. A previously studied word then appeared in one of the boxes for one second. The green box surrounding the presented word served as a cue to classify the presented word as living or nonliving (classify condition). A red box around the missing pair cued subjects to recall the pair of the presented word and classify the pair as living or non-living (recall condition). Subjects responded “living” or “non-living” in both tasks and were given a third response option of “unsure” in the recall task if they did not remember the pair of the presented word. Subjects were instructed to

respond as quickly and accurately as possible using their right hand on a four-button response box. The cue boxes remained on the screen for two seconds following word presentation, and trials were jittered with 1.5-15 seconds of fixation baseline, calculated to optimize the study design for modeling the hemodynamic response to trials (Dale and Buckner, 1997;Dale, 1999). Each word appeared once and both words of a pair were assigned to the same condition (classify or recall). Equal numbers of classify and recall trials were pseudorandomly distributed across four runs each lasting 403 seconds, and the two words comprising each pair were presented in different runs.

Following the scan, subjects completed a self-paced cued recall test (Figure 2.1C) to better evaluate retrieval success during the scanned recall test. One word from each pair was presented and subjects verbally reported the word's pair. Throughout the remainder of the manuscript, word pair associates correctly and incorrectly recalled during the post-scan recall test are respectively referred to as strongly remembered and poorly remembered.

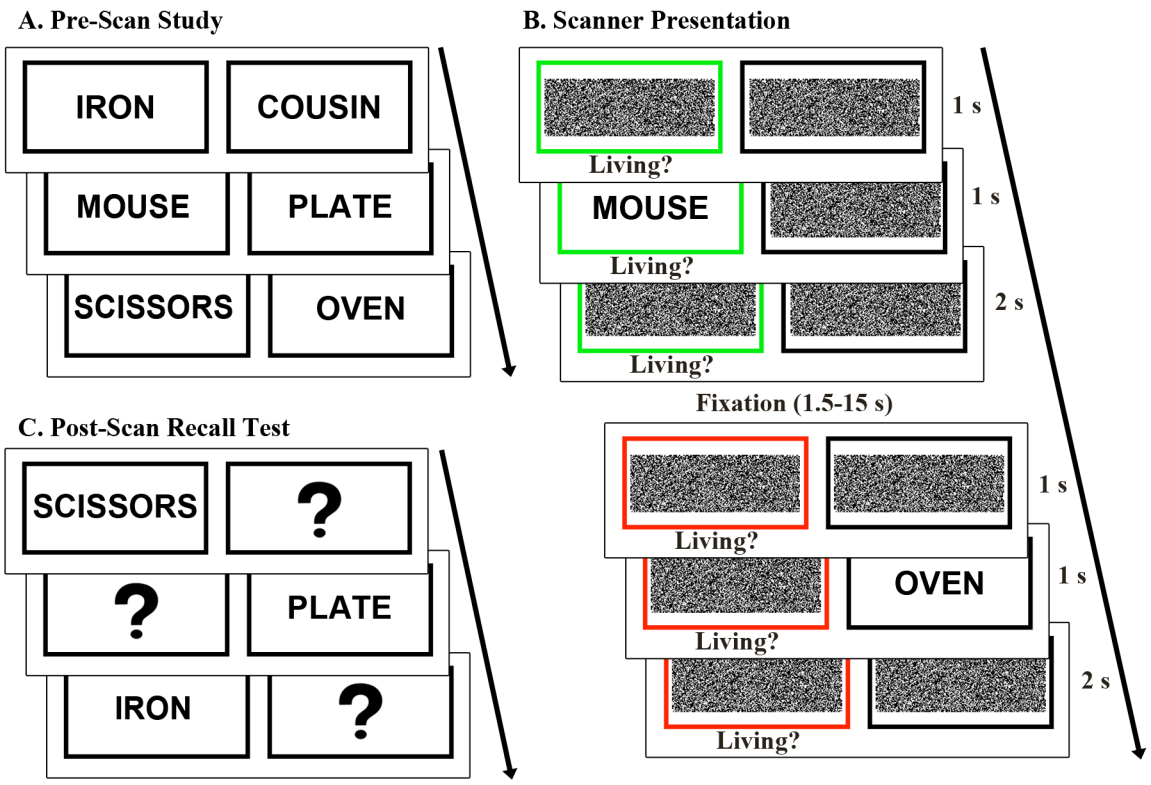

Figure 2.1: Experimental design. (A) Prior to scanning, 64 word pairs were presented sequentially and subjects were instructed to memorize each pair. (B) During scanning, trials randomly alternated between classify and recall task conditions. In the classify task, a green box cued subjects to classify the presented word as living or non-living. In the recall task a red box cued subjects to recall and classify the pair of the presented word. (C) In a post-scan recall test, subjects saw one word at a time from each pair and were asked to recall and vocally report the word's pair.

fMRI parameters

Imaging was performed using a 3.0 Tesla General Electric scanner at the UCSD Keck Center for Functional MRI. Functional data were acquired using a gradient-echo, echo-planar, T2*-weighted pulse sequence (time repetition [TR] = 2.5 s; one shot per repetition; echo time = 30; flip angle = 90°; bandwidth = 31.25 MHz). Each volume contained forty slices oriented perpendicular to the long axis of the hippocampus with 3.4 x 3.4 x 4 mm voxels. Field maps were acquired to measure and correct for static field

inhomogeneities (Smith et al., 2004). A T1-weighted structural scan was acquired in the same plane and of the same voxel size as the functional scans and a high resolution (1 × 1 × 1 mm) T1-weighted anatomical scan was acquired using an inversion recovery prepared fast spoiled gradient recalled sequence providing high grey-white contrast for anatomical delineation.

fMRI data analysis

Functional data were corrected for spatial distortions using field maps (Smith et al., 2004). Using the AFNI suite of programs (Cox, 1996), data from each run were reconstructed and slices were temporally aligned and co-registered using a three-dimensional image alignment algorithm. A threshold mask of the functional data was applied to remove voxels outside the brain and separate functional runs were smoothed with a 4 mm FWHM Gaussian blur, corrected for motion and concatenated. Anatomical scans and data output of the functional scans were normalized to Talairach space (Talairach and Tornoux, 1988) after standard landmarks were manually defined on the anatomical scans.

The region of interest large deformation diffeomorphic metric mapping (ROI-LDDMM) alignment technique was applied to improve alignment of the medial temporal lobe between subjects (Miller et al., 2005). Medial temporal lobe subregions, including bilateral hippocampus, perirhinal, entorhinal and parahippocampal cortices, were defined for each subject on Talairach transformed images. Previously described landmarks were used to define perirhinal, entorhinal (Insausti et al., 1998) and parahippocampal (Stark and Okado, 2003) cortex. These anatomical regions of interest were aligned with a

modified model of a previously created template segmentation (Kirwan et al., 2007) using ROI-LDDMM. Functional imaging data underwent the same ROI-LDDMM transformation to ensure alignment with each subject's anatomical data.

Multiple regression analysis was performed to generate general linear models for task conditions of interest. Each model included six motion regressors obtained from the registration process along with regressors for each condition. The hemodynamic response for the 17.5 seconds following the stimulus onset was estimated using signal deconvolution with TENT basis functions (Cox, 1996). Task regressors were included for three conditions: strongly remembered trials, defined as recall trials for which subjects correctly recalled the pair during the post-scan recall test; poorly remembered trials, defined as recall trials for which subjects incorrectly recalled or forgot the pair during the post-scan recall test; and correct classify trials. Three subtractions were computed to compare activity between 1) strongly remembered and classify, 2) poorly remembered and classify, and 3) poorly remembered and strongly remembered conditions. A conjunction of overlapping voxels from contrasts 1 and 2 was performed to identify voxels with greater activation or deactivation during strongly remembered and poorly remembered relative to classify.

To examine BOLD signal variation across subregions of the hippocampus, a structural mask that segmented the anatomically defined left and right hippocampus into eight 4 mm slices along the long axis was applied to each subject's data. Beta values for each 4 mm slice were extracted and a three-way ANOVA with factors of task (classify, strongly remembered, poorly remembered), hemisphere and slice (8 slices, anterior to posterior) was performed.

The across-subject average impulse response was extracted for a hippocampal seed region of interest functionally defined from the conjunction analysis. The average impulse response curves for each of the three conditions (classify, strongly remembered and poorly remembered) were used as model hemodynamic response functions. Multiple linear regression was used to estimate the fit of the hemodynamic response across the brain to these time-course models. Significant clusters in which the hemodynamic response fit the hippocampal model response across conditions were displayed on a statistical map overlaid onto an average structural image.

Amplitude-modulated regression was used to identify regions in which the hemodynamic response correlated with response time. Correlations were computed by examining the relationship between BOLD signal and response time on a trial by trial basis. At each voxel, a general linear model was constructed with regressors for both the mean hemodynamic response and the correlation between BOLD signal and response time for the classify and recall conditions. Correlations from the classify and recall tasks were compared to identify regions in which the correlation strength depended on task condition.

Voxel-wise t-tests compared parameter estimates from the 7.5-12.5 seconds of each condition. The hemodynamic response was expected to have the greatest deflection from baseline during this time interval, based on impulse response curves from previous studies using a similar recall task (Israel et al., 2010;Seibert et al., 2011). For whole-brain analyses, significant clusters, including at least seven contiguous voxels ($p < .01$, two-tailed and corrected for multiple comparisons), were displayed on a statistical map overlaid onto an average structural image. Applying a whole-brain correction for multiple

comparisons can prevent detection of significant activations within a small region of interest selected a priori; therefore, significant hippocampal clusters were corrected for multiple comparisons within the hippocampus by including at least four contiguous voxels ($p < .05$, two-tailed). Correction for multiple comparisons was performed using a Monte Carlo simulation in AFNI (afni.nimh.nih.gov/pub/dist/doc/program_help/3dClustSim.html), using a whole-brain functional volume (28,907 voxels) and a manually defined structural mask of the combined left and right hippocampus (139 voxels). The hemodynamic response function was then extracted for each condition within each cluster of interest and averaged across subjects.

Behavioral Results

Subjects took an average (± standard error) of 3.5 ± 0.4 study runs to memorize all 64 word pairs. During scanning, classification accuracies were similar between classify trials and recall trials for which a classification was made (classify: 92 ± 1%, recall: 87 ± 2%; $t(9) = 1.83$, $p > .10$). Subjects responded "unsure" to 15 ± 2% of recall trials. Response times were faster in the classify than in the recall task (classify: 1271 ± 60 msec, recall: 2396 ± 159 msec; $t(9) = 8.40$, $p < .001$). Reaction times during the scanned test were analyzed based on accuracy during the post-scan recall test. There was no difference in reaction time between trials that were correctly versus incorrectly recalled during the post-scan test for the classify condition (strongly remembered classify: 1266 ± 73 msec, poorly remembered classify: 1422 ± 151 msec; $t(9) = 1.16$, $p = .27$) and a trend toward a shorter reaction time for strongly versus poorly remembered

pairs in the recall condition (strongly remembered: 2371 ± 154 msec, poorly remembered: 2504 ± 207 msec; $t(9) = 1.85$, $p < .10$). Post-scan recall was better for pairs that appeared in the recall than in the classify condition (recall: 83 ± 4%, classify: 73 ± 7%; $t(9) = 2.72$, $p < .05$).

fMRI Results

Differential responses for strongly remembered, poorly remembered and classify trials

To evaluate consistency between these results and previous reports of BOLD signal changes during associative memory retrieval, a whole brain analysis was performed using contrasts between the classify, strongly remembered (correct post-scan cued recall responses) and poorly remembered (incorrect post-scan cued recall responses) conditions. Results from this traditional subtraction analysis allowed further examination of the hemodynamic response and associated cognitive functions that form the bases for such prior findings. Activations were compared between the strongly remembered and classify conditions to identify regions more active during memory retrieval followed by post-retrieval processing compared to a control task (Figure 2.2A), and between poorly remembered and classify trials to investigate activity related to retrieval effort (Figure 2.2B). BOLD signals during poorly and strongly remembered trials were compared to examine unsuccessful memory retrieval efforts relative to successful memory retrieval and post-retrieval processing (Figure 2.2C). All contrasts were significant at the $p < .01$ level and corrected for multiple comparisons as described in the section "fMRI data analysis". Regions with greater activity for poorly and strongly remembered than classify trials included left dorsolateral prefrontal cortex (PFC), dorsal anterior cingulate cortex,

anterior insula and superior parietal cortex. Impulse response curves confirmed that BOLD signal was activated above fixation baseline to a greater extent for the poorly and strongly remembered than classify condition in these regions. The reverse relationship of reduced activity for poorly and strongly remembered relative to classify trials was observed in bilateral amygdala, medial PFC, precuneus, posterior cingulate cortex (PCC), and temporal cortex. Impulse response curves revealed that these differences were due to greater signal deflection below baseline for poorly and strongly remembered than classify trials. Activity was also reduced in left anterior hippocampus for strongly remembered compared to classify trials, consistent with prior findings (Israel et al., 2010). PCC and left inferior parietal cortex demonstrated less activation for the poorly remembered than strongly remembered condition. Impulse response curves illustrated greater negative signal deflection in these regions for poorly remembered compared to strongly remembered trials.

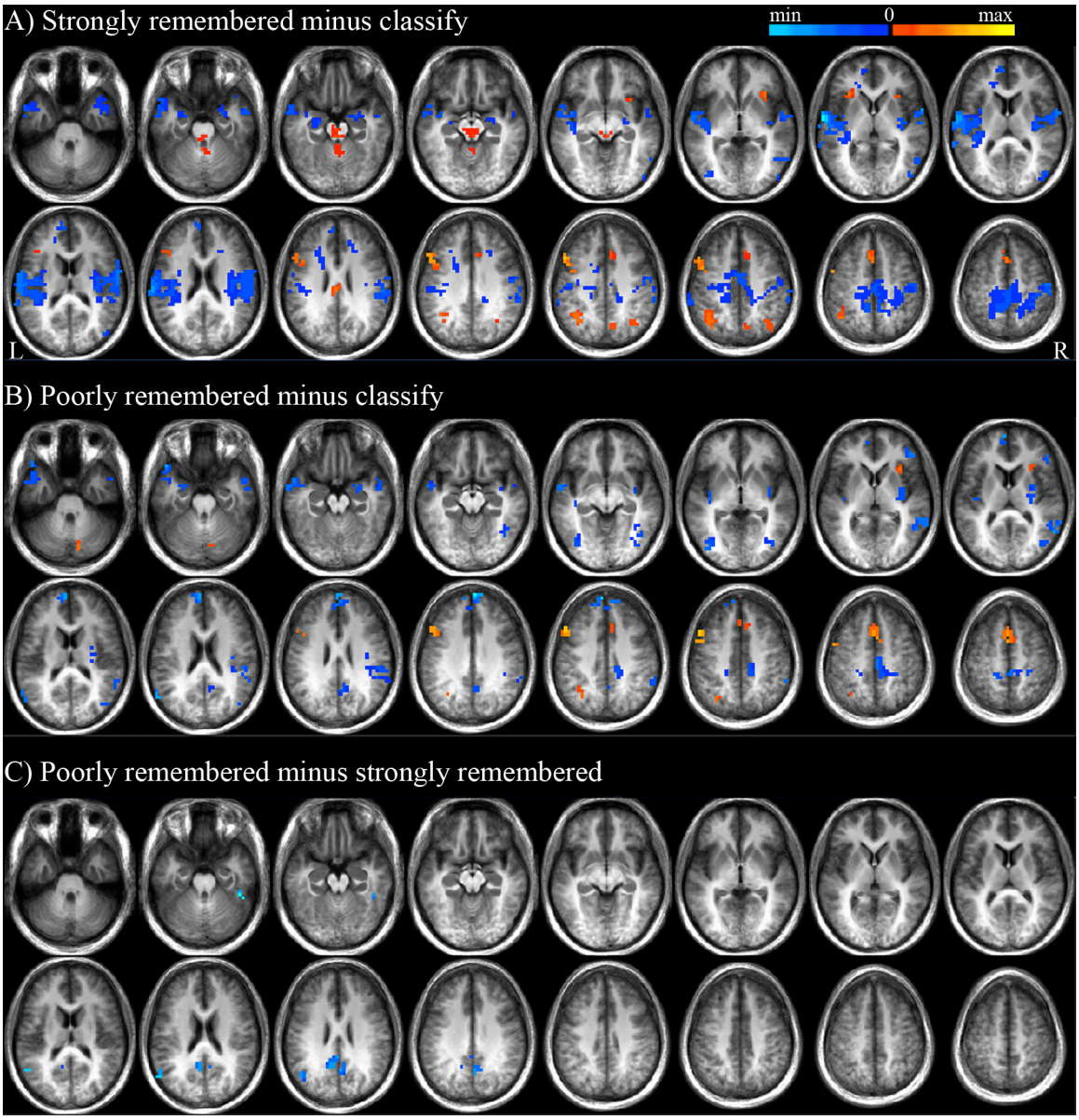

Figure 2.2: Strongly remembered minus classify, poorly remembered minus classify and poorly minus strongly remembered contrasts. Regions with significant BOLD signal differences ($p < .01$) between strongly remembered and classify trials (A), poorly remembered and classify trials (B), and poorly and strongly remembered trials (C). Positive activity differences are displayed in warm colors and negative activity differences are displayed in cool colors. Subtraction maps are overlaid on every five axial slices of an average anatomical image of all subjects. As depicted in Figure 2.5A, these activation differences are expected to represent processing related to search, retrieval and post-retrieval processing (A and C) or search only (B).

Anterior and posterior hippocampal activity

Because of the small region of interest, a probability threshold of $p < .05$ (corrected for multiple comparisons within the hippocampus as described in the section "fMRI data analysis") was used to examine BOLD signal changes in the hippocampus. Contrasts of strongly remembered versus classify, poorly remembered versus classify, and poorly versus strongly remembered trials were performed. These contrasts revealed less activation for strongly remembered than classify trials in bilateral anterior hippocampus, less activation for poorly remembered than classify trials in bilateral anterior and posterior hippocampus, and less activation for poorly than strongly remembered trials in left anterior and bilateral posterior hippocampus.

To identify regions in which activity was greater for both the poorly and strongly remembered than classify conditions, a conjunction analysis was used to identify the overlap of clusters more responsive during poorly remembered than classify and during strongly remembered than classify trials ($p < .05$). This conjunction yielded a cluster in left anterior hippocampus for which impulse response curves, relative to fixation baseline, demonstrated a stepwise decrease in activation from classify to strongly remembered to poorly remembered trials (Figure 2.3A). There was a main effect of task in this cluster ($F(2) = 19.14$, $p < .001$) and pair-wise comparisons confirmed greater deactivation for poorly remembered than classify ($t(9) = 4.63$, $p < .005$), for strongly remembered than classify ($t(9) = 4.42$, $p < .005$) and for poorly remembered than strongly remembered trials ($t(9) = 3.67$, $p < .01$). A cluster was also identified that survived whole brain correction and extended into right anterior hippocampus, but the hippocampal

portion of this cluster did not survive correction for multiple comparisons within the hippocampus.

Impulse response curves from the posterior hippocampal clusters identified in the poorly remembered versus strongly remembered contrast were examined and revealed a delayed posterior response compared to the anterior response. Posterior hippocampus showed a late-onset response with negative deflection from baseline for the poorly remembered condition (Figure 2.3B). Although these clusters were identified using the 7.5-12.5 second response interval selected a priori, the time-course of the response prompted additional post-hoc analysis of early and late time-points. A main effect of task was observed between 10-15 seconds ($F(2) = 12.17$, $p < .001$), driven by deactivation for poorly remembered trials relative to strongly remembered trials ($t(9) = 4.14$, $p < .005$) and classify trials ($t(9) = 3.46$, $p < .01$). At 7.5 seconds, a trend for early positive activation above baseline was observed during the strongly remembered condition ($t(9) = 2.16$, $p = .06$), but responses did not differ between task conditions ($p = .31$).

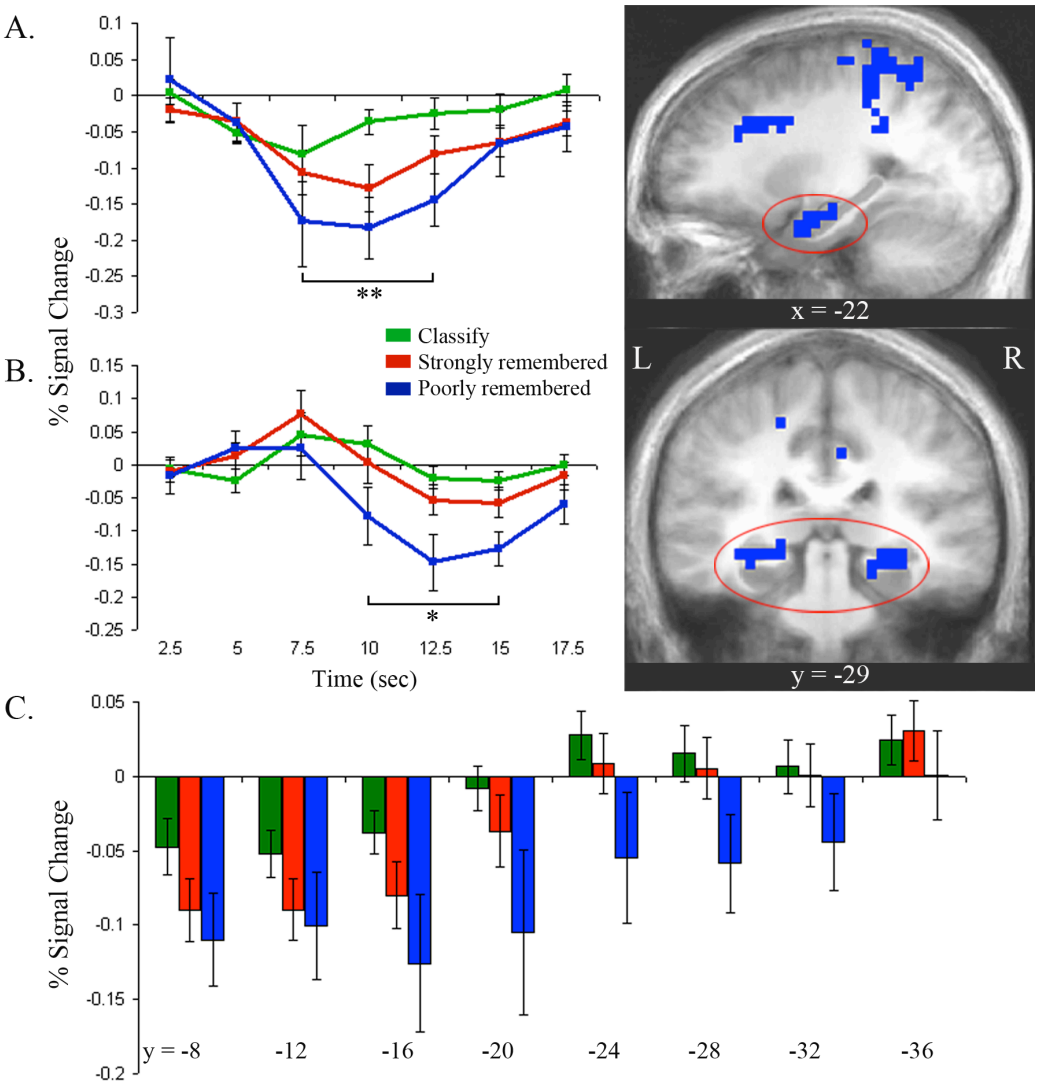

Figure 2.3: Anterior and posterior hippocampal activity. (A) Left anterior hippocampus showed greater deactivation during strongly and poorly remembered relative to classify trials (right, $p < .05$). Impulse response curves (left) illustrate a graded pattern of deactivation from fixation baseline greatest for poorly remembered (blue), intermediate for strongly remembered (red) and minimal for classify (green) trials. ** Indicates poorly remembered < classify, strongly remembered < classify and poorly remembered < strongly remembered (paired t-tests, $p < .01$). (B) Bilateral posterior hippocampus was more active for strongly versus poorly remembered trials ($p < .05$). Impulse response curves reveal late deactivation for poorly remembered trials only. * Indicates poorly remembered < classify and poorly remembered < strongly remembered (paired t-tests, $p < .01$). (C) Bilateral hippocampus showed a gradient of decreasing deactivation, from 7.5-12.5 seconds, from anterior to posterior regions. Each hippocampal subregion represents a 4mm thick slice along the long axis of the hippocampus. Error bars represent standard error of the mean. Subtraction maps are overlaid on coronal (A) and sagittal (B) slices of the average anatomical image of all subjects.

Hippocampal activation gradient

Figure 2.3 illustrates the distinct contributions of anterior and posterior hippocampal regions to poorly and strongly remembered trial responses. However, to directly examine how hippocampal activity varies along the anterior-posterior axis, left and right hippocampus were each segmented into eight slices perpendicular to the long axis and beta-values for each condition were extracted in each slice. No hemispheric differences were found ($p = .78$), but main effects of task ($F(2,18) = 3.64$, $p < .05$) and slice ($F(7,63) = 13.10$, $p < .001$) and a task by slice interaction ($F(14,126) = 1.99$, $p < .05$) were observed. Deactivation decreased along an anterior to posterior gradient across tasks (Figure 2.3C). Anterior regions showed deactivation below baseline during all conditions (y = -7 to -18, one-sampled t-tests: classify, $t(9) = 3.03$, $p < .05$; strongly remembered, $t(9) = 4.27$, $p < .005$; poorly remembered, $t(9) = 3.00$, $p < .05$) and a main effect of task (y = -15 to -22: $F(2) = 3.85$, $p < .05$), reflecting increasing deactivation from classify to strongly remembered to poorly remembered conditions. In contrast, posterior regions (y = -27 to -34) only showed deactivation in the poorly remembered condition, with a main effect of task ($F(2) = 5.11$, $p < .05$) driven by greater deactivation for poorly remembered relative to classify ($t(9) = 2.29$, $p < .05$) and to strongly remembered trials ($t(9) = 2.74$, $p < .05$).

Similar activation patterns in anterior hippocampus and default network

Results suggest that responses in the anterior hippocampus are modulated by both task and memory strength. To examine the effects of task and memory strength in the

whole brain we identified regions in which the time-course of the hemodynamic response matched that in anterior hippocampus. For each voxel and for each condition, the hemodynamic response was fit to the impulse response curves previously identified in left anterior hippocampus (Figure 2.3A). The activity time-courses in medial PFC, PCC, left inferior parietal cortex and temporal pole were modeled by the seed hippocampal response across all conditions ($p < .001$; Figure 2.4). Impulse response curves illustrated stepwise deactivation from classify to strongly remembered to poorly remembered conditions. The average response across these regions differed across task conditions ($F(2) = 11.90$, $p < .001$), confirming greater deactivation for poorly remembered than classify ($t(9) = 3.86$, $p < .005$), for poorly remembered than strongly remembered ($t(9) = 4.09$, $p < .005$) and a trend for greater deactivation for strongly remembered than classify trials ($t(9) = 2.17$, $p = .06$). In addition, dorsal anterior cingulate cortex and anterior insula fit the inverse of the response model. Impulse response curves for these clusters demonstrated task-positive activation for all conditions, with greater positive deflection above baseline for poorly remembered and strongly remembered trials than classify trials.

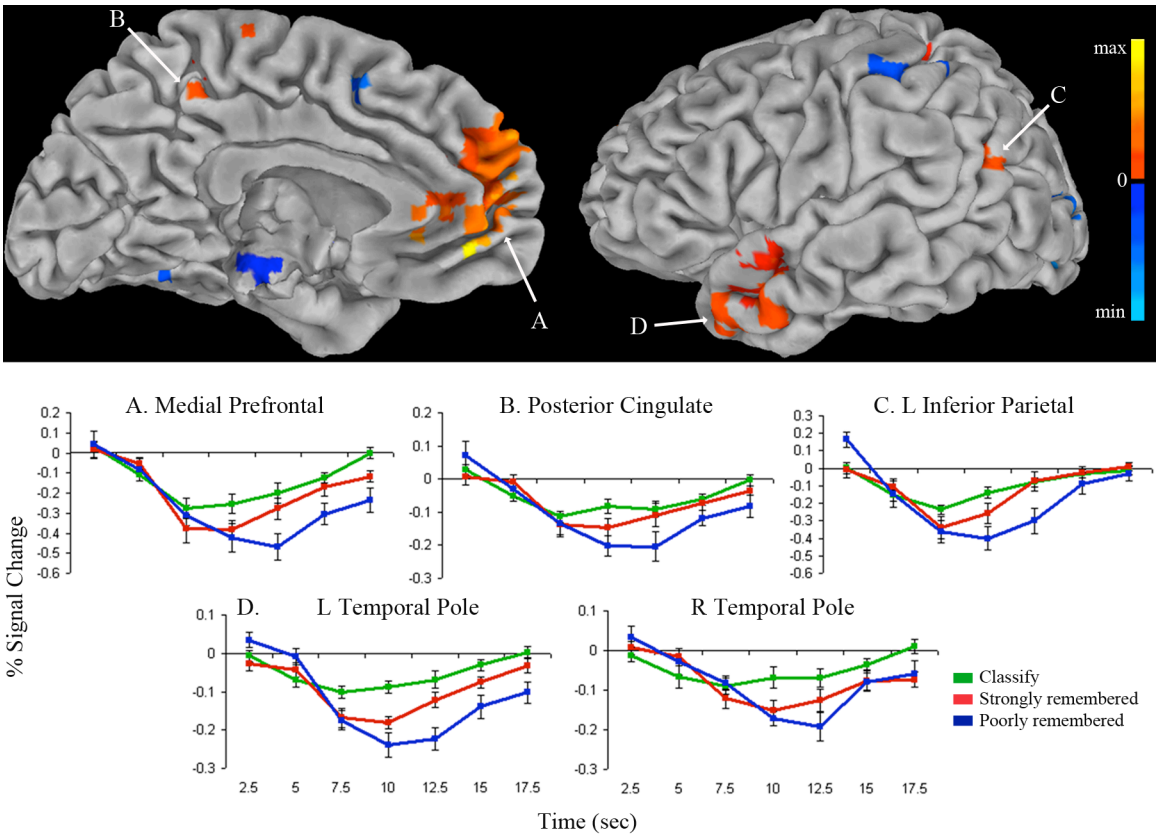

Figure 2.4: Regions fitting the anterior hippocampus response model. Clusters that directly fit the response model (warm colors) or fit the inverse of the response model (cool colors) for the classify, strongly remembered and poorly remembered conditions are overlaid on the left medial (top left) and lateral (top right) pial surface of the Talaraich and Tournoux N27 average brain ($p < .001$). Color intensity represents strength of fit with the anterior hippocampal impulse response model presented in Figure 2.3A. The average impulse response curves (bottom) from the medial prefrontal cortex (A), posterior cingulate (B), left inferior parietal cortex (C) and left and right temporal pole (D) show decreased activity below fixation baseline for classify (green), followed by greater deactivation for strongly remembered (red), and greatest deactivation for poorly remembered (blue).

Activity correlations with response time

To examine a possible relationship between response fluency and hippocampal and default network suppression, correlations between BOLD signal and response time were computed. Activity was negatively correlated with response time ($p < 0.05$) during both the classify and the recall tasks in bilateral superior temporal cortex and PCC.

During only the recall, but not the classify task, negative correlations with response time were additionally observed in bilateral anterior hippocampus, medial PFC, and inferior parietal cortex. Thus, greater activity in these regions was correlated with a faster response time.

Discussion

In the present study, negative BOLD signal deflection was observed in anterior hippocampus during the attempted recall of both strongly and poorly remembered word pair associates, and this deactivation was greatest for poorly remembered associations. The response in anterior hippocampal regions was distinct from that in posterior regions, which showed a late-onset deactivation only during the poorly remembered condition. A model of the hemodynamic response in anterior hippocampus was fit to the whole brain, and a similar pattern of graded deactivation across task conditions was identified in regions associated with the default network. Finally, response times were inversely correlated with BOLD signal in anterior hippocampus and default network regions, and this correlation was stronger in the recall than classify task.

Anterior hippocampus deactivates during attempted memory retrieval

Deactivation of hippocampal subregions may appear paradoxical in light of numerous studies reporting greater activity in anterior (Gabrieli et al., 1997;Cansino et al., 2002;Dobbins et al., 2003), posterior (Daselaar et al., 2006;Montaldi et al., 2006) or global (Nyberg et al., 1996;Eldridge et al., 2000;Henson, 2005;Eichenbaum et al., 2007) hippocampus for recollection versus familiarity, retrieval with increased confidence, or

old versus new judgments. Relative signal differences may be particularly susceptible to ambiguous interpretations, since they may be generated by either the more positively activating or negatively deactivating condition. Although relative signal increases during successful versus unsuccessful memory recall may reflect retrieval-driven activations, an alternative explanation might be that task-relevant deactivations contribute to such signal changes. The present results support a growing body of evidence that anterior or posterior hippocampus can deactivate during tasks that would otherwise be expected to engage the hippocampus, including retrieval of spatial memories (Rekkas et al., 2005) or visual paired associates (Israel et al., 2010), or during configural associative learning (Meltzer et al., 2008). Together, these findings highlight the possibility that both positively and negatively activating processes during retrieval provide task-relevant contributions to BOLD signal differences.

The current findings help to disentangle the contributions of memory search, retrieval success and post-retrieval processing to hippocampal responses during retrieval. In the recall task, memory search was encouraged by the instruction to recall a paired associate, retrieval success was assessed by post-scan recall accuracy, and post-retrieval processing included a classification judgment about the recalled word. Figure 2.5A presents a model of the hypothetical cognitive processes involved during successful and unsuccessful performance of this task. In contrast with poorly remembered trials, during which retrieval and post-retrieval processes are markedly reduced or absent, strongly remembered trials consistently involve these operations. Both strongly and poorly remembered trials engage search, as directed by the task, although poorly remembered trials are primarily comprised of search. All three of these retrieval-specific processes are

minimal during the classify task which does not require recall. The anterior hippocampal deactivation observed during both strongly and poorly remembered trials therefore appears to be associated with processes involved in memory search.

Studies that examined impulse responses have shown evidence for task-positive global (Eldridge et al., 2000;Wais et al., 2010) or regional (Gimbel and Brewer, 2011) hippocampal activation during retrieval, suggesting that either recollection or its associated processes increase hippocampal activation above baseline or pre-task levels. However, given the known function of the hippocampus in encoding the ongoing stream of experience, another consideration is how retrieval efforts might influence tonic encoding-related activity in the hippocampus. Encoding processes are known to occur during retrieval (Nyberg et al., 2000;Buckner et al., 2001) and many reports suggest that successful encoding (Lepage et al., 1998;Sperling et al., 2003) or novelty (Strange et al., 1999;Daselaar et al., 2006) engages anterior hippocampus. Findings from a recent word recognition study (Huijbers et al., 2009) indicate that incidental encoding can occur concurrently with intentional retrieval and that these operations may compete for shared neural resources in the medial temporal lobe. Figure 2.5B illustrates how task conditions might regulate hippocampal activity under the alternate assumptions that the subregion is engaged by either encoding or recall. Activity modulated by recall should increase during strongly remembered associations only. However, tonic encoding-related activity in the hippocampus may also be reduced by retrieval efforts regardless of retrieval success, as attention and neural resources are directed away from encoding. The magnitude or duration of this search-driven, hippocampal disengagement may be greatest for unsuccessful retrieval attempts, where search comprises the entirety of the trial.

Hippocampal disengagement would be intermediate for successful recall trials, which on average are comprised of brief search followed by retrieval success and post-retrieval processing, the latter of which evoke re-engagement of encoding processes as the retrieved and processed material is re-encoded. Thus, a task-positive hippocampal response for successful retrieval would not be inconsistent with the proposed model that hippocampal activity is primarily driven by encoding and not retrieval, especially if the task-positive responses occur under conditions where search processes are minimal. In most fMRI studies of episodic retrieval, recognition tasks are used, which would not typically engage guided search to the extent of cued recall.

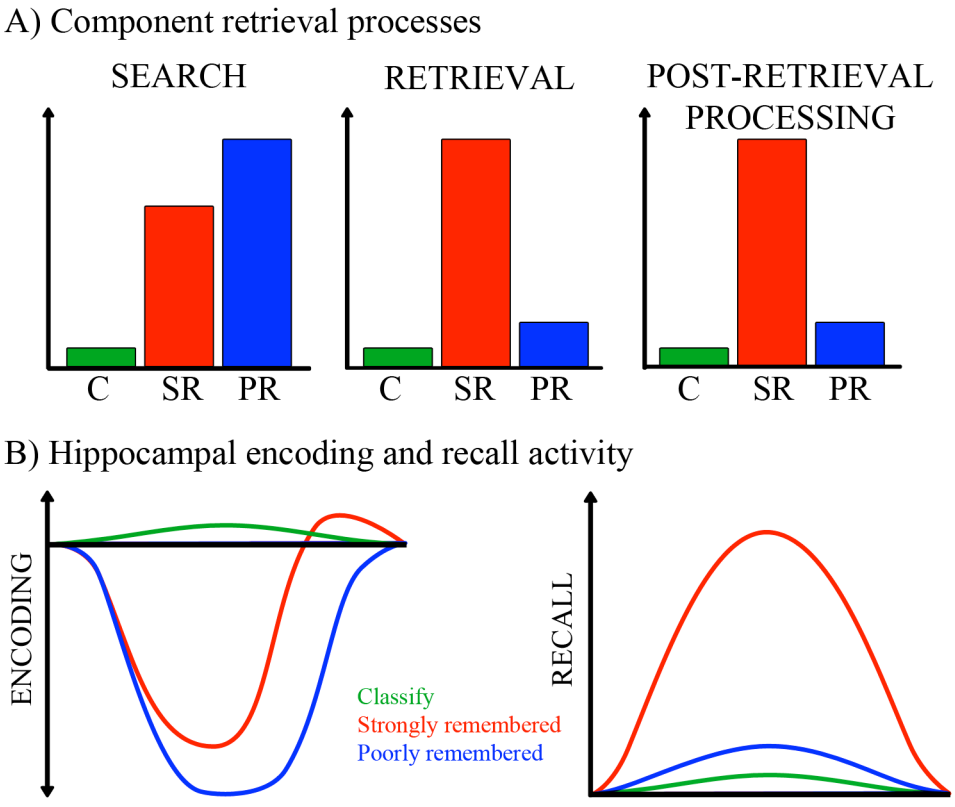

Figure 2.5: Cognitive and neural processing models. (A) The hypothetical cognitive processes involved in an elaborative associative retrieval task, and the magnitude to which each task condition engages these processes, are depicted. The y-axis represents arbitrary units measuring degree of engagement. From this model, the following cognitive processes are expected to result from task condition contrasts: If engaged more for strongly remembered than classify, the process(es) might be search, retrieval or post-retrieval processing; if engaged more for poorly remembered than classify and for poorly than strongly remembered, the process might be search. C = classify, SR = strongly remembered, PR = poorly remembered. (B) Hippocampal activity for each task condition is illustrated, under alternative models for encoding- and recall-mediated responses. Both strongly and poorly remembered trials are hypothesized to reduce encoding-related activity (left). Strongly remembered trials are expected to increase recall-related activity (right). The x-axes and y-axes are in arbitrary units of time and neural activity, respectively.

Retrieval-related anterior and posterior hippocampal responses are distinct

Hippocampal response patterns across task conditions were both spatially and temporally distinct. This dissociation is consistent with evidence from rodent and human

studies of subregion specialization within the hippocampus which suggests that the structure does not function as a single unit. Prior human neuroimaging studies provide additional support for the anterior to posterior functional gradient observed in the current study, reporting that anterior and posterior regions respectively subserve encoding (Strange et al., 1999;Sperling et al., 2003) and retrieval (Lepage et al., 1998;Daselaar et al., 2006) or that both encoding and retrieval functions may be posteriorly localized (Greicius et al., 2003a). Higher resolution functional imaging within the medial temporal lobe has allowed delineation of anatomical hippocampal subregions that perform distinct functions, including dentate gyrus / CA3 specialization for encoding or pattern separation, CA1 / subiculum specialization for retrieval or pattern completion (Eldridge et al., 2005;Bakker et al., 2008;Suthana et al., 2010;Lacy et al., 2011), and distinct roles of anterior and posterior CA1 in match/mismatch detection (Duncan et al., 2011). Such findings complement an expanding body of animal lesion and electrophysiology literature reporting unique contributions of hippocampal subfields to encoding, consolidation and retrieval, pattern completion and pattern separation, or different forms of temporal, spatial, episodic or working memory (Kesner et al., 2004;Lee and Kesner, 2004;Daumas et al., 2005;Hoge and Kesner, 2007;Leutgeb et al., 2007;Gilbert and Brushfield, 2009).

In the current study, deactivation during poorly remembered trials extended throughout the hippocampus, suggesting that similar neural mechanisms are at play in anterior and posterior subregions during failed retrieval efforts. However, the temporal lag of the posterior hippocampal deactivation may indicate regional delay of neural processing, an effect of the vascular anatomy and hemodynamic response, or a mixing of a modest positive response component with a more general and robust negative response

component. The trend for an early posterior hippocampal task-positive activation could possibly be related to retrieval itself, to encoding of the stimulus cue or to episodic re-encoding that accompanies retrieval events (see Figure 2.5B) (Buckner et al., 2001;Stark and Okado, 2003;Kirwan and Stark, 2004;Gimbel and Brewer, 2011). The presence of this peak early in the signal time-course and a lack of difference across task conditions suggest that it may reflect regional involvement of the posterior hippocampus in early task processing stages, such as encoding the word cue. Nevertheless, examination of the impulse response curves demonstrates that the robust difference between activations related to strongly and poorly remembered trials is primarily driven by suppression during poorly remembered trials rather than deviation from baseline for strongly remembered trials, at least in this task involving cued-recall.

Similar activity patterns in the default network and anterior hippocampus

Similar hemodynamic responses were elicited in anterior hippocampus and classic default network regions (medial PFC, precuneus, inferior parietal cortex and temporal pole), consistent with documented functional correlations between the hippocampus and default network (Greicius et al., 2004;Buckner et al., 2008). Default network function is a topic of active exploration, as it remains unclear to what degree these regions are regulated by specific thoughts or external stimulation. Default network activity is believed to reflect passive, task-irrelevant processing; this network inversely correlates with "task-positive" regions and attenuates in response to goal-directed behavior or externally focused thoughts (Raichle et al., 2001;McKiernan et al., 2003;Fox et al., 2005). The default network may be sensitive to task performance in general, which

should be considered as a potential factor underlying the hippocampal suppression observed in this study. However, areas deactivated during non-memory task performance only partially overlap with regions deactivated during elaborative memory retrieval, which have been found to include selective medial temporal regions (Israel et al., 2010). Components of overlapping default and memory networks may therefore be differentially regulated by general mental engagement and domain-specific task parameters, and broadly defined task-induced deactivations may not fully account for suppressed activity in the hippocampus.

While the functional significance of neural deactivation is a subject of ongoing investigation, it has been proposed that some deactivations are task-independent and arise when a goal-directed behavior attenuates a sustained level of resting-state activity (Shulman et al., 1997;Mazoyer et al., 2001;Raichle et al., 2001). This interpretation for task-induced default network deactivations may explain the decreased activity in regions of the default network observed in the present study. Alternatively, deactivations may be task-specific and represent reallocation of resources from task-irrelevant to task-critical regions (Drevets et al., 1995;Kawashima et al., 1995;McKiernan et al., 2003). This hypothesis provides a rationale for task-induced hippocampal suppression which may prevent interference with processes critical to the early stages of memory retrieval. While the function of the default network is less understood, the hippocampus is known to be highly specialized for associative encoding, which may compete with other functions important for efficient memory recall.

A recent associative memory fMRI study (Huijbers et al., 2011) demonstrated that the hippocampus and default network are coupled during retrieval but become uncoupled

during encoding, independent of whether a memory task demands internally or externally oriented attention. Although the present results expand upon these findings to reveal correlated activity between the anterior hippocampus and default network during attempted retrieval, it remains unclear whether search or concurrent correlated operations directly underlie default-hippocampal coupling. Whereas default activity may be suppressed by a variety of task demands, the hippocampus may be less sensitive to non-memory task engagement or general task difficulty (Israel et al., 2010;Gimbel and Brewer, 2011). During a retrieval attempt, the hippocampus may transition accordingly to a state in which hippocampal encoding functions are minimized in favor of retrieval efficacy, while the default network is simultaneously deactivated by correlated task effort. Since episodic search should also be required in the cued source retrieval paradigm employed by Huijbers et al. (2011), further exploration is required to determine if hippocampal-default correlations are maintained during spontaneous retrieval with minimal search demands.

Neural deactivations have been associated with high working memory or attentional demands (Greicius et al., 2003b). While such processes are needed to perform the directed search and post-retrieval classification required in the current experiment, evidence is inconclusive as to whether these factors may contribute to hippocampal suppression. Although a study of autobiographical memory recall did not report a hippocampal response to elaboration following recall (Daselaar et al., 2008), the present authors have observed anterior hippocampal deactivation during elaborative retrieval of visual paired associates (Israel et al., 2010) and greater anterior hippocampal deactivation during recollection with post-retrieval classification compared to non-elaborative

recollection (Gimbel & Brewer, unpublished observations). In the current experiment post-retrieval processing would not likely be initiated following unsuccessful recall. That deactivation occurred during poorly remembered trials suggests that this suppression may be specific to the search stages of memory retrieval. Regardless of retrieval success, search processes are presumably engaged during recall of both strong and poor memories, and retrieval efforts for weaker memories may require increased search. The stepwise modulation of deactivation in anterior hippocampus from classify to strongly remembered to poorly remembered trials supports the interpretation that this response may be associated with search. While post-retrieval judgments may further impact the hippocampus or default network, it appears likely that pre-retrieval search processes primarily drive the observed deactivation.

BOLD signal in the hippocampus and default network inversely correlates with response time

Neural responses to subcomponents of retrieval, such as searching for episodic information, may be influenced by response fluency (Herron, 2007), which can roughly be gauged by response time. The present study found a negative relationship between response fluency and deactivation in the hippocampus and default network; in other words, longer response times or less fluent responses were associated with greater deactivation. Furthermore, this correlation was strengthened when the task additionally required memory recall. Assuming an absence of retrieval attempts during the classify task, the dependence of deactivation on response fluency in this control task suggests that general task difficulty or effort may regulate default network suppression. Nevertheless

the correlation was much weaker in the control task and, indeed, despite instructions not to recall during the classify task, inadvertent memory search may have contributed to some degree of correlation in the classify condition. Such task-related differences in correlation strength support an interpretation that this deactivation could be modulated by task-specific retrieval fluency. Prior evidence indicates that memory strength may influence default network independent of task difficulty (Gimbel and Brewer, 2011). The present study extends this finding to suggest that effortful search, which may inversely correlate with memory strength, involves the concomitant suppression of the anterior hippocampus and default network.

Limitations

In the current study, hippocampal activation was reduced during task conditions involving guided memory retrieval effort. Although this response appears attributable to search processes and may reflect interactions between hippocampal encoding and retrieval functions, this interpretation relies on several assumptions that deserve consideration. First, the classify, strongly remembered and poorly remembered trials are assumed to respectively involve minimal, moderate and high levels of memory search. Although participants were explicitly instructed not to recall during classify trials, it is possible that incidental recall occurred during some classify trials. However, the significantly faster response times and lower post-scan recall accuracy for classify than recall trials suggest that subjects indeed performed the tasks as instructed.

Second, only strongly remembered trials are assumed to involve recollection and post-retrieval processing. Due to practical limitations, cued recall was not tested during

scanning and post-scan recall was instead used to approximate recall success. It is possible that post-scan recall did not correspond exactly with retrieval performance during the scanned recall test; however, pairs remembered during the post-scan test were classified with high accuracy (82 ± 3%) during scanning, and there was a trend ($p = .10$) for slower reaction times during scanning for pairs that were forgotten than remembered during the post-scan test. These behavioral findings support the assumption that pairs recalled and forgotten after scanning were strongly and poorly remembered during the scanned recall test.

Finally, since it was not feasible to directly evaluate encoding during the current recall task, it remains unclear whether encoding-related activations in fact depended on search demands. Further investigation is warranted to determine how processes such as simultaneous encoding of the external sensory environment, of the stimulus cue, or re-encoding of recalled associations, are modulated by search or other aspects of episodic memory retrieval.

Conclusions

The present study reports deactivation of anterior hippocampus and default network regions during elaborative verbal episodic memory retrieval, and suggests that effortful search may underlie this deactivation. Anterior and posterior hippocampus functionally dissociated during this task, suggesting that separate hippocampal subregions may coordinate with distinct networks subserving different neural processes. Further investigation will help clarify whether search- and task-difficulty-related deactivations are dissociable phenomena and whether they are differentially linked to tonic and

concurrent episodic encoding. These results shed light on both the complex factors regulating hippocampal engagement or disengagement and the functional significance of hippocampus-default network interactions during episodic memory retrieval.

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CHAPTER 3:

RETRIEVAL SEARCH AND STRENGTH EVOKE DISSOCIABLE BRAIN ACTIVITY DURING EPISODIC MEMORY RECALL

Abstract

Neuroimaging studies of episodic memory retrieval have revealed activations in the human frontal, parietal, and medial temporal lobes that are associated with memory strength. However, it remains unclear whether these brain responses are veritable signals of memory strength or are instead regulated by concomitant subcomponents of retrieval such as retrieval effort or mental search. The present study used event-related functional magnetic resonance imaging during cued recall of previously memorized word pair associates to dissociate brain responses modulated by memory search from those modulated by the strength of a recalled memory. Search-related deactivations, dissociated from activity due to memory strength, were observed in regions of the default network, whereas distinctly strength-dependent activations were present in superior and inferior parietal and dorsolateral prefrontal cortex. Both search and strength regulated activity in dorsal anterior cingulate and anterior insula. These findings suggest that, although highly correlated and partially subserved by overlapping cognitive control mechanisms, search and memory strength engage dissociable regions of frontoparietal attention and default networks.

Introduction

Experimental electroencephalographic and functional magnetic resonance imaging (fMRI) paradigms that manipulate encoding depth, acquire subjective recognition confidence ratings or compare recollection with familiarity have revealed distinct neural correlates of memory strength (Buckner et al., 1998; Eichenbaum et al., 2007; Henson et al., 2000; Kirwan et al., 2008; Montaldi et al., 2006; Smith, 1993; Staresina and Davachi, 2006; Wais et al., 2010; Yonelinas et al., 2005). However, procedures that effectively modulate memory strength will also influence concomitant processes that co-vary with strength, but that are only indirectly related to the retrieval event, itself (Tulving, 1984). Identifying such concomitant processes may be a particular challenge for fMRI studies where brain blood flow responses are recorded while subjects retrieve and evaluate memories. Both retrieval and its evaluation involve subprocesses that contribute to the recorded aggregate brain activity, and each may be differentially influenced by memory strength. Nevertheless, attempts to isolate neural responses related to memory will benefit from improved fractionation of these additional, correlated elements. In particular, our current understanding of the mechanisms of recollection is limited by an inability to fully differentiate effects related to retrieval success from those sensitive to retrieval attempt or effort.

Memory retrieval efforts, in addition to recruiting brain regions that are highly specialized to perform memory operations, may also recruit regions with broad functional overlap across cognitive domains. For example, cognitive control and attention critically contribute to episodic memory retrieval efforts and success (Ciaramelli et al., 2008; Moscovitch, 1992). A variety of attention-dependent processes might be sensitive to

retrieval strength, including directing attention towards a spontaneously recalled memory representation (Cabeza et al., 2008), activation of retrieval mode (Buckner, 2003) or guided memory search efforts (Reas et al., 2011). For instance, access to a stronger memory may elicit enhanced bottom-up attention to a salient internal stimulus representation (Cabeza et al., 2008; Ciaramelli et al., 2008). In contrast, during directed retrieval the strength of a target memory may inversely correlate with cognitive control demands, as such demands may be elevated to serve the more difficult retrieval of weaker memories. As opposed to recognition, cued recall attempts may rely more heavily on sequential search processes (Nobel and Shiffrin, 2001) and thus demand increased top-down attention.

Brain regions sensitive to the strength of the retrieved memory include areas of the medial temporal lobe (Kirwan et al., 2008; Wais, 2011) that human lesion and neuroimaging studies have shown are important for episodic memory encoding and retrieval (Gabrieli et al., 1997; Henson, 2005; Scoville and Milner, 1957; Squire et al., 2007; Squire and Zola-Morgan, 1991) as well as additional regions with functional and anatomical connections to core medial temporal memory structures (Greicius et al., 2003; Greicius et al., 2004; Vincent et al., 2006). For example, both task-positive activations in frontal and parietal cortex and task-negative responses in the default network can be regulated by retrieval effort, success or memory strength (Cabeza, 2008; Daselaar et al., 2009; Henson et al., 2005; Kapur et al., 1995; Kim, 2010; Moritz et al., 2006; Seibert et al., 2011). These areas comprise multiple interacting networks that integrate cognitive control and attention systems with memory regions (Kim, 2010; Spreng et al., 2010; Vincent et al., 2008). Thus, guided retrieval efforts that directly modulate search and

control processes might account for some strength-related responses in regions serving supportive attention functions.

Since retrieval effort is expected to negatively correlate with both the strength of a memory and success at recalling the memory, neural activations driven directly by mental search may confound findings attributed to strength or success. Yet it remains unknown the extent to which the neural circuitries underlying these interdependent components during attempted recollection overlap or diverge. Previous efforts to dissociate retrieval subprocesses have indentified frontal and parietal activations differentially mediated by retrieval success and retrieval effort or mode (Donaldson et al., 2001; Kahn et al., 2004). However, memory strength interacts with both success and effort. Recent evidence demonstrates that activations related to memory strength and successful recollection are separable, such that the hippocampus may support strength while prefrontal and inferior parietal cortex support recollection (Wais, 2011). Further research is necessary to fully disentangle responses associated with retrieval effort from those regulated by the strength of a recalled memory.

The current investigation sought to dissociate the contributions of retrieval effort and recollection strength to blood oxygen level dependent (BOLD) signal changes during episodic memory retrieval. Event-related fMRI was performed while subjects recalled previously studied word pair associates or performed a non-memory classification task. Memory strength was modulated by varying study repetitions and episodic memory search, a postulated component of retrieval effort, was examined by isolating both successful and unsuccessful recall attempts. Based on prior evidence, either or both search and strength were predicted to engage medial and lateral prefrontal, medial and

lateral parietal, and superior temporal cortices. By segregating conditions demanding memory search from conditions that varied in strength level, this study further sought to distinguish subregions that are differentially activated by search- and strength-dependent components of episodic retrieval.

Methods

Subjects

Participants included twenty-one volunteers from the University of California, San Diego (UCSD) community and surrounding areas. All subjects were healthy, right-handed, English-speaking with normal or corrected vision and gave informed written consent in accordance with criteria of the UCSD Institutional Review Board. Recall performance was poor in four subjects, including three subjects with fewer than 15% remembered trials in the low-study recall condition and one with no successfully recalled words from the post-scan cued recall test. Data from the remaining seventeen participants (seven male, mean age ± standard deviation = 24.7 ± 2.2 years) were included for analysis.

Stimuli

Stimuli were 240 English nouns, pseudorandomly combined into 120 pairs that were screened for obvious semantic associations. Half of the words represented living and half represented non-living items. Pairs were divided equally (40 pairs in each condition) into low, medium and high repetition study conditions.

Experimental design

During a pre-scan encoding task, subjects studied 120 word pairs presented one at a time on a laptop, and subjects were instructed to remember each word pair association. To avoid task-irrelevant sources of variability associated with subjective confidence ratings (de Zubicaray et al., 2010) memory strength was manipulated by varying study repetitions rather than evaluating retrieval confidence during scanning. Paired associates were repeated one, three or five times (henceforth referred to as low, medium and high-study) over the course of five 288-second study runs. Each pair was displayed for three seconds, followed by a fixation cross for one second (Figure 3.1A).

After a delay of approximately 20 minutes, event-related fMRI data were acquired while subjects completed a recall task and a control classify task. In each trial a black box and a colored box were presented for one second, after which a previously studied word appeared in one of the boxes for one second. The colored box surrounded the presented word or its missing pair and served as a cue to perform either a classify (green box) or recall (red box) task (Figure 3.1B). In the classify task, subjects were instructed to make a response indicating if the presented word was living or non-living. In the recall task, they were instructed to first indicate "remember" or "forgot" as soon as they recalled or decided they could not remember the word's pair, and, if recalled, to use a second response to classify the recalled word as living or non-living. Subjects were encouraged to respond as quickly and accurately as possible with their right hand using two buttons of a response box. The cue boxes remained on the screen for three seconds following word presentation, and trials were jittered with 0.5-7.5 seconds of fixation baseline, calculated to optimize the study design for modeling the hemodynamic response to trials

(Dale, 1999; Dale and Buckner, 1997). Equal numbers of classify and recall trials (120 trials per condition) were pseudorandomly distributed across five 388-second runs. The two words composing a pair were assigned to the same condition (classify or recall), and pairs from the three study levels (low, medium and high-study) were distributed evenly across both tasks.

Subjects then completed a post-scan self-paced cued recall test (Figure 3.1C) to allow for overt assessment of recall accuracy as compared to covert recall during the scanned recall task. One word from each pair was presented and subjects were instructed to verbally report the word's pair.

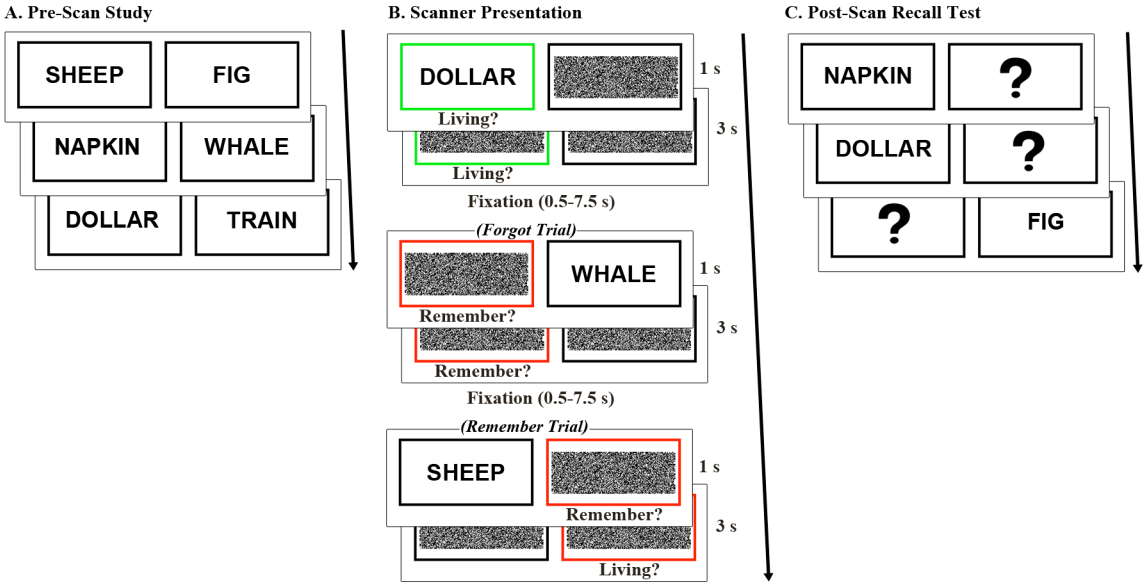

Figure 3.1: Experimental protocol. (A) Before scanning, subjects studied 120 word pair associates. Pairs were presented one, three or five times during the study session. (B) Event-related fMRI was conducted while subjects performed classify (green box) or recall (red box) tasks. During recall trials, a classification response was prompted after "remember" responses. (C) After scanning subjects performed a cued recall test on all studied word pairs.

fMRI parameters

Imaging was performed using a 3.0 Tesla General Electric scanner at the UCSD Keck Center for Functional MRI. Functional data were acquired using a gradient-echo, echo-planar, T2*-weighted pulse sequence (time repetition [TR] = 2.5 s; one shot per repetition; echo time = 30; flip angle = 90°; bandwidth = 31.25 MHz). Each volume contained forty slices oriented perpendicular to the long axis of the hippocampus with 3.4 x 3.4 x 4 mm voxels. Field maps were acquired to measure and correct for static field inhomogeneities (Smith et al., 2004). A high resolution (1 mm^3) T1-weighted anatomical scan was acquired using an inversion recovery prepared spoiled gradient recalled sequence providing high grey-white contrast for anatomical delineation. An additional T1-weighted structural scan was acquired in the same plane and of the same voxel size as the functional scans to confirm alignment between the functional and anatomical images.

fMRI data analysis

Functional data were corrected for spatial distortions using field maps (Smith et al., 2004), and data from each run were reconstructed using the AFNI suite of programs (Cox, 1996). Slices were temporally aligned and co-registered using a three-dimensional image alignment algorithm and a threshold mask of the functional data was applied to remove voxels outside the brain. Each functional run was smoothed with a 4 mm full-width half-maximum Gaussian blur, corrected for motion and concatenated. Standard landmarks were manually defined on the anatomical scans before normalizing the anatomical scans and the functional data to Talairach space (Talairach and Tornoux, 1988).

The region of interest large deformation diffeomorphic metric mapping (ROI-LDDMM) alignment technique was applied to improve alignment of the medial temporal lobe between subjects (Miller et al., 2005). Previously described landmarks were used to define perirhinal and entorhinal cortices (Insausti et al., 1998), parahippocampal cortex (Stark and Okado, 2003) and hippocampus (Chera et al., 2009) for each subject on Talairach transformed images. These anatomical regions of interest for each subject were normalized using ROI-LDDMM to a modified model of a previously created template segmentation (Kirwan et al., 2007). Functional imaging data underwent the same ROI-LDDMM transformation as was applied to the anatomical data.

Amplitude modulated regression was performed to examine how BOLD signal was modulated by trial-by trial response times, or by task conditions independent of response time. The general linear model included regressors for task conditions of interest, including remembered low-study, remembered medium-study and remembered high-study recall, forgotten recall, and classify trials. Trials were weighted by response times, and two regressors were included for each task condition: one for the magnitude of modulation by response time and one corresponding to the BOLD response for the mean response time (controlling for response time). The model additionally included six motion regressors obtained from the registration process. Signal deconvolution with TENT basis functions (Cox, 1996) was used to estimate the hemodynamic response for the 15 seconds following the stimulus onset.

To identify activity more strongly correlated with response time in the recall task than in the classify task, parameter estimates of the modulation by response time were contrasted between all recall trials (remembered and forgotten) and classify trials. Since

contrasting correlations between conditions leads to ambiguous information about the direction of correlation in each condition (i.e. more positively correlated in the recall task versus more negatively correlated in the classify task), a mask of positive recall response time correlations was applied to positive activations and a mask of negative recall response time correlations was applied to negative activations from the recall versus classify contrast.

To examine task-dependent activity independent of time-on-task, the following comparisons were performed on parameter estimates controlling for response time: 1) remembered versus classify, contrasting a condition where episodic and semantic memory search processes and retrieval are present against a condition where only semantic search is present but episodic search and retrieval are absent, 2) forgotten versus classify, contrasting a condition where episodic memory search processes are high and retrieval is absent against a condition where episodic search and retrieval are absent, and 3) recalled trials from the low, medium and high-study conditions (henceforth referred to as the *study-level* effect), contrasting variable degrees of memory strength under the condition of successful retrieval (Table 3.1).

Conjunctions of these contrasts were performed to identify voxels in which BOLD signal was modulated 1) by both memory search and strength, 2) by memory search but not strength, and 3) by memory strength but not search (Table 3.1).

1. Search and Strength

The search and strength analysis inclusively masked activations or deactivations from all three comparisons (i.e. examining the overlap across the following conditions: *remembered* > *classify*; *forgotten* > *classify*; and *study-level* effect (either *low* > *medium*

> *high-study* or *low* < *medium* < *high-study,* confirmed by examining impulse response plots) and, separately, the overlap across the following conditions: *remembered* < *classify*; *forgotten* < *classify*; and *study-level* effect). As such, these regions were modulated positively or negatively by both search and strength.

2. Search Only

The search only analysis inclusively masked activations or deactivations from recall conditions identified by memory performance (i.e. highlighting regions where the retrieval event was not necessary to yield modulation of activity as demonstrated by overlap between *remembered* > *classify* and *forgotten* > *classify* or an overlap of *remembered* < *classify* and *forgotten* < *classify*) with an exclusion mask of the *study-level* comparison. Thus, these regions were modulated by retrieval conditions in a way that neither depended on retrieval being present nor on memory strength.

3. Strength Only

The strength only analysis identified effects of *study-level* during successful recall and applied an exclusion mask of search-based activity (i.e. excluding *forgotten versus classify* activations and deactivations). Although search processes would also be engaged during remembered trials, the *remembered versus classify* contrast was not added as an exclusion mask since regions showing strength-driven responses may overlap with those activated during successful recall.

Table 3.1: Relative levels of search, strength differences and retrieval success (+++ high, ++ medium, + low) are presented for each of three comparisons: *remembered versus classify*, *forgotten versus classify*, and *study-level* during recall. The overlap of all three comparisons involves varying degrees of search and strength. Search is engaged during remembered and forgotten recall trials, relative to a baseline classification task and can be isolated from strength by excluding effects of *study-level*. Differences in memory strength are highlighted by comparing successful recall of low, medium and high-study word pairs and effects of search can be minimized by excluding the *forgotten versus classify* contrast.

	Remembered vs. Classify	**Forgotten vs. Classify**	**Study-Level**
Search	++ vs. absent	+++ vs. absent	Some decrease with strength
Strength	++ vs. absent	+ vs. absent	+ vs. ++ vs. +++
Retrieval Success	+++ vs. absent	absent	Equal

Comparisons were performed on parameter estimates from the 7.5-12.5 second period of each condition, when the hemodynamic response was expected to be most deflected from baseline based on a previous study using a similar task in a different set of subjects (Reas et al., 2011). Group-level two-tailed voxelwise t-tests were computed on each contrast and analysis of variance was conducted to examine effects of study-level (all analyses $p < .05$ and corrected for multiple comparisons). Significant clusters, including at least thirteen contiguous voxels, were displayed on a statistical map overlaid onto an across-subject averaged structural image. Correction for multiple comparisons was performed prior to conjunction analyses using a Monte Carlo simulation on a whole-brain functional volume in AFNI (http://afni.nimh.nih.gov/pub/dist/doc/program_help/3dClustSim.html) to determine the minimum cluster size necessary to achieve a family-wise error rate of $p < .05$. The

hemodynamic response function was then extracted for each cluster of interest and averaged across subjects to examine the signal time-course in an impulse-response plot.

Behavioral Results

Subjects correctly classified 98 ± 1% (mean ± standard error) of classify trials, responded "remember" to 64 ± 3% of recall trials, and correctly classified 86 ± 2% of remembered recall trials. While accuracy did not differ according to study level in the classify task ($p = .78$), effects of study level on both recall ($F(2,32) = 97.73$, $p < .001$) and classification ($F(2,32) = 11.44$, $p < .001$) accuracy were observed in the recall task. Pairwise comparisons revealed better recall with increasing study repetitions (36 ± 3%, 73 ± 4%, 84 ± 4%, p's < .001) and more accurate classification for the high than low-study recall conditions (90 ± 2 vs. 78 ± 4%, $p < .001$).

Response times were 1229 ± 76, 2205 ± 104 and 2840 ± 87 msec for the classify, recall, and recall plus classification responses, respectively. Recall responses were faster for remembered than forgotten pairs (2027 ± 104 vs. 2725 ± 142 msec; $t(16) = 5.17$, $p < .001$). Correct recall responses showed an effect of study level ($F(2,32) = 28.03$, $p < .001$), reflecting faster response times with increasing study repetitions (2399 ± 118, 2045 ± 114, 1866 ± 107 msec; p's < .001). Classify response times did not differ according to study level ($p = .75$).

During the post-scan test, subjects correctly recalled 78 ± 4% of pairs reported remembered during the recall task and forgot 75 ± 3% of pairs reported forgotten or to which subjects did not respond during the recall task, confirming relative consistency between subjective reports and overt assessment of recall. Post-scan recall was better for

pairs that had appeared in the recall than in the classify task (60 ± 4% vs. 51 ± 5%; $F(1,16) = 17.24$, $p < .001$), and a main effect of study level ($F(2,32) = 163.92$, $p < .001$) reflected better post-scan recall with increasing study repetitions (23 ± 5%, 64 ± 5%, 79 ± 5%; *p's* < .001).

fMRI Results

Response time correlations

Episodic memory search may involve distinct components that depend either upon the duration of the search process, or upon general engagement in search independent of the search duration. Using response times to approximate the duration of search, amplitude modulated regression was performed to identify voxels in which the hemodynamic response magnitude correlated with the response time of recall responses. The response time correlation for the recall task was contrasted with the correlation for the classify task to distinguish response modulation related to episodic memory search from modulation related to semantic memory search. Regions in which BOLD signal showed a greater negative correlation with recall than classify response times ($p < .05$, two-tailed and corrected for multiple comparisons) included bilateral dorsomedial prefrontal cortex (DMPFC), inferior parietal and inferior frontal cortex, and left precuneus and middle temporal cortex (Figure 3.2). Activity in these regions was more deactivated with longer response times during the recall than the classify task.

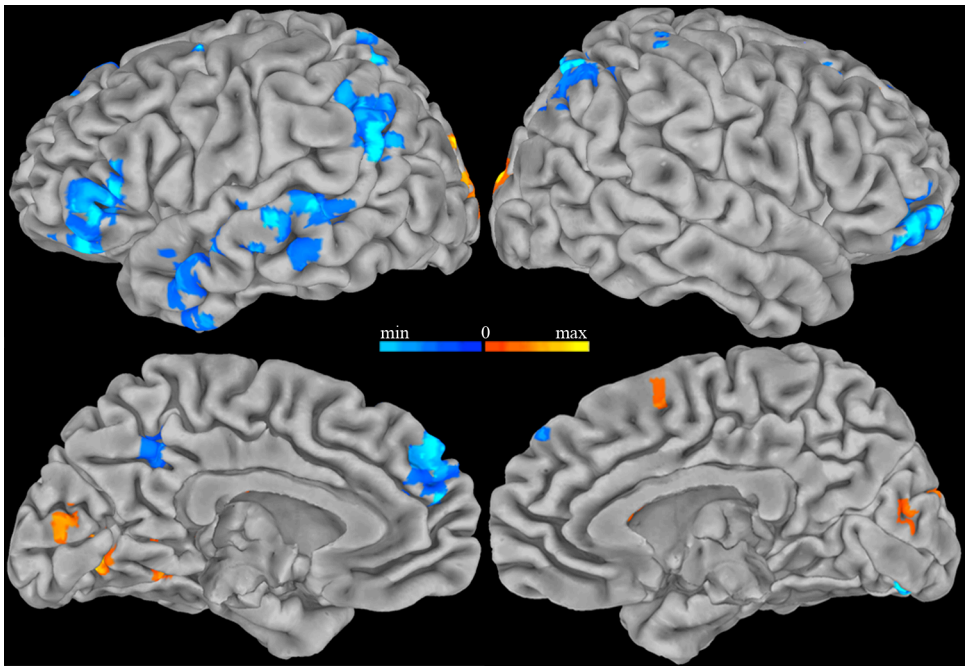

Figure 3.2: Regions correlated with response time. Areas more positively (warm colors) and negatively (cool colors) correlated with response times during the recall than the classify task ($p < .05$, corrected for multiple comparisons) are displayed on the Talaraich and Tournoux N27 average pial surface. Longer response times were associated with less activity in bilateral dorsomedial prefrontal, inferior frontal and inferior parietal cortex, and left precuneus and middle temporal cortex.

Search and Strength

To identify activity related with both episodic memory search and strength, independent of time-on-task, the overlap for the *remembered versus classify*, *forgotten versus classify*, and *study-level* comparisons was examined, controlling for response time in each comparison. Regions identified as responsive to both search and strength (Methods, analysis 1: Search and Strength; $p < .05$, two-tailed and corrected for multiple comparisons) included dorsal anterior cingulate cortex (DACC) and left anterior insula (Figure 3.3, Table 3.2A). Impulse response curves in these regions confirmed greater activation during both remembered and forgotten than classify trials, and increasing

activity from high to medium to low-study recall conditions. A main effect of task was observed in these regions ($F(2,32) = 26.83$, $p < .001$), and pair-wise comparisons revealed greater activation for remembered and forgotten than classify (p's < .001) with no difference between remembered and forgotten trials ($p = .18$). A main effect of study level ($F(2,32) = 11.74$, $p < .001$) confirmed greater activation for low than high-study recall ($p < .001$) and a stepwise increase in activation from the high to medium ($p < .01$) and medium to low-study ($p < .05$) recall conditions. No regions in this conjunction analysis showed the opposite *study-level* effect, with increasing activity with greater memory strength. Thus, regions activated by attempted memory retrieval, if modulated by strength, were always more activated by retrieval of weaker memories.

Table 3.2: Significant clusters ($p < .05$) for the Search and Strength (A), Search (B) and Strength (C) analyses. Regions more active for remembered and forgotten than classify trials, and modulated by study-level (A), more active for remembered and forgotten than classify trials with no effect of study-level ($p < .05$) (B), and modulated by study-level with no significant difference ($p < .05$) between forgotten and classify trials (C) are presented. Only cortical clusters including at least 13 voxels are presented. Talairach coordinates (x, y, z) correspond to the center of mass for each cluster. Maximum t- or F-values are presented for each comparison. BA = Brodmann area; L = left; R = right.

						Remembered	***Forgotten***	***Study-***
Region	**BA**	**Volume (mm3)**	**X**	**Y**	**Z**	***> Classify***	***> Classify***	***level***
						Max t	**Max t**	**Max F**
(A) Search and Strength								
DACC	32	8704	1	21.8	41	6.98	6.48	16.18
L DLPFC	9	1088	-45.5	13.5	32.5	7.86	3.55	11.76
L Anterior Insula	13	1024	-29.4	22.8	6.5	7.74	6.79	14.64
(B) Search								
L Occipital	18	9408	-5.8	-76.2	2.7	6.47	4.18	2.8
R Superior Temporal	42	9344	51	-12.4	12.6	-5.11	-5.55	5.1
L Anterior Insula	13	5824	33.2	20.5	4.7	6.45	6.9	6.36
L Superior Temporal	22	4672	-55.5	-8	0.3	-4.79	-6.16	6.16
R Inferior Parietal	39	3008	49.7	-58.6	27.8	-4.14	-4.86	3.1
DMPFC	9	2880	-6	49.5	28.1	-5.18	-4.9	6.02
L Temporal Pole	38	2688	-44.6	8.6	-24.8	-4.27	-6.98	2.44
DACC	32	2368	1.1	24	31.3	5.75	4.79	3.27
L Posterior Insula	13	2240	-30.4	23.2	4.8	5.66	4.88	3.18
L DLPFC	9	1920	-41.5	6.2	33.6	7.31	3.01	3.97
L Inferior Parietal	39	1408	-59.5	-60.5	26.9	-3.62	-4.66	3.63
L Middle Frontal	8	1344	-24.2	15.5	36.9	-4.34	-5.82	2.75
Medial Parietal	3	1280	6	-33.7	61.8	-2.88	-5.45	1.09
R Superior Frontal	6	1216	21.5	29.1	53.8	-4.49	-3.36	2.2
L Posterior Insula	13	1088	-38	-21.2	22.8	-4.17	-3.16	3.1
R Temporal Pole	38	1024	50.2	10.1	-18.7	-3.57	-3.57	7.48
R Superior Frontal	6	896	-1.1	8	61.4	6.59	4.13	3.29
(C) Strength (high > low)								
L Inferior Parietal	40	14400	-48.6	-44.9	22.3	5.25	-2.32	17.35
R Superior Parietal	40	7168	38.3	-38.4	56.2	3.61	-2.8	10.98
R Superior Temporal	22	4480	50.5	-44.6	14.2	3.47	-2.09	12.78
L Medial Frontal	6	3904	-11.8	-18.1	52.9	3.2	-2.14	11.26
R Inferior Parietal	39	3840	34.9	-70.6	23.1	5.42	2.44	7.06
L Superior Parietal	7	1408	-23	-47.8	54.1	3.92	-2.11	10.48
Strength (low > high)								
L Medial Frontal	8	6464	-1.4	28	46.9	5.95	2.09	22.27
L DLPFC	10	3648	-37.4	45.4	8.9	4.58	-2.08	9.86
L DLPFC	46	3328	-45.3	17.5	26.6	6.8	2.1	11.44
L Middle Frontal	6	1088	-33.3	5.7	58.9	5.53	-1.92	6.68
L Fusiform	20	832	-45.5	-12.9	-21.2	3.33	-1.74	6

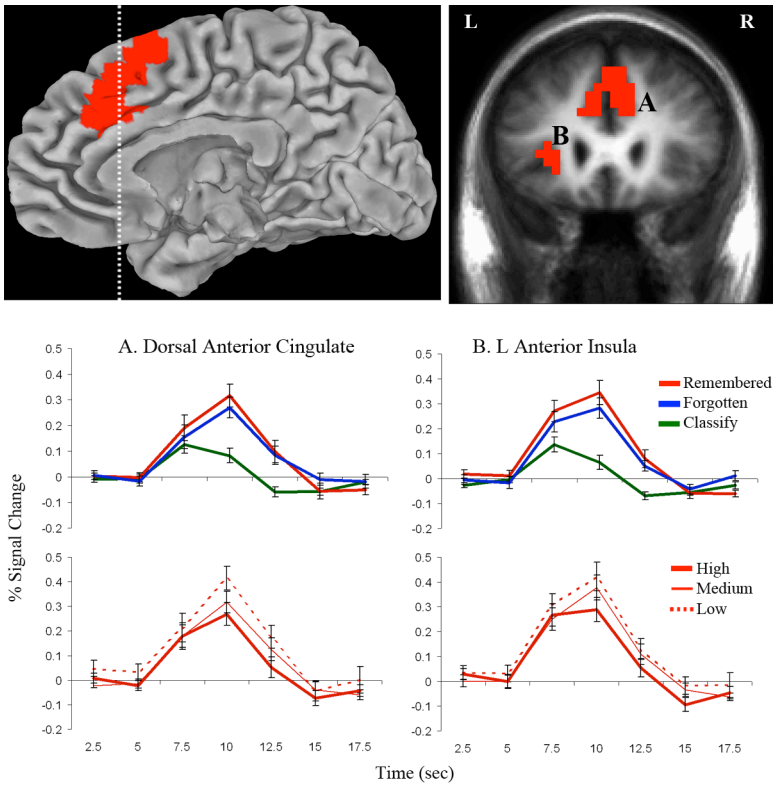

Figure 3.3: Activity in dorsal anterior cingulate (A) and left anterior insula (B) increased during search and was modulated by memory strength. Statistical activation maps show the conjunction of regions with greater activity during remembered and forgotten recall trials than classify trials and during increasing activity from the high to medium to low-study recall conditions ($p < .05$, corrected for multiple comparisons). Clusters are overlaid on the right medial pial surface of the Talaraich and Tournoux N27 average brain and a coronal cross-section (indicated with dashed line) of the mean anatomical image of all subjects. Impulse-response plots display the time-course of the percent signal change (± standard error) in these clusters for the remembered, forgotten and classify trials and high, medium and low-study recall conditions.

Search only

Responses associated with search but not modulated by memory strength or response time (Methods, analysis 2: Search only; $p < .05$) were observed in bilateral DMPFC, temporal pole, superior temporal, medial parietal and inferior parietal cortex (Figure 3.4, Table 3.2B), a subset of the default network. Impulse response curves from these regions illustrated greater negative deflection from baseline during both

remembered and forgotten relative to classify trials. Since no hemispheric differences were found in inferior parietal cortex (p =.41), superior temporal cortex (p =.57) or temporal pole (p =.55), left and right impulse response curves for these clusters were averaged for display. A task effect in these clusters ($F(2,32) = 34.08$, $p < .001$) was driven by greater deactivation for remembered and forgotten than classify (p's < .001) with no difference between remembered and forgotten trials (p = .09). There was no effect of *study-level* in these regions (p = .60).

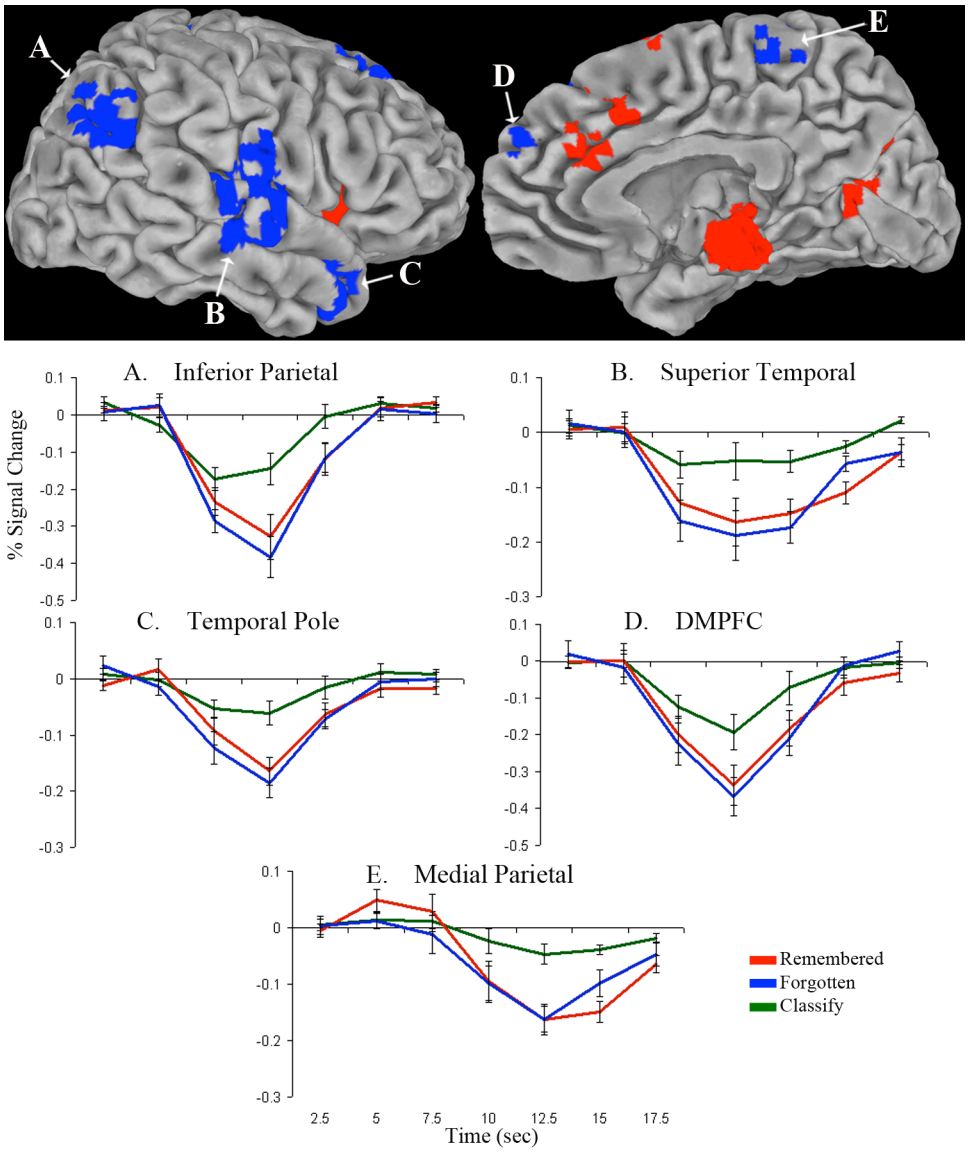

Figure 3.4: Regions activated by search but not memory strength. Statistical activation map displaying the conjunction of regions more (red) or less (blue) active during remembered and forgotten than classify trials ($p < .05$, corrected for multiple comparisons), with an exclusion mask of regions in which activity differed ($p < .05$) between low, medium and high-study recall conditions. Clusters are overlaid on the right pial surface of the Talaraich and Tournoux N27 average brain. Graphs depict the time-course of the percent signal change (± standard error) in bilateral inferior parietal cortex (A), superior temporal cortex (B), temporal pole (C), dorsomedial prefrontal cortex (D) and medial parietal cortex (E), illustrating greater negative deflection from baseline during remembered and forgotten relative to classify trials.

Strength only

Regions showing a *study-level* effect but not strongly activated by search nor modulated by response time (Methods, analysis 3: Strength only; $p < .05$) included left dorsolateral prefrontal cortex (DLPFC) and bilateral superior and inferior parietal cortex (Figure 3.5, Table 3.2C). Parietal impulse response curves showed a stepwise increase in activity from low to medium to high-study recall conditions, and greater activity during remembered than both forgotten and classify trials. An effect of study level ($F(2,32) = 20.34$, $p < .001$) and a study level by region interaction ($F(6,96) = 3.42$, $p < .01$) reflected greater activation for high than low-study recall (p's $< .001$), and for medium than low-study recall (p's $< .01$) in all parietal regions, and for high than medium-study recall in right superior parietal cortex ($p < .01$). Left DLPFC demonstrated an inverse strength effect, with increasing activity from high to medium to low-study conditions. An effect of study level ($F(2,32) = 8.77$, $p < .001$) confirmed greater activation for the low than high-study ($p < .01$) and medium than high-study ($p < .01$) recall conditions. Activity in parietal regions ($F(2,32) = 13.64$, $p < .001$) and left DLPFC ($F(2,32) = 37.21$, $p < .001$) showed task effects, driven by greater activation for remembered than both forgotten (p's $< .001$) and classify (parietal, $p < .01$; DLPFC, $p < .001$) trials, with no difference between forgotten and classify trials (p's $> .05$).

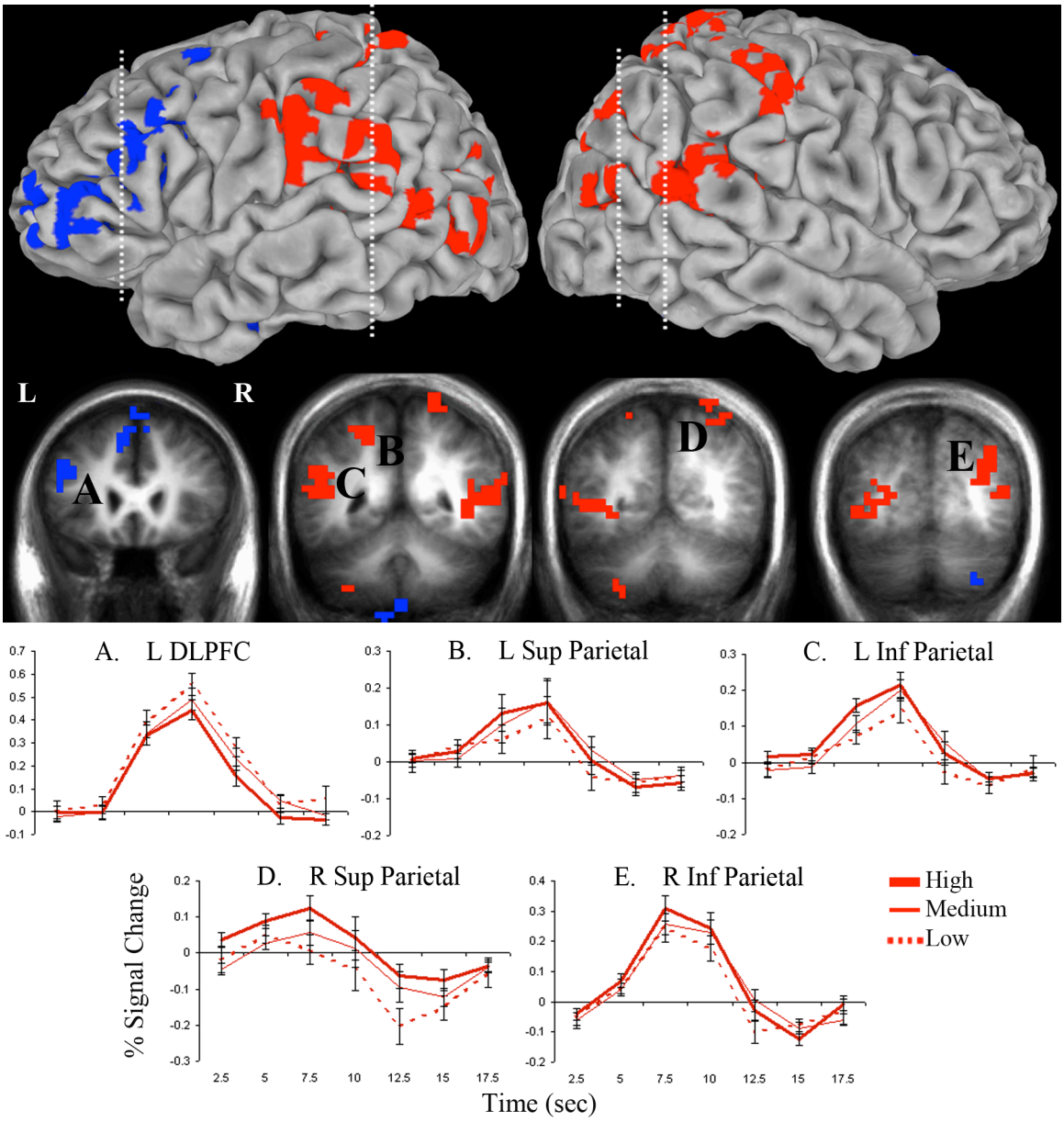

Figure 3.5: Regions modulated by memory strength, but not significantly activated by search. Statistical activation map showing areas with increasing (red) or decreasing (blue) activity with increasing study-level during recall ($p < .05$, corrected for multiple comparisons), with an exclusion mask of regions in which activity differed ($p < .05$) between the forgotten and classify trials. Clusters are overlaid on the lateral pial surface of the Talaraich and Tournoux N27 average brain and coronal cross-sections (indicated with dashed lines) of the mean anatomical image of all subjects. Graphs display the time-course of the percent signal change (± standard error) in left dorsolateral prefrontal cortex (A) and left and right superior (B, D) and inferior (C, E) parietal cortex for low, medium and high-study recall conditions.

Discussion

The present study identified distinct sets of brain regions in which BOLD signals were differentially regulated by the attempt to retrieve an episodic memory and the strength of a recalled memory. Although behavioral measures of mental search and memory strength may be highly correlated, these findings indicate that these separable components of memory retrieval evoke dissociable brain activity. Areas of the default network, including medial and inferior lateral parietal cortex, DMPFC, superior temporal cortex and temporal pole, were more strongly deactivated during task conditions that required retrieval attempts than during a non-memory task, but were not modulated by memory strength. In contrast, activations in DLPFC and regions of superior and inferior parietal cortex depended on the strength of a recalled memory but were not differentially modulated by retrieval attempt. Search- and strength-driven responses overlapped in dorsal anterior cingulate and anterior insula, which were both activated during attempted retrieval and modulated by memory strength.

Dissociating retrieval strength from search

The cascade of neural processes required for recollection may be initiated by control or attentional mechanisms that guide sequential search processes necessary for any non-spontaneous, effortful recall attempt (Nobel and Shiffrin, 2001). The extent to which brain regions subserving mental search are engaged during successful recall may be modulated in part by the strength of the recalled memory; however, strength should contribute minimally if at all, to search-driven signals when a memory is not retrieved. Although memory strength is expected to increase parametrically with increasing study

repetitions (de Zubicaray et al., 2010), the degree of mental search required to retrieve a studied association may not necessarily follow an identical parametric modulation, but may be influenced by alternative factors.

This study developed distinct operational definitions of search and recall strength to dissociate 1) activations related to retrieval attempt that do not vary according to memory strength from 2) responses that depend on the strength of a recalled memory but are not strongly modulated by retrieval attempt. In the current study directed search for an episodic memory should not occur during the classify task, which should only require semantic search processes, but is expected to be engaged during the recall task regardless of retrieval success. Therefore, search-related activity was operationalized as a greater response during both remembered and forgotten recall trials than classify trials. The subset of activations related to retrieval strength, which might be weakly present in these contrasts (Table 3.1), was excluded by identifying effects of study repetition on the activity.

Differences in retrieval strength were identified by comparing successful recall of word pairs recently encountered with varying repetition. Critically, since these conditions did not differ according to recall success, effects should be predominantly driven by the variable strengths of the retrieved associations. To better isolate differences associated with recollection strength from confounding effects of search associated with unsuccessful retrieval, only remembered trials were included in the study-level comparison and an exclusion mask of the forgotten versus classify contrast was applied. Nevertheless, due to the inherent correlation between search and strength, this definition cannot comprehensively capture all strength-related activity while purely excluding

search; rather than perfectly isolating strength-driven responses, it more likely reflects above-threshold strength signals that are minimally contaminated by search processes.

Default network deactivates during effortful retrieval attempts

Task conditions that selectively required memory search deactivated several regions traditionally associated with the default network. This finding is consistent with prior research that default network activity is reduced during the performance of attentionally demanding, goal-directed tasks (Buckner et al., 2008; McKiernan et al., 2003; Raichle et al., 2001; Shulman et al., 1997), such as the effortful mental search required in this cued recall task. Activity in the default network positively correlates with medial temporal memory regions and negatively correlates with regions subserving attention and working memory (Fox et al., 2005; Greicius et al., 2003; Greicius et al., 2004; Newton et al., 2010), and is regulated by retrieval effort, success or memory strength (Daselaar et al., 2009; Gimbel and Brewer, 2011; Henson et al., 2005; Kim, 2010). Prior studies have shown correlated activity in the hippocampus and default network during attempted recall, which is most strongly deactivated for poorly remembered associations (Reas et al., 2011). In the present study, although the hippocampal response during successful recall was below threshold, the hippocampal response during failed recall was robustly deactivated, consistent with Reas et al. (2011). Despite evidence for default network activations during memory retrieval, which are generally attributed to autobiographical or self-referential task conditions (Andreasen et al., 1995; Maguire, 2001; Spreng and Grady, 2010), these results provide further evidence for task-negative responses in these regions during effortful episodic memory

retrieval (Gimbel and Brewer, 2011; Israel et al., 2010) which may be driven by mental search processes (Reas et al., 2011). Furthermore, they expand upon prior studies, which did not simultaneously assess effects of search and associative memory strength, to reveal that default network deactivations are more likely attributable to search than retrieval strength differences.

BOLD signal magnitude during retrieval can correlate with factors linked to response-time, including the temporal duration of memory search or linear summation of the physiological response to time-on-task (Yarkoni et al., 2009). The primary search and strength analyses therefore controlled for this potential confound by including response time as an independent regressor. However, since more demanding, extended search efforts are expected to delay responses, this study also examined how retrieval response times modulate BOLD signal amplitude. Subregions of the default network demonstrated a negative correlation with response time during episodic retrieval attempt. This correlation was not as strong during the non-memory classification task; however the dynamic range of reaction time was smaller for this task, and so one cannot conclude that default network activity is uniquely modulated by episodic memory search. Nevertheless, together with results from the primary search analysis, these findings support the interpretation that default network suppression is regulated to some degree by episodic memory search, including and beyond its effects on reaction time.

Parietal and dorsolateral prefrontal cortex are modulated by memory strength

Although the parietal cortex is known to serve an essential role in visuospatial attention, working memory and sensory association (Corbetta and Shulman, 2002; Posner

and Petersen, 1990), parietal subregions are also engaged during memory retrieval. However, whether parietal involvement is necessary versus auxiliary for memory retrieval remains unresolved. Imaging studies report increased BOLD responses and event-related potential amplitudes during recognition of previously studies items (Donaldson and Rugg, 1998; Kahn et al., 2004; Konishi et al., 2000; McDermott et al., 2000), as well as signal modulation by recognition confidence level, memory strength, perceived oldness or recollection versus familiarity (Henson et al., 1999; Montaldi et al., 2006; Rugg et al., 1998; Shannon and Buckner, 2004; Smith, 1993; Wheeler and Buckner, 2003; Wheeler and Buckner, 2004; Wilding and Rugg, 1996; Yonelinas et al., 2005). However, inconsistent reports of episodic memory deficits following parietal lesions, and that any impairments are generally mild, suggest that parietal regions indirectly support memory retrieval. In accordance with prior research, the present study confirmed that subregions of superior and inferior parietal cortex are regulated by the strength of a recalled memory, and further demonstrated that this modulation was not significantly associated with the attempt to retrieve.

FMRI studies have identified regions of superior parietal cortex that are sensitive to strength but are also engaged by search. For example, activity in the intraparietal sulcus is regulated by retrieval confidence (Kim and Cabeza, 2007; Montaldi et al., 2006; Moritz et al., 2006; Yonelinas et al., 2005) and is more active for familiarity than recollection. This same region has been implicated in visual and memory search and directing attention for strategic retrieval (Corbetta et al., 2000; Sestieri et al., 2010; Shulman et al., 2001) and demonstrates an early electrophysiological response during episodic memory recall associated with pre-retrieval search processes (Seibert et al.,

2011). Notably, the strength-specific parietal activations in this study did not directly overlap with previously reported attention-related responses in intraparietal sulcus (Corbetta et al., 2000; Seibert et al., 2011; Shulman et al., 2001), consistent with evidence that lateral parietal cortex includes multiple sub-modules that perform distinct supportive roles during memory retrieval (Nelson et al., 2010). Although superior parietal regions might be expected to be engaged by recalling weaker memories or by more effortful retrieval attempts, in the present cued recall task superior parietal responses showed greater activity for the successful retrieval of stronger memories. The diverse functions performed by superior parietal cortex may account for discrepant reports of its activation by search, familiarity and recall of stronger memories (Kim and Cabeza, 2007; Moritz et al., 2006; Seibert et al., 2011; Wheeler and Buckner, 2003). These regions have been implicated in various operations such as allocating attention to task-relevant features, guiding retrieval mode, or performing post-retrieval evaluation (Buckner, 2003; Cabeza, 2008; Ciaramelli et al., 2008; Donaldson et al., 2010; Dosenbach et al., 2007; Vilberg and Rugg, 2008), processes that may be highly engaged during recollection of a strong memory.

Inferior parietal regions are activated during recollection and recognition of more deeply encoded memories (Henson et al., 2005; Iidaka et al., 2006; Shannon and Buckner, 2004; Wheeler and Buckner, 2004; Yonelinas et al., 2005) but are not modulated by familiarity, and inferior parietal lesions selectively impair spontaneous recall while sparing guided retrieval (Berryhill et al., 2007). Consistent with these reports, in this study inferior parietal subregions were regulated by memory strength, demonstrating greater BOLD signal during recall of stronger associations. Critically,

these findings expand upon evidence that recollection activates inferior parietal cortex to reveal that even within recollection, the magnitude of this activation depends upon the strength of the recalled memory. These strength-sensitive parietal regions overlapped with the supramarginal and angular gyri of the temporo-parietal junction, areas implicated in multiple convergent cognitive functions involved in attentional shifts during retrieval (Cabeza et al., 2012). Inferior parietal regions may subserve the spontaneous detection of task-relevant stimuli or reverting attention from the environment to an internal stimulus (Astafiev et al., 2006; Cabeza et al., 2012; Ciaramelli et al., 2008), processes which may be more strongly engaged by the attentional capture of a more deeply encoded memory.

While both dorsolateral prefrontal and parietal cortices were sensitive to memory strength, these effects were inverted between regions, such that DLPFC was more active during weaker recall. DLPFC is functionally connected with superior parietal regions (Dosenbach et al., 2007; Nelson et al., 2010; Seeley et al., 2007) and may interact with these areas to guide retrieval mode or perform strategic monitoring during retrieval (Ciaramelli et al., 2008; Donaldson et al., 2010; Henson et al., 1999; Rugg et al., 2003). A reversal of strength effects in DLPFC supports previous interpretations that during retrieval, parietal responses signal retrieval success whereas frontal regions may perform error monitoring processes (Donaldson et al., 2010) that would be enhanced during retrieval of poorer memories. It is possible that differences associated with performing post-retrieval classification may have contributed to differences between strength conditions. However, this is unlikely to be the predominant source of the observed strength effects, given prior reports that the same prefrontal and parietal regions are

engaged during retrieval tasks that do not involve semantic classification. Collectively, these findings suggest that lateral prefrontal and parietal regions integrate distinct retrieval-related attention and cognitive control processes that depend upon the strength of the retrieval event.

Dissociable networks with overlapping nodes subserve retrieval strength and search

Although search- and strength-driven responses were largely dissociable, dorsal anterior cingulate and anterior insula were both responsive to memory search and more active during recall of weaker associations. This is consistent with evidence that these areas are involved in the execution of various cognitive control processes that may indirectly support episodic memory retrieval such as goal-directed cognition, stimulus salience processing and task set maintenance, and may mediate these functions by integrating information from external and internal sources, or across multiple domains such as attention or working memory. Activation of these regions by both retrieval effort and memory strength provides support for their role in multi-domain control processing and is consistent with reports that these regions subserve functions as diverse as working memory, personal salience assessment, autobiographical or spatial planning (Seeley et al., 2007; Spreng et al., 2010; Vincent et al., 2008).

Furthermore, dorsal anterior cingulate and anterior insula have been identified as nodes of a centralized control center, or frontoparietal control network, that integrates widespread signals from distinct, interactive neural networks. The functional-anatomical correlates of strength and search identified in this study correspond well with these intersecting attention and default networks. Prior studies have reported that these

networks are anti-correlated or are engaged by tasks demanding attention or externally directed thought on the one hand, and passive or internally directed processing on the other (Dosenbach et al., 2007; Kim, 2010; Seeley et al., 2007; Spreng et al., 2010; Vincent et al., 2008). Regions of these networks functionally dissociated during performance of this associative recall task, demonstrating differential sensitivities to retrieval effort and memory strength.

Conclusions

Multiple interactive neurocognitive processes may underlie brain activations during guided episodic memory retrieval. The present investigation reveals that, although highly correlated, retrieval effort and recollection strength mediate distinct responses in dissociable sets of brain regions. The finding of separable but overlapping search and strength areas, which correspond anatomically with three previously identified cortical networks, advances our understanding of the functional role of these default, attention and cognitive control networks in episodic memory retrieval.

Acknowledgments

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CHAPTER 4:

EFFORTFUL RETRIEVAL REDUCES HIPPOCAMPAL ENCODING ACTIVITY AND IMPAIRS INCIDENTAL ENCODING

Abstract

Functional imaging studies frequently report that the hippocampus is engaged by successful episodic memory retrieval. However, considering that concurrent encoding of the background environment occurs during retrieval and influences medial temporal lobe activity, it is plausible that hippocampal encoding functions are reduced with increased attentional engagement during effortful retrieval. Expanding upon evidence that retrieval efforts suppress activity in hippocampal regions implicated in encoding, this study examines the influence of retrieval effort on encoding performance and the interactive effects of encoding and retrieval on hippocampal and neocortical activity. Functional magnetic resonance imaging was conducted while subjects performed a word recognition task with incidental picture encoding. Both lower memory strength and increased search duration were associated with encoding failure and reduced hippocampal and default network activity. Activity in the anterior hippocampus tracked encoding, which was more strongly deactivated when incidental encoding was unsuccessful. These findings highlight potential contributions from background encoding processes to hippocampal activations during neuroimaging studies of episodic memory retrieval.

Introduction

Episodic memory is frequently investigated as a system comprising two distinct yet complementary functions. The first involves encoding the features of an experience into memory, a process mediated largely by the brain's medial temporal lobe. The second is the subsequent retrieval of a memory from storage, via interactions between medial temporal regions and neocortical association areas to reactivate representations of the episodic features (for review of the medial temporal lobe in episodic encoding and retrieval, see Schacter and Wagner, 1999; Squire et al., 2004; Squire and Zola-Morgan, 1991). However, encoding processes cannot be cleanly dissociated from retrieval, and a deeper understanding of their functional interactions is critical to elucidating the mechanisms of episodic memory. For instance, the intent to retrieve a memory (Buckner et al., 2001) or retrieval success (Huijbers et al., 2009) can influence further encoding of both task-relevant and task-irrelevant information, and memory decisions can bias subsequent operations towards encoding or retrieval (Duncan et al., 2012). Psychological models of memory propose that encoding and retrieval can operate concurrently and may facilitate or compete with one another (Glover, 1989; Storm et al., 2006; Tulving and Thomson, 1973). While evidence suggests medial temporal lobe subregions play distinct roles that span encoding and retrieval, it remains unclear how the interaction between encoding and retrieval is mediated by such subregions, which are integrated and mostly thought to subserve both functions.

The role of the hippocampus in encoding episodic memories has been established by evidence from patients with hippocampal damage (Scoville and Milner, 1957), animal electrophysiology and lesion studies (Leutgeb et al., 2005; Suzuki and Eichenbaum,

2000; Wirth et al., 2003; Wood et al., 2000; Zola-Morgan et al., 1994), and supported by human local field potential (Fernandez et al., 1999) and functional neuroimaging studies (Brewer et al., 1998; Wagner et al., 1998), demonstrating post-lesion anterograde and temporally graded retrograde amnesia as well as increased neuronal and metabolic activity during successful encoding. Although the medial temporal lobe has also been strongly implicated in memory retrieval, there is conflicting evidence over the circumstances under which the hippocampus is involved in retrieval. While some human neuroimaging studies fail to report hippocampal responses during retrieval, others indicate that the hippocampus signals successful recollection or familiarity (Eldridge et al., 2000; Gabrieli et al., 1997; Schacter et al., 1996; Stark and Squire, 2000; Wais et al., 2010b) or the retrieval of strong memories or contextual details (Cansino et al., 2002; Ross and Slotnick, 2008; Wais, 2011; Yu et al., 2011). Thus, while functional imaging has failed, as yet, to delineate the bases for hippocampal involvement in retrieval, a general consensus over hippocampal involvement in encoding exists. As such, it is important to consider possible contributions from encoding processes to hippocampal responses observed during retrieval tasks that would otherwise be attributed directly to retrieval functions. Activity in the medial temporal lobe has been shown to vary with shifts in attentional focus that fluctuate with dynamic retrieval demands (Nee and Jonides, 2008). Thus, any component of retrieval, including 1) reactivation that facilitates memory recovery or 2) cognitive control operations directing search efforts, could interfere with ongoing encoding functions, an interaction that would be evidenced by a diminished response in hippocampal regions that mediate encoding.

Indeed, there is evidence that encoding processes remain online during memory retrieval and are tracked by medial temporal lobe regions that support episodic memory. Incidental encoding of novel stimuli occurs during recognition tasks and is associated with encoding-dependent modulation of frontal (Buckner et al., 2001) and hippocampal (Stark and Okado, 2003) activity. For instance, Stark and Okado (2003) report that hippocampal responses during a scene recognition task were greater to subsequently remembered than forgotten non-target foils, an effect also observed during an intentional scene encoding task. Additional evidence demonstrates that even task-irrelevant information of the background environment can be encoded during memory retrieval and suggests a competitive interaction between encoding and retrieval mechanisms (Huijbers et al., 2009). In their study, Huijbers et al. (2009) report that successful, relative to failed, word recognition, impaired incidental encoding of simultaneously presented scenes, and activity in areas of the medial temporal lobe and visual cortex associated with encoding success was reduced during encoded hit compared to encoded miss trials. Together, these observations suggest that encoding of both task-relevant and task-irrelevant information remains active during retrieval, may be mediated by retrieval task demands and, in conjunction with retrieval processes, interactively regulates activity in regions of the medial temporal lobe.

Prior functional magnetic resonance imaging (fMRI) studies provide evidence for an increased hippocampal blood oxygen level dependent (BOLD) signal by retrieval success (for review see Eichenbaum et al., 2007), as well as increasing hippocampal activity with increasing recognition confidence, consistent with nonlinear recollection (Daselaar et al., 2006) or linear familiarity signals (Kirwan et al., 2009). However,

memory strength is correlated with attention and cognitive control functions that support retrieval efforts. Recent findings suggest that the hippocampal response to retrieval success or strength can be driven in part by attentional demands of the retrieval task, such as engaging in retrieval mode or directed memory search (Israel et al., 2010; Reas et al., 2011). These studies identified a negative BOLD signal change in anterior hippocampus associated with retrieval attempt that is amplified by both response time and difficulty of retrieving the memory. Anterior hippocampal activity during retrieval is correlated with activity in regions of the default network (Huijbers et al., 2011; Israel et al., 2010; Reas et al., 2011), which has been shown to deactivate in response to increasing attentional demands across a variety of cognitive states (Buckner et al., 2008; McKiernan et al., 2003; Raichle et al., 2001). Considering the previously discussed evidence that episodic memory encoding is heavily dependent on the hippocampus and that brain processes underlying concomitant encoding functions may contribute to activations during retrieval, hippocampal deactivation during retrieval has been linked to a reduction in background encoding processes, which may be modulated by attentional engagement during the retrieval attempt (Reas et al., 2011).

The present study directly tested whether the magnitude of deactivation in the anterior hippocampus during retrieval, previously associated with memory search efforts, is related with incidental encoding of task-irrelevant information. During event-related fMRI subjects performed a recognition test on previously studied words with concurrent picture presentation, and incidental encoding was measured by a subsequent picture recognition test. Based on evidence for a dissociation of memory functions along the long axis of the hippocampus (Daselaar et al., 2006; Lepage et al., 1998; Prince et al., 2005),

region of interest analyses of encoding-retrieval interactions were performed in anterior, middle and posterior hippocampus. Whole brain analysis was conducted to identify regions outside the hippocampus sensitive to retrieval search demands and correlated with hippocampal activity. Words were studied as paired associates in order to trigger greater search for associated episodic features in response to word cues as well as to increase dependence of the retrieval response on the hippocampus, which may selectively support memories with multiple attributes (Wixted and Squire, 2011). Study repetitions were varied to manipulate memory strength, and hence the degree of search required for retrieval. Given the correlation between memory strength and retrieval search demands, behavioral or neural effects of study repetitions could be explained either by higher memory strength or attenuated search levels driven by greater study. While we acknowledge the longstanding semantic ambiguity that exists for the term "search", it will henceforth be used to refer broadly to the attentional operations under an individual's control that guide the evaluation of stored information during a directed retrieval attempt (Atkison and Shiffrin, 1968).

Competing hypotheses were tested to investigate the behavioral interactions between encoding and retrieval as well as the neural correlates of such interactions. Activity in the anterior hippocampus was expected to be regulated by incidental encoding, resulting in greater activation during trials with subsequently remembered than forgotten pictures. Alternative hypotheses were constructed regarding the interaction between encoding performance and memory strength or success. First, based on the interpretation that the previously reported hippocampal deactivation during effortful retrieval is associated with suppressed encoding functions (Reas et al., 2011), we

proposed that encoding would be impaired during word recognition trials for lower strength memories. Such lower strength memories are assumed to elicit more demanding search efforts, relative to trials for higher strength memories. If memory search was found to reduce encoding, hippocampal activity was predicted to be modulated by pre-retrieval search duration, approximated by response times, and correlated with activity in regions previously shown to be sensitive to retrieval search efforts including medial prefrontal, superior temporal and medial and lateral parietal cortex. Second, if retrieval success rather than the attentional demands of the retrieval task interfere with encoding (Huijbers et al., 2009), then encoding should be worse during word recognition hit than miss trials. This might be expected if the neural resources for encoding and retrieval directly overlap and are depleted by concurrent retrieval, or if a recovered memory captures internal attention and diverts it away from the external environment.

Methods

Participants

Twenty right-handed, English-speaking volunteers with normal or corrected vision participated in this study. All subjects were recruited from the University of California, San Diego (UCSD) community and surrounding areas and gave informed written consent in accordance with criteria of the UCSD Institutional Review Board. Three participants were excluded from further analysis due to excessive motion, word recognition accuracy more than three standard deviations below the mean, or below chance picture recognition accuracy. Data from the remaining seventeen participants (seven male, mean age ± standard deviation = 26.2 ± 4.0 years) are reported.

Stimuli

Stimuli for the word recognition task included 240 English nouns (Reas et al., 2011), divided into sets of 80 low-study targets, 80 high-study targets and 80 novel foils. 360 color pictures of everyday objects (Bakker et al., 2008) were used in the incidental picture encoding task, including 240 target images and 120 novel foils.

Experimental paradigm

During a pre-scan associative memorization task, participants were presented word pairs and instructed to remember each word pair association. Half of the paired associates were presented once and half were presented four times and are thus referred to as low-study and high-study, respectively. Words were pseudorandomly combined into 80 pairs and presented in 200 trials over the course of four 200-second study runs. Each pair was displayed for three seconds, followed by a fixation cross for one second (Figure 4.1, left).

After a delay of approximately 20 minutes, event-related fMRI data were acquired while participants performed a word recognition task with concurrent incidental picture encoding. In each trial a black box and a red box were presented for 1000 msec, the red box serving as a cue for the stimulus location, which was the same as the location at study. A previously studied or novel word appeared in the red box for 250 msec, followed by a picture for 750 msec and visual masking noise for 2000 msec (Figure 4.1, right). Participants were instructed to respond “old” or “new” to indicate whether the presented word was previously studied or novel by responding with their right hand using

two buttons of a response box. They were given no explicit instructions to remember the pictures, but were told to respond as quickly and accurately as possible while attending to both the word and picture in each trial. Trials were jittered with 0.5-10 seconds of fixation baseline, calculated to optimize the study design for modeling the hemodynamic response to trials (Dale, 1999; Dale and Buckner, 1997). Eighty low-study, 80 high-study and 80 novel words were pseudorandomly distributed across five 388-second runs. Word assignment to the three conditions was randomized and counterbalanced across participants. Each picture was randomly paired with a word, and pairing between pictures and word-condition (low-study, high-study, novel) was counterbalanced across participants.

After scanning, participants completed a brief distractor task of serial 7s subtraction to minimize recency effects before proceeding to further testing. A surprise, self-paced picture recognition test was then administered using the 240 target pictures that had been previously presented during the word recognition test along with 120 novel foils. Participants were instructed to respond “old” or “new” to indicate whether the picture was previously shown or novel. Lastly, a self-paced cued recall test was administered to assess associative memory for each word pair. One word from each pair was presented and participants verbally reported the word’s pair.

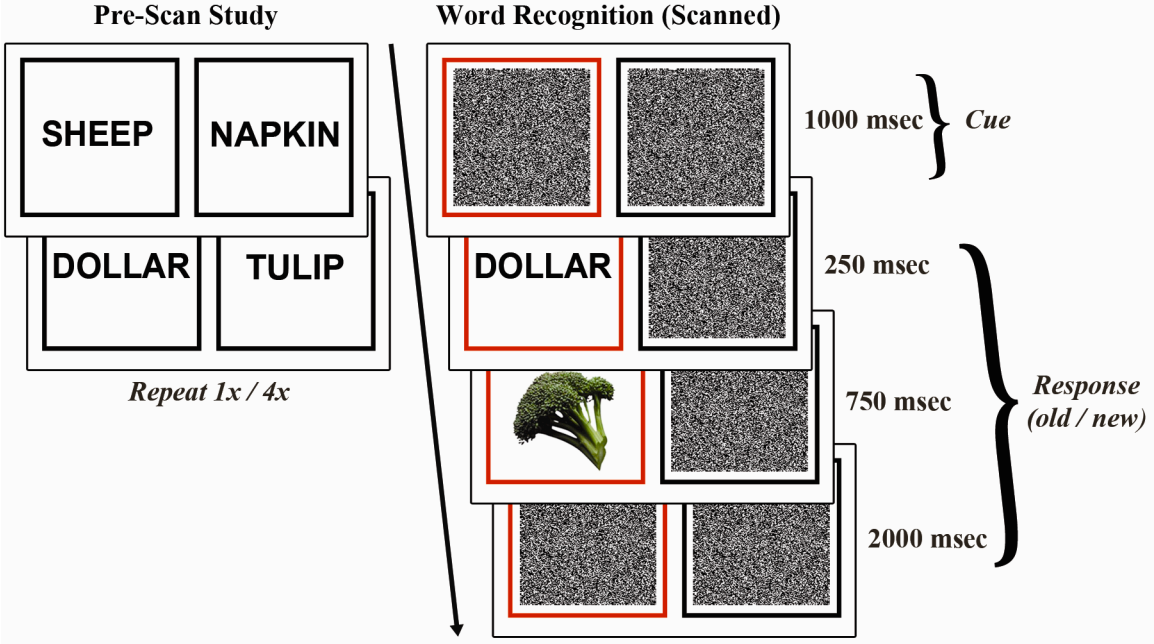

Figure 4.1: Behavioral protocol. Left: Prior to scanning, subjects studied word pair associates. Low-study pairs were presented once and high-study pairs were presented four times. Right: During event-related fMRI, subjects performed a word recognition task with incidental picture encoding. A previously studied or novel word was presented, immediately followed by a picture. Subjects were instructed to respond "old" or "new" to the word and attend to both the word and picture.

fMRI data acquisition

Imaging was performed using a 3.0 Tesla General Electric scanner at the UCSD Keck Center for Functional MRI. Field maps were acquired to measure and correct for static field inhomogeneities (Smith et al., 2004). Functional data were acquired using a gradient-echo, echo-planar, T2*-weighted pulse sequence (time repetition = 2.5 s, one shot per repetition, echo time = 30, flip angle = 90°, bandwidth = 31.25 MHz, field of view = 220 mm, matrix = 64 x 64). Each functional volume contained forty slices (in-plane resolution = 3.4 x 3.4 mm, slice thickness = 4 mm) oriented perpendicular to the long axis of the hippocampus. The first five volumes were discarded to allow for signal

equilibration. A high resolution T1-weighted anatomical scan (1 × 1 × 1 mm) was acquired using an inversion recovery prepared spoiled gradient recalled sequence providing high grey-white contrast for anatomical delineation. An additional T1-weighted structural scan was acquired in the same plane and of the same voxel size as the functional scans to confirm alignment between the functional and high-resolution anatomical images.

fMRI data processing

Functional data were corrected for spatial distortions using field maps (Smith et al., 2004), and data from each of five runs were reconstructed using the AFNI suite of programs (Cox, 1996). Slices were temporally aligned and co-registered using a three-dimensional image alignment algorithm. Non-brain voxels were removed using a threshold mask of the functional data. Functional runs were smoothed with a 4 mm full-width half-maximum Gaussian blur, corrected for motion and concatenated. Anatomical images and the functional data were normalized to Talairach space (Talairach and Tornoux, 1988) after manually defining standard landmarks on the anatomical images.

The region of interest large deformation diffeomorphic metric mapping (ROI-LDDMM) alignment technique was applied to improve alignment of the medial temporal lobe between subjects (Miller et al., 2005). For each subject, previously described landmarks were used to define medial temporal lobe subregions, including the hippocampus (Chera et al., 2009), perirhinal and entorhinal cortices (Insausti et al., 1998) and parahippocampal cortex (Stark and Okado, 2003), on Talairach transformed images. These anatomical regions of interest for each subject were normalized using ROI-

LDDMM to a modified model of a previously created template segmentation (Kirwan et al., 2007). Functional imaging data underwent the same ROI-LDDMM transformation as was applied to the anatomical data.

Whole brain analysis

To examine effects of study repetitions and incidental encoding during retrieval, word recognition trials were sorted according to word condition (low-study, high-study, novel) and picture encoding (subsequently remembered or forgotten, henceforth referred to as "encoded" and "not-encoded"), yielding six trial classes for multiple regression analysis: low-study encoded, low-study not-encoded, high-study encoded, high-study not-encoded, novel encoded and novel not-encoded. In a separate regression analysis to examine effects of retrieval success and encoding, trials were sorted according to word recognition success (hits, misses, correct rejections, and false alarms) and picture encoding. Multiple regression analysis was performed by generating a general linear model with regressors for each of the task conditions along with six motion regressors obtained from the registration process. Signal deconvolution with TENT basis functions (Cox, 1996) was used to estimate the hemodynamic response for each condition for the 15 seconds following the stimulus onset. T-tests ($p < .01$, two-tailed and corrected for multiple comparisons) were performed on parameter estimates from the 5-10 second period of each condition, selected based on reported peak of impulse response curves from a prior study using a similar task (Reas et al., 2011).

Amplitude-modulated regression was conducted to identify regions in which the magnitude of the BOLD response correlated with response time. A general linear model

was constructed with six regressors for each condition, sorted according to word type and encoding (low-study words, encoded pictures; low-study words, not-encoded pictures; high-study words, encoded pictures; high-study words, not-encoded pictures; novel words, encoded pictures; novel words, not-encoded pictures), six regressors for each condition weighted by response times, and six motion regressors. The magnitude of BOLD signal modulation by response time across all trials was estimated from the response-time-weighted regressors. Group-level t-tests were performed on the resulting correlation maps ($p < .01$, corrected for multiple comparisons).

Functional connectivity analysis was performed using the anatomically defined bilateral anterior hippocampus as a seed region (http://afni.nimh.nih.gov/sscc/gangc/SimCorrAna.html). Each subject's whole brain connectivity map was tested for an interaction of the correlation with study-level (low-study vs. high-study) and encoding (encoded vs. not-encoded), and group-level t-tests ($p < .01$, corrected for multiple comparisons) were performed on the resulting interaction maps.

For all whole-brain analyses, correction for multiple comparisons was computed using a Monte Carlo simulation on a whole-brain functional volume in AFNI (http://afni.nimh.nih.gov/pub/dist/doc/program_help/3dClustSim.html) to determine the minimum cluster size necessary to achieve a family-wise error rate of $p < .05$ with a voxel-wise threshold of $p < .01$. Significant clusters, including at least six contiguous voxels, were displayed on a statistical map overlaid onto an across-subject averaged structural image.

Hippocampal ROI analysis

A structural mask was drawn on the across-subject averaged T1-weighted anatomical image to divide the hippocampus into left and right anterior (y = -7 to -18), middle (y = -19 to -26) and posterior (y = -27 to -38) regions of interest. The hemodynamic response function in each hippocampal subregion was extracted and averaged across subjects to examine the signal time-course in an impulse-response plot, and beta-values from 5-10 seconds after stimulus onset were submitted to repeated-measures analysis of variance (ANOVA).

Behavioral Results

In the word recognition task, subjects responded "old" to 64 (± 4) % (mean ± standard error) of low-study words, 90 (± 2) % of high-study words and correctly rejected 88 (± 3) % of novel words (Figure 4.2, top left). D' values, computed as *z(hit rate) – z(false alarm rate)*, were higher for high-study than low-study words (2.8 ± 0.2 vs. 1.7 ± 0.2; $t(16) = 10.24$, $p < .001$). Response times differed by word condition ($F(2,32) = 17.33$, $p < .001$) and were faster for high-study (1086 ± 65 msec) than low-study (1264 ± 77; $p < .001$) and novel (1276 ± 82 msec; $p < .001$) trials (Figure 4.2, bottom left). Post-scan cued recall was more accurate for high-study than low-study word pairs (78 ± 5 vs. 37 ± 6%; $t(16) = 9.48$, $p < .001$), confirming better associative memory for more highly studied pairs.

D' scores were calculated for the post-scan picture recognition task to assess incidental picture encoding during the scanned word recognition task. D' values were significantly above chance (.78 ± .10; $t(16) = 7.76$, $p < .001$), indicating that subjects

successfully encoded the pictures despite no explicit memorization instructions. Picture encoding differed by word condition ($F(2,32) = 4.17$, $p < .05$), with better subsequent memory for pictures paired with high-study than low-study words (.86 ± .10 vs. .68 ± .10; $p < .01$; Figure 4.2, top right). Encoding did not differ between pictures paired with novel words and those paired with either of the old-word conditions (ps > .05) or between hit and miss trials ($p = .22$). To test the effect of study-level on incidental encoding with retrieval success held constant, the analysis was performed on hit trials only, comparing the low-study versus high-study conditions. In addition, to test effects of retrieval success within a strength condition, low-study hits were compared to low-study misses. Picture encoding d' scores were better for high-study than low-study hits (.86 ± .11 vs. .65 ± .11; $t(16) = 2.74$, $p < .05$), but did not differ between low-study hits and misses ($p = .71$), indicating an effect of study-level, but not retrieval success, on encoding. High-study misses were too infrequent to allow analysis of this effect within the high-study condition on all subjects. However, a separate ANOVA on a subset of fourteen subjects confirmed a main effect of study-level on incidental encoding (high-study: .85 ± .12, low-study: .58 ± .09; $F(1,13) = 8.23$, $p < .05$), but no effect of retrieval success ($p = .45$) nor interaction between study-level and retrieval success on encoding ($p = .54$). Response times were longer for trials associated with unsuccessful than successful picture encoding (1240 ± 72 vs. 1157 ± 71 msec; $t(16) = 4.58$, $p < .001$). Response times remained longer for not-encoded than encoded trials when comparing low-study trials alone (1293 ± 77 vs. 1210 ± 81 msec; $t(16) = 2.71$, $p < .05$) and a trend for this effect was observed for the high-study condition ($p = .09$), suggesting an effect of response time on encoding success beyond the effect of study-level.

To investigate whether subjects with superior word recognition would also demonstrate better incidental encoding or conversely, might more effectively inhibit task-irrelevant information and thus show diminished encoding, the Pearson's correlation between word and picture recognition d' scores were computed. Word and picture recognition d' scores were positively correlated, such that subjects with better word recognition also demonstrated better incidental encoding ($r = 0.75$, $p < .001$). Although encoding did not significantly differ between word recognition hit and miss trials, if successful encoding were more frequent during successful word recognition, this correlation could have been related to the higher frequency of word hits in higher performing subjects. Therefore, to control for word recognition hit rates, picture recognition d' scores were computed separately for word recognition hit and miss trials and hit and miss d' scores were subsequently averaged. After correction, word recognition and picture encoding remained positively correlated across subjects ($r = 0.76$, $p < .001$, Figure 4.2, bottom right).

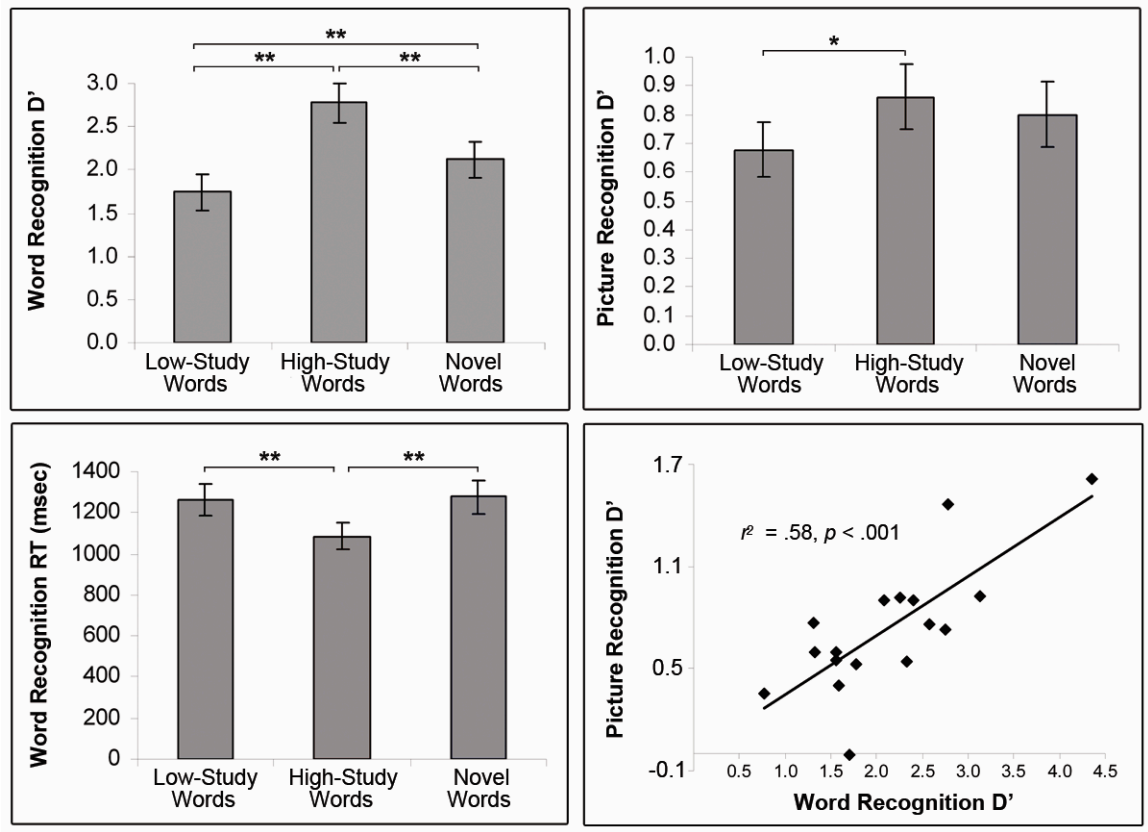

Figure 4.2: Behavioral performance. Mean (± standard error) word recognition accuracy (top left; low-study vs. high-study d': 1.7 ± 0.2 vs. 2.8 ± 0.2; $t(16) = 10.24$, $p < .001$), word recognition response times (bottom left) and picture recognition d' values (top right) for low-study, high-study and novel word trials. Recognition d' scores are plotted for old words (x-axis) and for pictures presented during old-word trials (y-axis) for each subject (bottom right). * $p < .01$, ** $p < .001$

fMRI Results

Hippocampal responses to encoding and retrieval

To confirm consistency with prior reports of hippocampal activity associated with memory strength, retrieval success or encoding success, general linear tests contrasted 1) high-study > low-study trials, 2) word hits > misses, 3) word hits > correct rejections, and 4) encoded > not-encoded pictures. Greater BOLD responses ($p < .01$) were observed for

hits than misses throughout bilateral hippocampus, for hits than correct rejections throughout left and middle right hippocampus, and for encoded than not-encoded pictures in bilateral anterior hippocampus. At a reduced threshold ($p < .05$, corrected for multiple comparisons), activity throughout the body of the right hippocampus was greater for high-study than low-study trials.

BOLD responses in the anatomically defined anterior, middle and posterior hippocampus were analyzed to examine how concurrent picture encoding and memory strength or search might interact to influence hippocampal activity. Repeated measures ANOVA was performed with factors of region (anterior, middle, posterior), hemisphere, word condition (low-study, high-study, novel) and incidental picture encoding (encoded, not-encoded). A main effect of region ($F(2,32) = 8.56$, $p < .01$) reflected less activity in anterior than middle ($p < .05$) and posterior ($p < .01$) subregions, and an effect of word condition ($F(2,32) = 3.50$, $p < .05$) revealed that high-study words elicited greater activation than novel words across all regions ($p < .01$). An interaction between region and encoding ($F(2,32) = 4.41$, $p < .05$) was also observed. Bilateral anterior hippocampus demonstrated greater activation during trials with successful than unsuccessful picture encoding ($F(1,16) = 5.74$, $p < .05$; Figure 4.3, top), and a trend for an encoding by word condition interaction ($p = .05$). Impulse response curves revealed a task-negative BOLD signal change, such that anterior hippocampus was more strongly deactivated during not-encoded than encoded trials. In contrast, responses in middle and posterior bilateral hippocampus were not associated with subsequent picture memory ($ps > .10$), but showed main effects of word condition (middle: $F(2,32) = 4.13$, $p < .05$; posterior: $F(2,32) =$

3.63, $p < .05$), reflecting greater task-positive activation to high-study than novel words (ps < .01; Figure 4.3, bottom).

Behavioral results indicated that incidental picture encoding success was influenced by study-level, but not by recognition success. However, to test whether recognition success and encoding might interactively regulate hippocampal activity, a second ANOVA was performed on old word recognition trials with factors of region, hemisphere, recognition success (hit, miss) and incidental picture encoding. One subject was excluded from this analysis due to word recognition performance at ceiling. Across all regions, hippocampal activity was greater for hit than miss trials ($F(1,14) = 7.50$, $p < .05$) and recognition success interacted with region $F(2.28) = 5.63$, $p < .01$). Anterior ($F(1,14) = 6.02$, $p < .05$) and middle ($F(1,14) = 14.16$, $p < .01$) hippocampus demonstrated greater activity during hit than miss trials, and posterior hippocampus showed a trend for this effect ($p = .09$). Notably, recognition success did not interact with encoding ($p = .52$), consistent with the behavioral findings that study-level, and not recognition success, interacted with incidental concurrent encoding.

While the between-condition contrasts suggested a general hippocampal sensitivity to memory strength and success, further subregion analyses revealed a spatially selective sensitivity to incidental encoding behaviorally associated with study-level. To investigate encoding-related activity during opposing memory strength or retrieval success conditions, BOLD responses were compared between low-study trials with successful picture encoding and high-study trials with unsuccessful encoding, as well as between word miss trials with successful encoding and word hit trials with unsuccessful encoding. No hippocampal activations were observed for either of these

contrasts, suggesting possible spatial overlap of hippocampus-mediated encoding and retrieval functions.

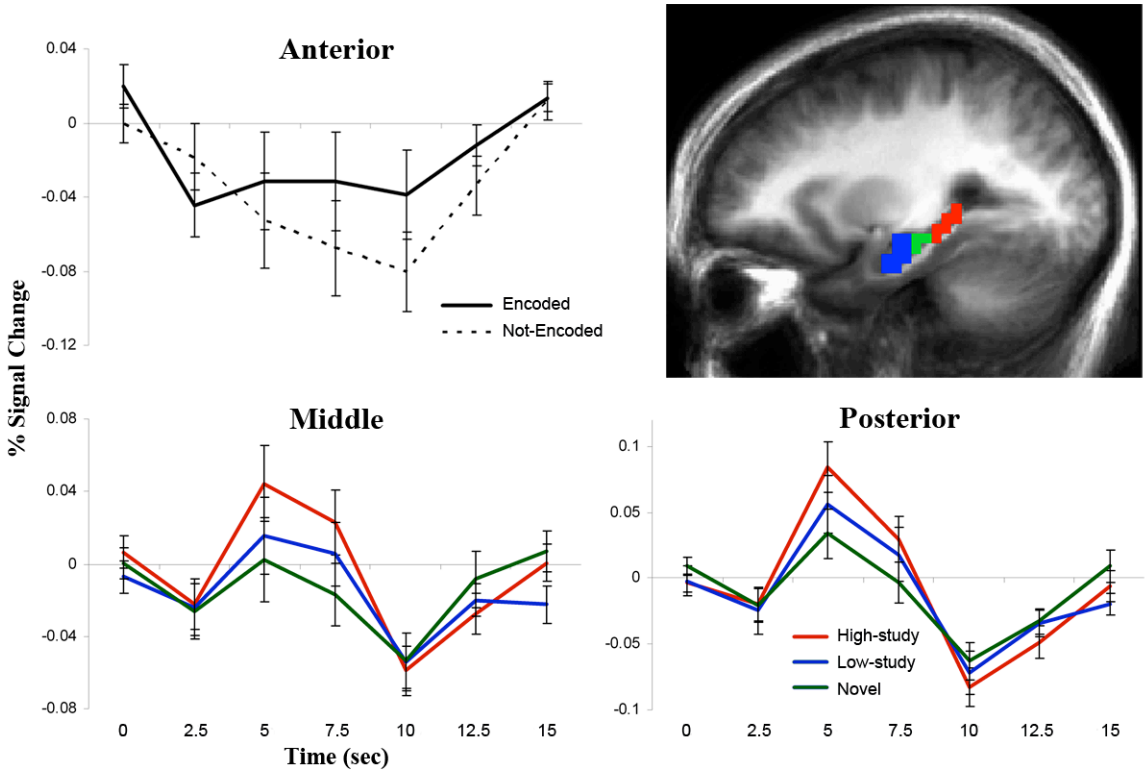

Figure 4.3: Hippocampal BOLD responses. Anterior (blue), middle (green) and posterior (red) hippocampal ROIs are overlaid on a sagittal cross-section of the mean anatomical image of all subjects (top right). Impulse-response plots display the time-course of the percent signal change (± standard error) in anatomically-defined bilateral anterior, middle and posterior hippocampus. Anterior hippocampus was more deactivated during word recognition trials when pictures were not-encoded than encoded ($p < .05$, top left). Middle and posterior hippocampus, which were not influenced by incidental encoding during retrieval ($ps > .10$), were more activated during high-study than novel word recognition trials ($p < .01$, bottom).

Hippocampal and default network deactivation by search

Although hippocampal activity differed between word conditions, time spent at study is correlated with both increased memory strength and reduced search requirements at retrieval; this inherent correlation renders it difficult to dissociate effects of strength

and search based on study-level alone. Since response times are known to positively correlate with degree of memory search (Sternberg, 1966), trial-by-trial BOLD signal modulation by search was measured by correlating BOLD responses with response times across all word recognition trials. Bilateral anterior hippocampus, medial prefrontal cortex, posterior cingulate, superior temporal and left inferior parietal cortex were negatively correlated with response times ($p < .01$), reflecting greater deactivation with longer response times (Figure 4.4). To confirm that this correlation was not influenced by differences in response times between low-study and high-study trials, the analysis was performed separately on these conditions. Response times remained negatively correlated with activity in these regions for the high-study condition ($p < .01$), and for the low-study condition at a reduced threshold ($p < .05$). Neither study-level nor encoding success interacted with the reaction time correlation in these regions. Thus, hippocampal and default network activations were more strongly negative for trials requiring longer pre-response search times, and this dependence upon search duration was robust against differences in memory strength and encoding success.

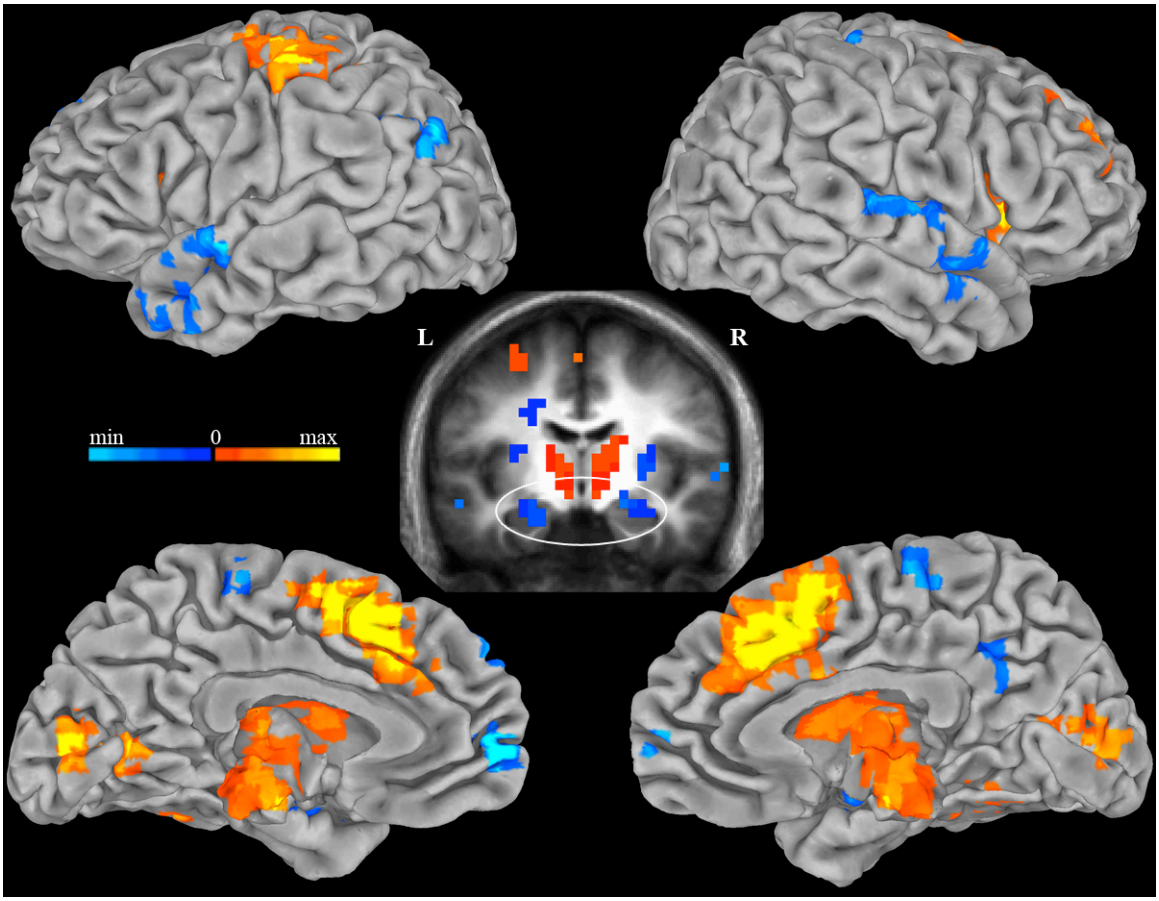

Figure 4.4: Correlation between BOLD signal and response times. Negative correlations between BOLD signal and response times are displayed in cool colors and positive correlations are shown in warm colors ($p < .01$). Significant clusters are overlaid on the pial surface of the Talaraich and Tournoux N27 average brain. A coronal cross-section (y = -10) of the mean anatomical image of all subjects (middle) displays clusters in bilateral anterior hippocampus negatively correlated with response times.

Functional connectivity with the anterior hippocampus

Activity in the anterior hippocampus and default network demonstrated a similar negative correlation with search duration, suggesting possible interactions between these regions that may vary according to attentional fluctuations across retrieval trials. Using a seed region of the structurally-defined bilateral anterior hippocampus, functional

connectivity analysis was conducted to identify hippocampal network activity. To examine how hippocampal connectivity is modulated by study-level and encoding, whole-brain correlation maps were contrasted between low-study and high-study trials, and between encoded and not-encoded trials. Left dorsolateral prefrontal cortex, cingulate gyrus and intraparietal sulcus were more strongly correlated with the hippocampus during the low-study condition ($p < .01$). Hippocampal connectivity with the medial prefrontal cortex, posterior cingulate and left superior temporal cortex was stronger when pictures were not encoded than encoded ($p < .01$, Figure 4.5). Together, these findings show that hippocampus and default network regions simultaneously deactivate with increasing search duration and functionally interact in a manner regulated by trial-by-trial encoding processes.

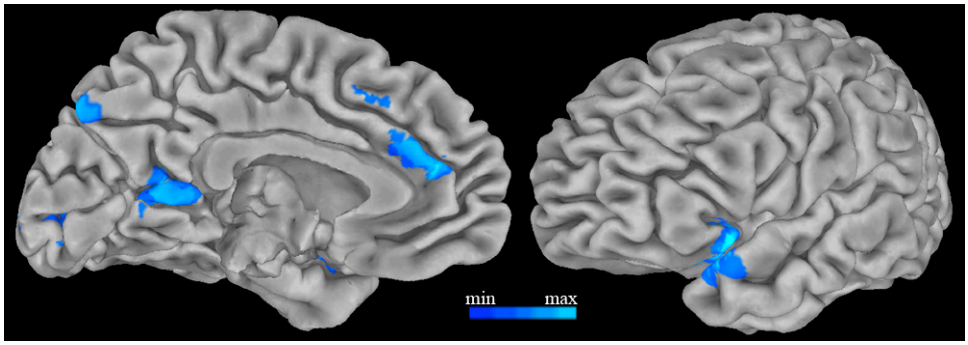

Figure 4.5: Functional connectivity with the anterior hippocampus. Regions showing more strongly correlated activity with the bilateral anterior hippocampus during trials when pictures were not-encoded than encoded ($p < .01$) are displayed on the pial surface of the Talaraich and Tournoux N27 average brain.

Discussion

Hippocampal deactivation tracks encoding performance

Prior findings suggest that regional deactivation of the hippocampus during effortful episodic memory retrieval may reflect suppression of encoding functions by memory search (Reas et al., 2011). The present study examined BOLD responses in anatomically defined hippocampal regions of interest during a combined intentional retrieval with incidental encoding task to determine whether retrieval effort 1) influences concurrent encoding and 2) modulates hippocampus-dependent encoding activity.

Consistent with previous reports, regions of the hippocampus exhibited reductions in activity and the degree of reduction was associated with recall performance. The anterior hippocampal deactivation observed during this recognition task has been previously documented during cued recall of visual (Israel et al., 2010) and verbal (Reas et al., 2011) paired associates. This consistently observed, retrieval-related reduction in hippocampal activity from baseline warrants further discussion. Although retrieval-related differences in hippocampal activity levels are frequently attributed directly to retrieval success, this interpretation fails to account for the finding of highest hippocampal activity before task onset. Any number of mental processes may be active during the less restricted task-free or lower-load inter-trial intervals, including mind wandering, reflection upon a previous trial or anticipation of the next. Though specific cognitive processes comprising the periods between retrieval trials are difficult to fully characterize, the pre-stimulus baseline would not be expected to elicit greater mnemonic retrieval than the retrieval task itself. It is therefore challenging to interpret the reduced BOLD response during recognition as a neural signature of memory retrieval without considering other factors.

The present study demonstrates that during retrieval the anterior hippocampus is also modulated by encoding of task-irrelevant information, exhibiting a larger negative deflection from baseline on word recognition trials during which background pictures were not encoded, relative to trials when pictures were successfully encoded. Simple subtraction of absolute activity level showed greater hippocampal activity for subsequently remembered versus forgotten task-irrelevant stimuli, extending prior evidence for involvement of the hippocampus and adjacent medial temporal lobe in incidental encoding of task-relevant novel (Stark and Okado, 2003) and task-irrelevant background stimuli (Huijbers et al., 2009). Taken together, the results support the hypothesis that baseline elevated hippocampal activity is associated with encoding processes, including those that encode the ongoing stream of task-irrelevant information, that are reduced during effortful retrieval.

Memory search is associated with reduced encoding and deactivation of hippocampus and default network

Hippocampal suppression during episodic memory retrieval has been attributed to retrieval effort and attentional engagement during the recall task, as it is present regardless of retrieval success and maximally deactivated for the attempted recall of weaker memories (Reas et al., 2011). Several lines of evidence from the current study support the proposal that more effortful retrieval attempts inhibit background encoding processes subserved by the anterior hippocampus, resulting in deactivation associated with both elevated search and impaired encoding function.

First, encoding performance depended upon the study-level of the memory to be retrieved, rather than retrieval success. Encoding was impaired for low-study recognition trials, relative to high-study trials, the former which are presumed to represent weaker memories and thus demand greater search effort at retrieval. These assumptions are supported by lower recognition and cued recall accuracy and longer response times for low-study than high-study words. Furthermore, responses were faster for trials with successful than unsuccessful encoding, indicating that encoding success was related with reduced search time. Notably, encoding was not influenced by recognition success, and the difference between the low-study and high-study conditions remained while holding retrieval success constant. Thus, the current findings suggest that although recognition success does not influence encoding, the attempted retrieval of lower strength memories disrupts incidental encoding of concurrent, task-irrelevant stimuli. These results differ from those of a prior study where successful recognition was associated with reduced incidental encoding accuracy and encoding-related medial temporal lobe activity (Huijbers et al., 2009). Variation in experimental design may partially account for these differences. For example, D' scores for both the recognition and encoding tasks were substantially lower in the Huijbers et al. (2009) study than for the present low-study condition, raising the possibility that the recognition task used in the prior study was more attentionally demanding. Degree of search engagement might further be influenced by whether a stimulus is perceived as weakly familiar versus novel, even if both were previously encountered during study. It is possible that weakly familiar items might engage more search, and thus greater interference with concurrent encoding, than those items erroneously perceived as novel and rejected outright. Additionally, both retrieval

search and success could interact competitively with encoding; though the present study did not identify an effect of retrieval success on incidental encoding, this does not exclude the possibility that retrieval success might also regulate encoding but that its effect here was below detection threshold. While the preceding interpretation supposes that fluctuations in retrieval-dependent attentional processes influence encoding, the reverse relationship, that encoding functions affect retrieval, is also possible. For example, interference from distracting stimuli has been shown to diminish recall performance and reduce the hippocampal response to retrieval (Wais et al., 2010a). In the present study, attentional capture by the external environment might monopolize attention resources to facilitate encoding while impairing retrieval, reducing retrieval accuracy when pictures are concurrently encoded. However, given that this effect was not observed, and that levels of distraction were balanced across trials, this scenario seems less likely.

Second, activity in the anterior hippocampus was simultaneously modulated by incidental encoding success and memory search, as approximated by retrieval response times (Sternberg, 1966). Longer search duration was associated with greater deactivation in bilateral anterior hippocampus and regions of the default network. Although trial-by-trial variability in response times cannot be cleanly dissociated from differences in memory strength, this finding suggests a direct relationship between suppression of these regions and the temporal duration of the retrieval effort. Other studies have presented similar evidence for a dependence of medial temporal lobe responses on attentional fluctuations during retrieval, in that retrieval demands that vary according to the present

attentional focus correspondingly regulate medial temporal lobe responses to retrieval (Nee and Jonides, 2008).

Given prior evidence that the default network deactivates with focused, goal-directed tasks (McKiernan et al., 2003; Raichle et al., 2001), a correlated suppression of hippocampal and default network activity suggests that the encoding-related response in the anterior hippocampus might be mediated by the attentional demands of the retrieval task. Functional connectivity analysis confirmed that activity between the anterior hippocampus and default network regions was more strongly correlated when incidental encoding failed. The hippocampus has been found to correlate with the default network during episodic memory retrieval but not intentional encoding, such that the hippocampus activates during both successful encoding and retrieval, but the default network deactivates during successful encoding and unsuccessful retrieval (Huijbers et al., 2011; Vannini et al., 2010). However, in accordance with other reports of hippocampus-default network correlations when learning and retrieval occur simultaneously (Zeithamova et al., 2012), in the present study the hippocampus effectively tracked incidental encoding even while remaining coupled with regions of the default network. The present findings suggest that, beyond encoding or retrieval success, the degree of engagement in an intentional task may be an additional factor underlying functional correlations between the hippocampus and default network.

Concurrent hippocampal encoding and retrieval responses

Notably, the anterior to posterior extent of the hippocampus was more active during high-study than low-study trials as well as during hit relative to miss or correct

rejection trials, consistent with a large body of literature illustrating that the hippocampus supports recognition success or retrieval of strong memories (for review see Eichenbaum et al., 2007). The detection of a concomitant encoding response does not necessarily invalidate the interpretation of such retrieval-related activations as veritable signatures of retrieval, as the hippocampus may subserve the balance between new learning and recovering old memories. For instance, reactivation of an old association can facilitate new learning (Zeithamova et al., 2012), while new learning can in turn diminish an original memory and the corresponding posterior hippocampal retrieval response (Kuhl et al., 2010). The present study extends support for a complex interplay between ongoing hippocampus-mediated encoding and retrieval processes, which may depend upon the successful recovery of old or the formation of new memories, the strength of the memory trace or the attentional processes supporting memory operations.

The dissociable anterior, middle and posterior hippocampal responses further suggests that the structure supports both encoding and retrieval, but that these functions may be subserved by distinct subregions. BOLD responses in anterior regions were modulated by encoding while those in posterior regions were predominantly modulated by retrieval. This finding is consistent with prior human neuroimaging studies reporting an antero-posterior functional gradient that dissociates encoding and retrieval functions (Lepage et al., 1998; Prince et al., 2005; but see Schacter and Wagner, 1999), novelty versus recollection or memory for prior experiences (Daselaar et al., 2006; Poppenk et al., 2010), or content-specificity (Liang et al., 2012). In addition to hippocampal subfield specialization documented in animals (Daumas et al., 2005; Kesner et al., 2004; Leutgeb et al., 2007) and humans (Chen et al., 2011; Eldridge et al., 2005; Lacy et al., 2011),

anterior versus posterior specialization is in agreement with distinct anatomical projections (Aggleton, 2011) and cytoarchitectonic and gene expression profiles (Fanselow and Dong, 2010) along the longitudinal axis of the hippocampus. The anterior overlap of encoding- and retrieval-related activations in the present study underscores the possibility that the hippocampus may actively continue to process or filter information from the external environment even when task demands do not require conscious encoding, and thus highlights the importance of considering contributions of underlying encoding-related activity when interpreting responses during retrieval.

Conclusions

The present study identified an anterior hippocampal BOLD signal sensitive to incidental encoding that overlapped with responses to retrieval success, strength and memory search. Reduced memory strength and extended search efforts were associated with impaired encoding performance and anterior hippocampus and default network deactivation, demonstrating that encoding-related processing in the hippocampus may be regulated by attentional engagement during retrieval. Together, these results suggest that encoding of task-irrelevant information remains active during intentional memory retrieval, influences activity in the anterior hippocampus and depends upon memory search. Such findings may explain why hippocampal activity is reduced from baseline during retrieval and most strongly deactivated during unsuccessful retrieval, highlighting potentially significant contributions of encoding functions to hippocampal responses during episodic memory retrieval.

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CHAPTER 5:

IMBALANCE OF INCIDENTAL ENCODING ACROSS TASKS: AN EXPLANATION FOR NON-MEMORY RELATED HIPPOCAMPAL ACTIVATIONS?

Abstract

Functional neuroimaging studies have increasingly noted hippocampal activation associated with a variety of cognitive functions such as decision-making, attention, perception, incidental learning, prediction and working memory, which have little apparent relation to declarative memory. Such findings might be difficult to reconcile with classical hippocampal lesion studies that show remarkable sparing of cognitive functions outside the realm of declarative memory. Even the oft-reported hippocampal activations during confident episodic retrieval are not entirely congruent with evidence that hippocampal lesions reliably impair encoding but inconsistently affect retrieval. Here we explore the conditions under which the hippocampus responds during episodic recall and recognition. Our findings suggest that anterior hippocampal activity may be related to the imbalance of incidental encoding across tasks and conditions, rather than due to retrieval, per se. Incidental encoding and hippocampal activity may be reduced during conditions where retrieval requires greater attentional engagement. During retrieval, anterior hippocampal activity decreases with increasing search duration and retrieval effort, and this deactivation corresponds with a coincident impaired encoding of the external environment (Israel et al., 2010; Reas and Brewer, 2013; Reas et al., 2011). In light of this emerging evidence, we discuss the proposal that some hippocampal activity

observed during memory retrieval, or other non-memory conditions, may in fact be attributable to concomitant encoding activity which is regulated by the attentional demands of the principal task.

Introduction

Lesion, electrophysiology and neuroimaging studies on humans, monkeys and rodents have established that the hippocampus is critical for declarative memory (for review see Eichenbaum, 2004; Squire et al., 2004). Neuroimaging studies report activation of the human hippocampus during a range of experimental paradigms evoking the formation or retrieval of episodic memories (Cohen et al., 1999; Schacter and Wagner, 1999). The hippocampus is frequently activated during successful memory encoding (Brewer et al., 1998; Wagner et al., 1998), recognition of previously encountered stimuli (Gabrieli et al., 1997; Stark and Squire, 2000), retrieval of stronger memories (Wais, 2011; Wais et al., 2010) or recollection of contextual details (Daselaar et al., 2006; Eldridge et al., 2000; Yu et al., 2011). Such activations are often identified by contrasting signal levels between conditions using cognitive subtraction techniques intended to isolate the targeted memory function, but which may incidentally capture additional mnemonic and non-mnemonic processes. Thus, it is challenging to disentangle activity related to retrieval from that driven by interwoven encoding or non-mnemonic processes using neuroimaging techniques alone, which cannot inform whether these neural operations are essential for memory recovery.

Neuropsychological studies of patients with selective lesions can provide more definitive insight into the necessity of the hippocampus for specific cognitive functions. The earliest evidence that the hippocampus is critical for learning declarative information came from patient H.M. Following bilateral medial temporal lobe resection, including the hippocampus, he exhibited selective deficits in establishing new memories, yet had relatively spared retrograde memory abilities (Scoville and Milner, 1957), indicating that

the medial temporal lobe is essential to acquire new episodic memories, but not to retrieve previously stored and consolidated memories. Some studies of patients with more isolated hippocampal damage demonstrate impaired recollection, yet intact familiarity-based memory, while others report deficits in both recognition processes (Jeneson et al., 2010; Yonelinas et al., 2002). However, since both the study and retrieval phases of these investigations occurred post-lesion, they do not distinguish between deficits at the time of memory acquisition or retrieval. Studies that allow for such disambiguation by testing the integrity of autobiographical memories acquired before amnesia onset report mixed findings. Some patients with hippocampal lesions manifest anterograde and temporally graded retrograde amnesia, with memory deficits for events following and immediately preceding amnesia onset (Manns et al., 2003). Yet others report amnesia extending back throughout the lifespan, albeit again in a time-dependent manner (Bartsch et al., 2011), or that the degree of retrograde amnesia depends on the extent of hippocampal damage (Rosenbaum et al., 2008). In rodents with hippocampal lesions, the timespan of retrograde amnesia differs between spatial and fear memories (Winocur et al., 2013), suggesting that the nature of the memory is an additional factor determining how long a declarative memory remains hippocampus-dependent. Retrieval can also be supported by the parahippocampal gyrus recently after memory acquisition, and by surrounding neocortex following reorganization over time (Squire and Wixted, 2011), accounting for some observations of hippocampus-independent retrieval. Critically, these lesion studies, which serve as a gold standard for whether a brain region makes a necessary contribution to a given function, consistently report intact non-declarative memory performance. Those impairments that are not strictly mnemonic, such as future simulation and

imagining, appear closely related to memory-based processes (Addis and Schacter, 2012).

Together, these lesion studies indicate that the hippocampus is not required for non-mnemonic functions, but is essential for forming episodic memories. Yet, neuroimaging studies imply a rather promiscuous hippocampal involvement across a breadth of cognitive domains, including reward, emotion, working memory and decision-making (Curtis et al., 2000; Elliott et al., 2000; Koelsch et al., 2006; Viard et al., 2011). Reports of such non-memory, and some retrieval-related, activations are thus incongruent with more decisive evidence from amnesic patients indicating a selective role for the hippocampus in establishing declarative memories. How then, does one reconcile the frequent, yet variable, conditions under which hippocampal responses are observed during neuroimaging studies? This review will discuss several lines of evidence from functional magnetic resonance imaging (fMRI) studies that may account for discrepant reports of some hippocampal activations, which may be misattributed to processes that are independent of the hippocampus or preserved following hippocampal lesions. These findings suggest that hippocampal responses during recognition or recall are less directly linked to retrieval than to the modulation of encoding processes by concomitant non-mnemonic task components.

Hippocampal deactivation during retrieval

Recent fMRI findings reveal that anterior hippocampal activity is reduced during cued recall relative to both baseline and a non-memory control task (Israel et al., 2010; Reas et al., 2011; Figure 5.1), suggesting either that the hippocampus is not reliably

engaged by retrieval or that any retrieval-related response may be overridden by competing influences. Although there are challenges to interpreting the baseline blood-oxygen-level-dependent (BOLD) signal during unrestrained periods which may evoke a range of mental states (Gusnard and Raichle, 2001), the rest and control conditions in these studies are not expected to engage memory to a greater extent than during the recall task. Thus, any retrieval activity would be expected to present as a task-positive response, rather than the observed task-negative deflection from baseline. Follow-up investigations revealed that the magnitude of this reduction corresponds with the difficulty of the retrieval trial (Reas et al., 2011). Specifically, the anterior hippocampus deactivates during recall of strongly remembered paired associates and deactivates further during the attempted recall of weaker memories (Figure 5.1B). Such evidence is consistent with numerous reports of higher hippocampal activity for more confident retrieval or successful recollection (Cohen et al., 1999; Schacter and Wagner, 1999), yet conflicts with the interpretation that such relative differences are driven by recollection-related task-positive activations.

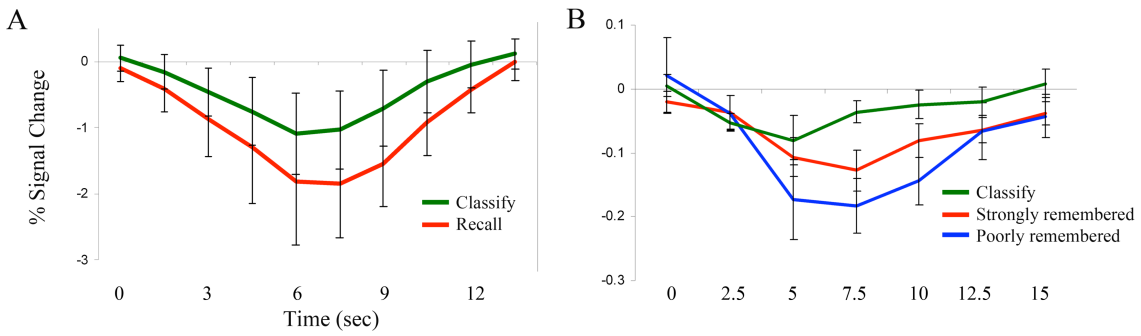

Figure 5.1: Hippocampal deactivation during cued recall. A. Right anterior hippocampus was more strongly deactivated ($p < .05$) during recall of visual paired associates than during a non-memory classification task. (Israel et al., 2010). B. Left anterior hippocampus was more deactivated ($ps < .01$) during recall of strongly remembered verbal paired associates than during classification, and during recall of poorly versus strongly remembered associates (Reas et al., 2011). Error bars represent standard error of the mean.

Neuroimaging studies that report retrieval-related activations often compare successful and failed retrieval, recollection and familiarity, or memory strength levels. These subtractions coincidentally contrast levels of other processes highly integrated with retrieval, including cognitive control to execute directed recall efforts, sustained attention to search through a memory store, re-encoding of a recovered memory, or working memory engaged during post-retrieval monitoring. If functionally connected to brain networks subserving such concomitant processes, the hippocampus could correlate with activity that covaries with attention or cognitive control. In turn, these interactions might serve to modulate hippocampus-dependent memory functions such as monitoring and encoding the ongoing stream of experience. This may explain the paradoxical finding of hippocampal activity levels during recollection that lie intermediate between levels during weak retrieval and non-retrieval conditions (Figure 5.1B).

Although hippocampal activity increases with the strength of the target memory, it also correlates with the response time of the retrieval decision, posing a challenge to disentangling effects of memory strength from associated attentional factors. Israel et al. (2010) and Reas et al. (2011) report that anterior hippocampal activity negatively correlates with response times, such that longer duration retrieval attempts more strongly deactivate the hippocampus. This correlation is present during both cued recall and recognition tasks and persists after controlling for differences in memory strength (Reas and Brewer, 2013; Reas et al., 2011), but is not observed during a non-memory classification task (Israel et al., 2010) (Figure 5.2A, Figure 5.3A). These findings suggest that the hippocampal response during both recognition and recall is modulated by response time-dependent factors, and that this relationship is stronger under conditions demanding attentional control of mnemonic operations. Since psychological models of memory propose that sequential search processes in retrieval can be estimated with response times (Sternberg, 1966), a correlation between response times and the retrieval-related BOLD response indicates a potential modulatory effect of memory search on the hippocampus. While the attentional demands of the retrieval effort thus appear to strongly regulate the hippocampus, additional research is warranted to examine the influence of other sub-processes of retrieval, including working memory, error monitoring and post-retrieval evaluation.

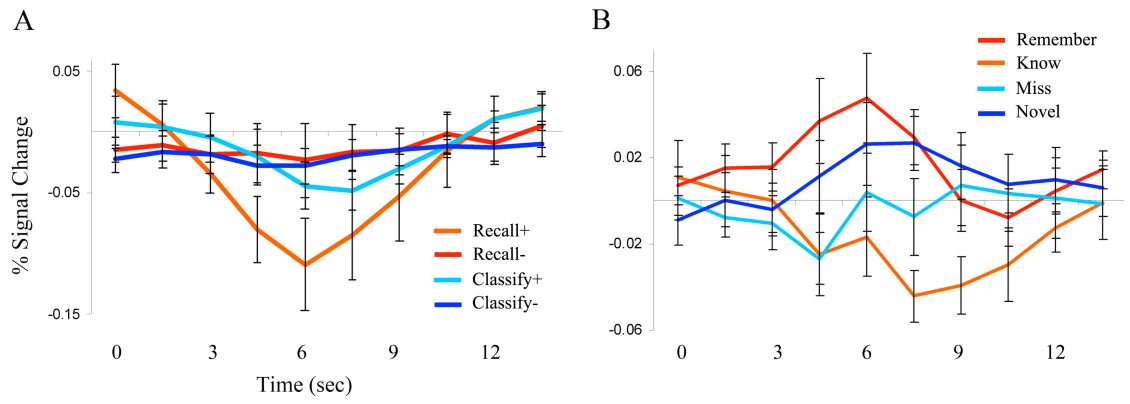

Figure 5.2: Hippocampal modulation by response time, recognition judgment. A. Deactivation of the right anterior hippocampus is greater for recall trials with longer (Recall+) versus shorter (Recall-) response times, but does not differ between long and short classification (Classify+ vs. Classify-) responses (Israel et al., 2010). B. "Remember" recognition judgments elicit task-positive responses, whereas "know" judgments elicit task-negative responses in bilateral hippocampus (Gimbel and Brewer, 2011). Error bars represent standard error of the mean.

These findings do not imply that the hippocampus subserves memory search. Rather, it may receive input from upstream regions directing search operations, which in turn regulate persistent memory functions performed by the hippocampus. Functional connectivity studies have revealed that the hippocampus is not only a component of a cortical memory system, but, likely through indirect connections via the parahippocampal gyrus (Ward et al., 2013), also correlates with a set of regions referred to as the default network (Greicius et al., 2004; Huijbers et al., 2011; Vincent et al., 2006). The default network, comprising regions of medial frontal, medial and lateral parietal, and temporal cortex, is most active during passive rest or internally-directed cognition and is deactivated during goal-directed, externally-orientated tasks (Anticevic et al., 2012; Buckner et al., 2008; Raichle et al., 2001). The magnitude of this task-induced suppression correlates with greater task difficulty (McKiernan et al., 2003), retrieval

effort and trial-by-trial recall response times, and is greater for “know” than “remember” recognition judgments (Gimbel and Brewer, 2011; Reas et al., 2011, Figure 5.3). Thus, input from the default network may account for some correlations between hippocampal activity and fluctuations in attention or cognitive control. It has been proposed that task-induced deactivations serve to reallocate resources away from inefficient neural processing towards those that support the intended neural operation (Drevets et al., 1995; McKiernan et al., 2003). Under this interpretation, cognitive control and attention engaged during goal-oriented retrieval might inhibit hippocampal memory processes, for example, monitoring and encoding the external environment, that interfere with successful recovery of the target memory trace.

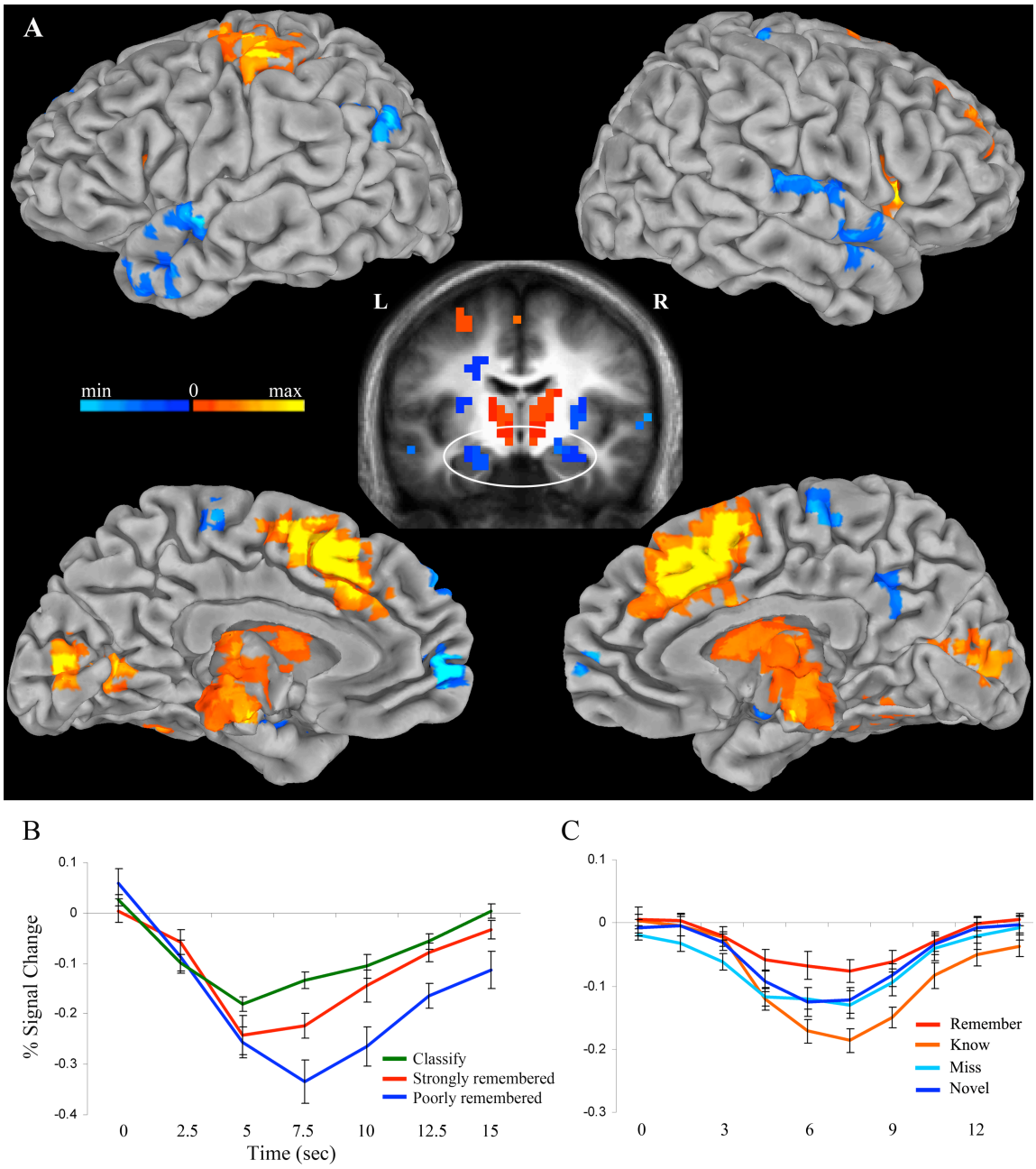

Figure 5.3: Hippocampus and default network deactivation by response time, search and strength. A. BOLD responses in bilateral anterior hippocampus, medial prefrontal cortex, posterior cingulate, superior temporal and left inferior parietal cortex were negatively correlated with recognition response times ($p < .01$, cool colors). (Reas and Brewer, 2013) B, C. Average default network activity is more strongly reduced during recall of poorly than strongly remembered paired associates (B, Reas et al., 2011) and during "know" than "remember" recognition responses (C, Gimbel and Brewer, 2011) ($ps < .01$). Error bars represent standard error of the mean.

Hippocampal responses during retrieval track incidental encoding

We have thus far discussed evidence that hippocampal activity during retrieval can correlate with cognitive functions outside the domain of declarative memory, but have yet to address how these interactions relate to the established function of the hippocampus in forming new episodic memories (Scoville and Milner, 1957; Squire et al., 2004). It is feasible that fluctuations in hippocampal activity track ongoing encoding processes even during states that do not intentionally manipulate encoding. Features of episodic events are continually monitored and encoded during intentional retrieval, serving to re-encode previously encountered stimuli (Nyberg et al., 1996) and to form novel memories for both task-relevant (Buckner et al., 2001; Stark and Okado, 2003) and task-irrelevant (Huijbers et al., 2009) background information. Furthermore, incidental learning during retrieval can be facilitated (Zeithamova et al., 2012) or impaired (Huijbers et al., 2009) by retrieval and correlates with activity in the hippocampus (Stark and Okado, 2003) and other medial temporal lobe regions (Huijbers et al., 2009). Therefore, hippocampal responses that vary according to retrieval success, strength or effort, may alternatively be attributable to how these conditions regulate encoding of the ongoing stream of experience, rather than or in conjunction with, veritable retrieval processes.

Based upon previously discussed findings that anterior hippocampal activity tracks retrieval effort, a recent study examined how retrieval search influences incidental encoding, and regulates encoding-sensitive hippocampal responses (Reas and Brewer, 2013). In this experiment, subsequent memory was evaluated for pictures presented

during recognition of strong and weak verbal memories. Picture encoding was less successful during attempts to retrieve lower strength memories or when the recognition response was prolonged, indicating that higher levels of search impair concurrent encoding processes (Figure 5.4A). These findings expand upon prior work that reported diminished subsequent memory for scenes presented during successful recognition and suggested that retrieval and encoding competitively regulate medial temporal lobe activity (Huijbers et al., 2009). Together, these studies demonstrate that multiple aspects of a retrieval task, including successful recovery, search or memory strength can collectively regulate hippocampal functions associated with simultaneous memory formation.

Replicating numerous prior studies, Reas and Brewer (2013) found that hippocampal responses were greater during successful than failed recognition and during retrieval of stronger memories. But critically, bilateral anterior hippocampus deactivated and the signal magnitude tracked encoding success, with stronger negative deflections when concurrent encoding failed (Figure 5.4B). As also observed in cued recall (Reas et al., 2011), the BOLD response in this region negatively correlated with recognition response times (Figure 5.3A), suggesting that anterior hippocampal activity is reduced both when search duration is increased and incidental encoding is unsuccessful. Thus, while hippocampal activity often correlates with retrieval success or strength, it is also modulated by the degree to which coincident encoding functions are suppressed during effortful, goal-directed retrieval attempts.

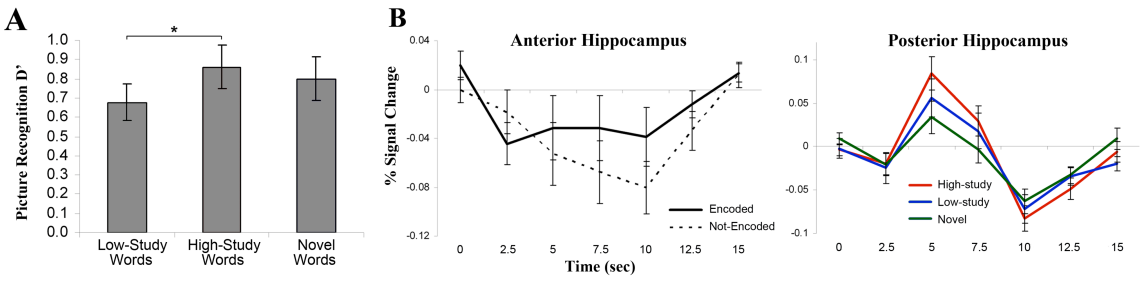

Figure 5.4: A. Recognition d' scores for pictures presented during a word recognition test. Incidental encoding was impaired for pictures presented concurrently with words studied once compared to words studied four times. * $p < .01$. B. Impulse response curves for the anterior and posterior bilateral hippocampus during a word recognition test with incidental picture encoding. Responses in anterior hippocampus (y = -7 to -18) were modulated by picture encoding, whereas activity in posterior hippocampus (y = -27 to -38) differed according to word retrieval condition ($ps < .05$). (Reas and Brewer, 2013) Error bars represent standard error of the mean.

Functional specialization of anterior and posterior hippocampus

The previously discussed findings demonstrate that hippocampus-mediated encoding operations that are persistently online may act concurrently, and possibility interactively, with retrieval. If the hippocampus is necessary both for acquiring and retrieving memories, dynamic shifts between these functions might either competitively engage a region, or concurrently recruit distinct specialized regions. Both encoding-sensitive deactivations and retrieval-sensitive activations are present during a given retrieval task (Reas and Brewer, 2013; Figure 5.4B), as are task-positive activations to "remember" recognition judgments and task-negative activations to "know" judgments (Gimbel and Brewer, 2011) (Figure 5.2B). However, these retrieval-related hippocampal responses were non-uniform, exhibiting a transitioning response gradient along the longitudinal axis of the hippocampus (Figure 5.5). Whereas the anterior hippocampus is consistently deactivated while tracking retrieval effort, search and incidental encoding,

posterior regions exhibit positively activating responses to retrieval success (Figures 5.1B, 5.4B). Yet, even posterior activity that covaries with retrieval success or confidence may be influenced by the simultaneous re-encoding of a recovered memory, as similar BOLD patterns are engaged at retrieval as during encoding (Kuhl et al., 2010; Nyberg et al., 2000; Woodruff et al., 2005).

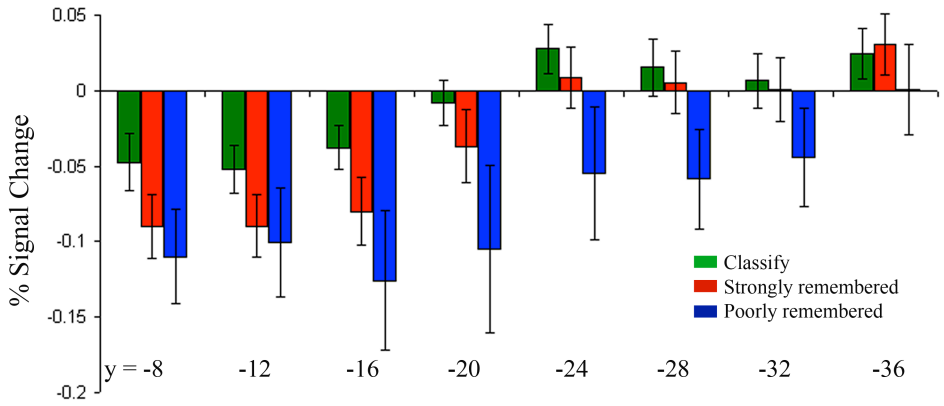

Figure 5.5: Hippocampal activity during a non-memory classification task, cued recall of strongly remembered word pair associates and cued recall of poorly remembered word pair associates. Beta-values (± standard error) are presented for 4 mm slices along the longitudinal axis of the bilateral hippocampi, from anterior (left) to posterior (right). (Reas et al., 2011)

Although additional research is needed to thoroughly disentangle effects of these concomitant memory processes within the hippocampus, evidence of regional specialization for memory functions in the hippocampus may account for its heterogeneous responses. In the human and animal hippocampus, highly specialized behavioral functions, anatomical circuitry and gene expression patterns distinguish subregions (dentate gyrus, CA3, CA1, subiculum) as well as anterior versus posterior regions. For instance, computations such as pattern separation or completion that possibly

subserve the creation, evaluation or recovery of memories are preferentially performed by distinct subregions (Bakker et al., 2008; Chen et al., 2011; Eldridge et al., 2005; Suthana et al., 2011). Functional dissociations within subfields have been observed in rodents, with ventral and dorsal dentate gyrus respectively associated with anxiety and contextual learning (Kheirbek et al., 2013). Human neuroimaging studies provide further evidence for the involvement of anterior regions in encoding, novelty, relational binding and the construction of future events, and posterior regions in retrieval, recollection or elaboration of past and future events (Addis and Schacter, 2008; Daselaar et al., 2006; Giovanello et al., 2004; Lepage et al., 1998; Poppenk et al., 2010; Prince et al., 2005), consistent with distinct anterior versus posterior anatomical circuitry (Aggleton, 2011). Collectively, these findings suggest that the hippocampus supports both encoding and retrieval, but that these functions may be non-uniformly distributed. The interdependent, reciprocally regulating nature of these processes complicates efforts to cleanly dissociate their influences on hippocampal activity, and, further, suggests additional caution in interpreting modulations of hippocampal activity during non-mnemonic tasks.

Future Directions

Together, the discussed findings help reconcile inconsistent reports of hippocampal involvement in non-mnemonic processes. Given evidence that retrieval search regulates hippocampus-mediated encoding, it is feasible that other non-mnemonic processes similarly modulate ongoing memory functions. For example, additional research will help determine how working memory, error monitoring or post-retrieval evaluation during retrieval influence encoding of the external environment or the

retrieved memory. Future fMRI studies will benefit from assessing the directionality of parametric influences on these activations with impulse-response curves to supplement simple subtraction techniques, accounting for response times and considering covariance with cortical regions modulated by task difficulty. Functional and anatomical connectivity analyses as well as integrated multimodal neuroimaging techniques will aid in elucidating the neural circuitry underlying hippocampal-cortical interactions along with their spatial distribution and temporal dynamics.

Conclusions

Despite conclusive evidence that the hippocampus is essential for the construction of new episodic memories, contention remains over its contribution to memory retrieval and non-memory-based functions that inconsistently elicit hippocampal responses. There is emerging evidence that such conditions, which engage a breadth of cognitive processes encompassing cognitive control, sustained attention, working memory and error monitoring, may modulate concurrent, persistent background encoding functions. These findings provide a cohesive interpretation for hippocampal activity that inherently correlates with non-memory components of a diverse set of tasks, but is fundamentally driven by the degree to which the hippocampus is actively monitoring and encoding the external environment.

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CHAPTER 6:

MULTIVOXEL SIGNALS OF CONTEXTUAL RETRIEVAL IN THE MEDIAL TEMPORAL LOBE

Abstract

The medial temporal lobe supports integrating the "what," "where," and "when" of an experience into a unified memory. However, it remains unclear how representations of these contextual features are neurally encoded and distributed across medial temporal lobe subregions. The present study conducted high-resolution functional magnetic resonance imaging of the medial temporal lobe while participants retrieved item, spatial, and temporal source memories. Multivoxel classifiers identified activity in perirhinal and parahippocampal cortex linked to memory for associated items and hippocampal activity linked to memory for spatial context. However, perirhinal and hippocampal classifiers were respectively driven by effects of mean signal amplitude and task difficulty, whereas the parahippocampal classifier survived correction for these effects. These findings demonstrate dissociable coding mechanisms for episodic memory context across the medial temporal lobe, and further highlight a critical distinction between multivoxel representations driven by spatially distributed activity patterns, and those driven by the regional signal.

Introduction

Episodic memories comprise multiple contextual details about a prior experience, integrating information about people or objects that were present, with their location and the temporal sequence of events that occurred. The brain's medial temporal lobe (MTL) is known to support episodic memories (Squire et al., 2004), with convergent inputs from subregions that integrate these details into a cohesive memory trace. Electrophysiology studies in rodents and non-human primates suggest that ensemble activity of neurons in distinct MTL subregions encode spatial, temporal and item memory content. Furthermore, there is evidence that reactivation of the same neural subpopulations activated at encoding elicits retrieval of the original memory engram (Garner et al., 2012; Liu et al., 2012). While some of these findings have been extrapolated to humans, it is unclear whether the human MTL adopts similar means of coding contextual memories as those observed in animals.

Animal electrophysiology studies indicate that the context of an experience is represented in the coordinated activity of neurons tuned to particular features. Perhaps the best studied examples of such coding mechanisms are hippocampal place cells and entorhinal grid cells which selectively fire in preferred spatial locations of the animal's environment (Moser et al., 2008). Similarly, other studies have demonstrated hippocampal time cells that signal memory for specific moments in time, as well as stimulus-selective item cells in the perirhinal cortex (Eichenbaum, 2013; Naya and Suzuki, 2011). In support of an analogous neural coding method in humans, single-neuron recordings in neurosurgical patients have shown MTL activity that signals item

identity (Quiroga et al., 2005), hippocampal activity signaling temporal order (Paz et al., 2010), and grid-like spiking in the entorhinal cortex (Jacobs et al., 2013).

Human neuroimaging studies are broadly consistent with the animal literature, indicating that MTL subregions integratively support item and spatiotemporal memory context (Davachi, 2006; Eichenbaum et al., 2012). In particular, the perirhinal cortex has been implicated in item novelty and recognition (Davachi et al., 2003; Kohler et al., 2005; Staresina et al., 2012). Activity in the parahippocampal cortex signals memory for both temporal order (Jenkins and Ranganath, 2010; St Jacques et al., 2008; Tubridy and Davachi, 2011) and spatial location (Ekstrom et al., 2011), and has been proposed to subserve memory for the contextual background of an experience (Bar et al., 2008). These and other studies consistently report hippocampal responses during item, spatial and temporal memory, as well as successful recollection, source retrieval or relational memory (Ekstrom et al., 2011; Giovanello et al., 2004; Jenkins and Ranganath, 2010; Kohler et al., 2005; Ross and Slotnick, 2008; Tubridy and Davachi, 2011), indicating that the hippocampus integrates multiple episodic details into a cohesive memory. While these findings together suggest that a distributed neural code in the MTL represents episodic memory context, it is unclear whether such a distributed code characterizes the type of contextual details brought up by directed source memory retrieval.

Functional magnetic resonance imaging (fMRI) studies have traditionally been used to inform about the regional involvement of brain structures in a given task, but such techniques offer little insight into additional coding mechanisms beyond aggregate regional signal magnitude. Rather than averaging signal across an area, as is typical of univariate analyses, multivariate analysis techniques can examine multivoxel activity

patterns that may be sensitive to nonuniformly distributed patterns of neural activity (Mur et al., 2009; Serences and Saproo, 2012). Recent applications of these methods indicate that activity patterns in the MTL may encode the content or context of a remembered experience (For review of mvpa applications of episodic memory, see also Rissman and Wagner, 2012). For example, studies report that voxel-wise blood oxygen level dependent (BOLD) responses in the MTL can predict subsequent memory (Watanabe et al., 2011), code subjective recognition success (Rissman et al., 2010), identify an individual's virtual location (Hassabis et al., 2009), represent distinct stimulus categories (Liang et al., 2013) or distinguish between retrieval of distinct past experiences (Chadwick et al., 2011).

Given this evidence that distributed MTL activity may support multiple levels of retrieval processing, from representing specific memory content or categorical information to predicting memory acquisition and subjective mnemonic states, it is feasible that it also characterizes the domain of a retrieved context. For instance, distinct neural ensembles might represent variants of a given feature, such as left versus right spatial location. Such populations would more highly overlap with one another than with a population coding a less similar property such as temporal order. Thus, within a region that supports spatial memory, the multivoxel activation patterns common to spatial retrieval events might be distinguishable from those during non-spatial retrieval. Indeed, in comparing activity elicited by retrieval of memories containing even distinct content, the more related the learned context, the more similar their MTL activation patterns (Hseih et al., 2014). A region's activity patterns might show greatest overlap when retrieving instances of memory features it supports, and be discriminable from more

random activity patterns during retrieval of features it does not support. The present study combined high-resolution fMRI of the MTL with multivoxel pattern classification to test the hypothesis that spatially distributed activity patterns in MTL subregions differentially inform about the class (spatial, temporal or item) of retrieved contextual information.

A critical assumption of multivoxel classification analyses is that class discrimination is driven by differences in the pattern of voxel-wise activity between classes of interest. However, classifier models may heavily weight additional sources of between-class differences if those signals improve classifier performance. Of particular concern is that pattern classifiers may detect between-condition differences in the global signal rather than variations in its spatial pattern. Furthermore, classifiers may be sensitive to behavioral effects that covary with the conditions of interest, such as task difficulty. Additional steps can be taken to more fully characterize the underlying signal and expose the contribution of distributed activation patterns. The contribution of global signal can be explored by examining the effects of controlling for the mean signal intensity before performing classification. The contribution of task difficulty can be explored by examining the effects of controlling for a behavioral proxy, such as response time, before performing classification (Todd et al., 2013). Thus, to account for the influence of differences between classes in the mean signal intensity or task difficulty, classifiers were trained both with and without controlling for mean signal and response times.

Materials and methods

Participants

Twenty young adults were recruited from the University of California, San Diego (UCSD) and surrounding community and gave informed written consent according to UCSD Institutional Review Board requirements. All subjects were right handed, free of psychiatric or neurological disorders and had normal to corrected vision. One session was aborted due to participant claustrophobia and two others were excluded due to excessive motion artifacts. Data from the remaining seventeen subjects (seven male, mean age ± standard deviation = 23.0 ± 3.7 years) were included for analysis.

Stimuli and experimental paradigm

240 color pictures of common objects (Bakker et al., 2008) were pseudorandomly combined into pairs screened for obvious semantic associations. Prior to fMRI scanning, participants completed an associative encoding task on sequentially presented object pairs (Figure 6.1, left). Each object was displayed at either the left or right of a computer screen for two seconds. Objects from the same pair were separated by a two-second blank screen and trials were separated by a two-second fixation cross. Participants were instructed to memorize each object pair, but were given no explicit instructions to remember the location or order of the objects. Each pair was studied three times, distributed across six blocks.

Approximately twenty minutes after encoding, participants performed three retrieval tasks during event-related fMRI scanning (Figure 6.1, right). Each studied pair was assigned to either a spatial, temporal or item retrieval condition, and condition assignments were counterbalanced across subjects. Trials were initiated with a red, blue or green box in the center of the screen for one second to cue the onset of a spatial,

temporal or item retrieval trial. A previously studied object was displayed in the box for one second, followed by a two-second post-stimulus period. Subjects were instructed to recall the presented object from the encoding task and respond whether the object appeared at left or right or they forgot (spatial condition), first or second in the pair or they forgot (temporal condition) or to report whether they recalled or forgot the paired object (item condition). Subjects were instructed to respond as quickly and accurately as possible with their right hand using a four-button response box. Trials were jittered with 0.5–13 seconds of fixation, calculated to optimize the study design for modeling the hemodynamic response to trials (Dale, 1999; Dale and Buckner, 1997) , and to ensure that intervals following each trial were optimally balanced across conditions. Eighty trials of each condition were distributed across five 387.5-second runs.

After scanning, a cued recall test was administered to assess reliability of self-reported recall judgments from the scanned item retrieval task. One object from each pair presented in the item condition was displayed, and subjects were instructed to report the associated object.

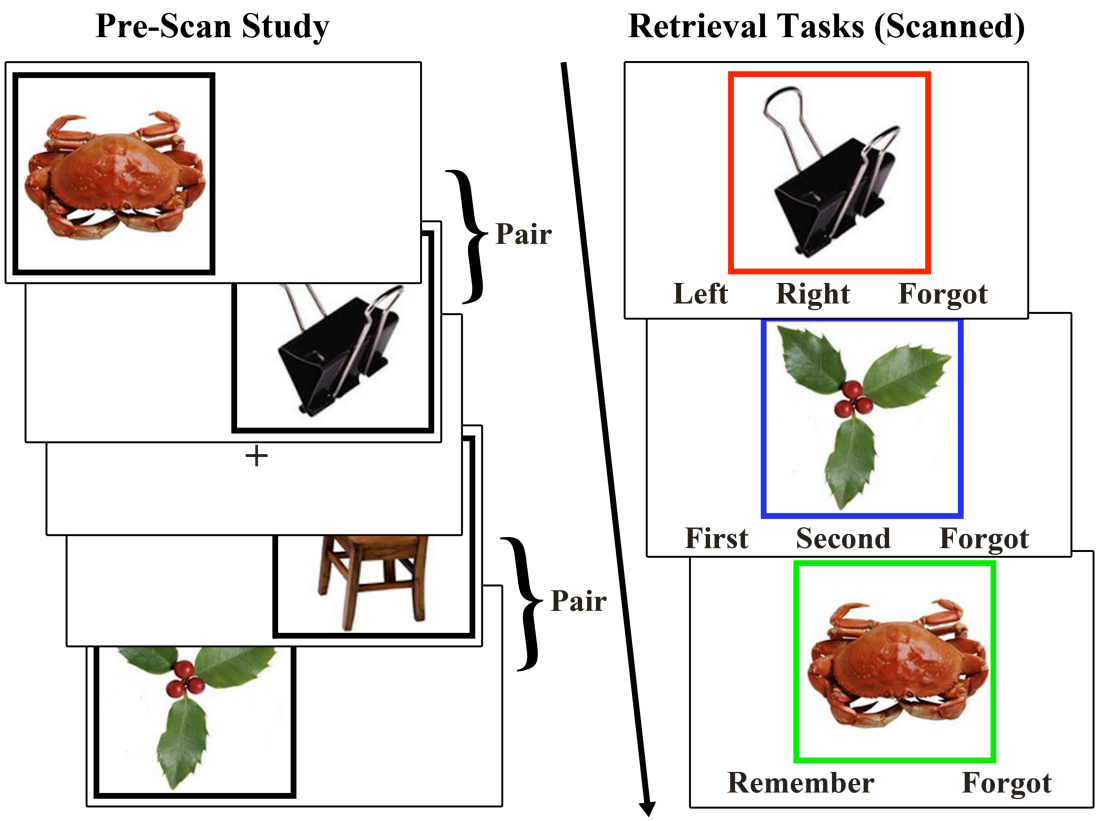

Figure 6.1: *Behavioral protocol***.** Prior to scanning, participants studied sequentially presented object pairs, presented at either the left or right. During fMRI scanning, participants were cued with a previously studied object and performed three contextual retrieval tasks: recall the spatial location of the item (spatial, red cue), recall the temporal order of the item (temporal, blue cue), or recall the item's pair (item, green cue).

Image data acquisition and pre-processing

Imaging data were acquired on a 3.0 Tesla General Electric scanner at the UCSD Keck Center for Functional MRI. Echo-planar images were collected using a gradient-echo T2*-weighted pulse sequence (2 x 2 mm in-plane resolution, 2500 ms repetition time, 30 ms echo time, 90° flip angle, 128 x 128 matrix, 256 mm field of view, 2 mm slice thickness, no gap). Each volume contained 27 slices oriented perpendicular to the long axis of the hippocampus (Figure 6.2, left). The first five volumes were discarded to

allow for signal equilibration. ASSET calibration was performed to enable parallel imaging and field maps were acquired to correct for static field inhomogeneities (Smith et al., 2004). A high-resolution anatomical scan (1mm x 1mm in-plane resolution, 1.2 mm slice thickness) was collected using an inversion recovery prepared spoiled gradient recalled T1-weighted sequence.

Functional data were corrected for spatial distortions using field maps (Smith et al., 2004) and reconstructed using the AFNI suite of programs (Cox, 1996). Images were slice-time corrected, corrected for motion and concatenated, and non-brain voxels were removed using a threshold mask of the functional data.

Univariate fMRI analysis

Prior to univariate analysis, standard landmarks were manually defined on the anatomical images, and both anatomical and functional images were normalized to Talairach space (Talairach and Tornoux, 1988). The region of interest large deformation diffeomorphic metric mapping (ROI-LDDMM) alignment technique was applied to improve alignment of the MTL between subjects (Miller et al., 2005). For each subject, previously described landmarks were used to define the left and right hippocampus (Chera et al., 2009), perirhinal and entorhinal cortices (Insausti et al., 1998) and parahippocampal cortex (Stark and Okado, 2003), on Talairach transformed images. These anatomical regions of interest for each subject were normalized using ROI-LDDMM to a modified model of a previously created template segmentation (Kirwan et al., 2007). Functional imaging data underwent the same ROI-LDDMM transformation as was applied to the anatomical data.

Functional runs were smoothed with a 4 mm full-width half-maximum Gaussian blur. Trials were sorted according to retrieval condition (spatial, temporal, item) and response (correct / incorrect / forgot for spatial and temporal trials; remember / forgot for item trials), and incorrect and forgotten trials were combined for analysis. A general linear model was constructed with regressors for each task condition (spatial correct, temporal correct, item remember, spatial incorrect / forgot, temporal incorrect / forgot, item forgot) along with six motion regressors obtained from the registration process. Signal deconvolution with TENT basis functions (Cox, 1996) was used to estimate the hemodynamic response for the 15 seconds following the stimulus onset. General linear tests contrasted correct spatial versus non-spatial (temporal and item), temporal versus non-temporal (spatial and item), and item versus non-item (spatial and temporal) trials. Group level t-tests ($p < .05$, two-tailed and corrected for multiple comparisons) were performed on parameter estimates from the 5-10 second period of each condition. Multiple comparisons correction was computed using a Monte Carlo simulation on a whole-brain functional volume in AFNI (http://afni.nimh.nih.gov/pub/dist/doc/program_help/3d-ClustSim.html) to determine the minimum cluster size necessary to achieve a family-wise error rate of $p < .05$ with a voxel-wise threshold of $p < 0.05$. Significant clusters, including at least eleven contiguous voxels, were displayed on a statistical map overlaid onto an across-subject averaged structural image.

Multivariate fMRI analysis

Before multivariate analyses, no smoothing or registration to standard space was performed. MTL regions of interest were drawn on each subject's anatomical image in native space (Figure 6.2, right). General linear regression was performed, with each trial modeled as a separate regressor to estimate the response amplitude to each stimulus (3dDeconvolve –stim_times_IM in AFNI; http://afni.nimh.nih.gov/pub/dist/doc/program_help/3dDeconvolve.html), and motion parameters included as regressors of no interest.

Multivoxel classification analysis was performed to identify MTL activity patterns that distinguish between spatial, temporal and item retrieval. Analyses were conducted on each subject using the LIBLINEAR support vector machine (SVM) package (http://www.csie.ntu.edu.tw/~cjlin/liblinear/) implemented in a custom Matlab script. Features were voxel-wise signal estimates from the third (5 sec) or fourth (7.5 sec) scans. These time-points were selected to capture the peak hemodynamic response, which may vary across brain regions and is estimated to occur at a 6-8 second delay (Friston et al., 1994). Feature examples included correct retrieval trials, coded according to spatial, temporal or item condition. Binary classifiers were trained and tested on anatomically defined regions of interest, including left and right hippocampus, perirhinal cortex, entorhinal cortex and parahippocampal cortex, to distinguish spatial from non-spatial, temporal from non-temporal, and item from non-item retrieval conditions. Binary classifiers were selected to isolate activity patterns selectively associated with a single condition, in contrast to a three-way classifier which may indicate a difference between conditions, but would carry ambiguous information about the most informative class.

Trials from the larger class were randomly down-sampled prior to training to ensure equal trial numbers in each training class.

Eighty percent of trials were allocated to training, and the remaining twenty percent reserved for testing. Five-fold cross-validation, divided along run boundaries, was performed on the training data to determine the optimal regularization parameter C from a range of 10^{-10} to 1. This C value was used to train a classifier model on the full training dataset which was then tested on the independent test dataset.

Group-level classifier accuracy was computed using a one-sampled t-test versus chance (50%) and assessed for significance with permutation testing. For permutation testing, class trial labels were randomized and the training and testing were conducted as described above. For each of 3000 permutations, a t-value was computed from classification accuracies across all subjects versus chance. The real t-value was compared to the permutation distribution of t-values, and t-values in the top 5% were considered significant.

Classifier accuracy may be sensitive to between-class differences in the mean signal amplitude or levels of task difficulty. To further characterize the bases of the classifiers, voxel-wise projection matrices were constructed to remove 1) the mean signal amplitude, and 2) signal modulation by response time. Before classifier training, the voxel-by-trial matrix of response amplitudes (D) was corrected for the mean signal or response times as follows, where P = the relevant projection matrix: $D = D - PD$.

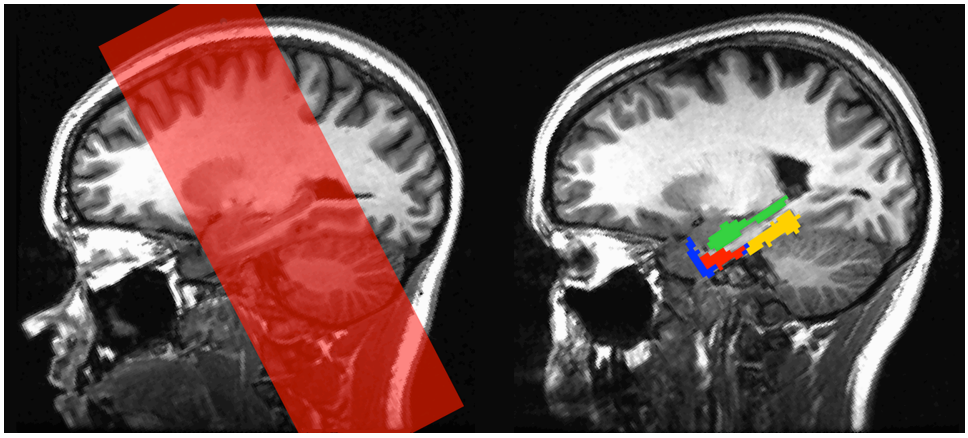

Figure 6.2: *Functional imaging protocol and MTL regions of interest.* For functional imaging, 27 slices (2 mm) were oriented perpendicular to the long axis of the hippocampus (left). Medial temporal lobe regions of interest (hippocampus, green; perirhinal cortex, blue; entorhinal cortex, red; parahippocampal cortex, yellow) were manually drawn on each subject's high-resolution structural image (right). Images show examples from single subjects.

Behavioral Results

Participants correctly recalled 84 ± 3% (mean ± standard error) of both spatial and temporal retrieval trials and reported remembering 79 ± 4% of item trials. They reported forgetting 10 ± 2% of spatial, 6 ± 2% of temporal and 16 ± 4% of item retrieval trials. 88 ± 4% of items reported remembered during scanning were correctly recalled during the post-scan cued recall test, suggesting that participants' self-reported memory judgments were reliable.

Mean response times to correct spatial, correct temporal, and remembered item trials were, respectively, 1284 ± 76, 1384 ± 74 and 1183 ± 81 msec. Response times differed between conditions ($F(2,32) = 17.41$, $p < 0.001$). Pairwise comparisons indicated longer response times for temporal than spatial ($p < 0.01$) or item ($p < 0.001$) and for spatial than item ($p < 0.01$) trials.

fMRI Results

Univariate fMRI

General linear modeling was used to examine MTL activity selectively associated with spatial, temporal or item retrieval. Activity in the left hippocampus, bilateral perirhinal cortex and left parahippocampal cortex was greater when items were reported remembered than when spatial or temporal information was correctly recalled ($p < 0.05$, corrected for multiple comparisons; Figure 6.3, left and middle). Follow-up contrasts revealed that anterior and middle / posterior MTL activations were respectively related to differences between the item and spatial conditions, and the item and temporal conditions (ps < 0.05, corrected for multiple comparisons).

Activity in the anterior MTL, including the left hippocampus, bilateral entorhinal cortex and left perirhinal cortex, was less active during spatial than temporal or item retrieval ($p < 0.05$, corrected for multiple comparisons; Figure 6.3, right). These activations were predominantly driven by the difference between the spatial and item conditions ($p < 0.05$, corrected for multiple comparisons), No differences in MTL activity were observed between temporal and spatial or item retrieval trials ($p > 0.05$).

The contrast between item and spatial retrieval contributes, in opposing directions, to both the *item versus non-item* and *spatial versus non-spatial* contrasts, so there is some overlap in the activated regions of these contrasts. Differences include increased activity in the left posterior hippocampus and parahippocampal cortex and reduced activity in the bilateral precentral gyrus for the *item versus non-item* contrast, each not present in the *spatial versus non-spatial* contrast (Figure 6.3).

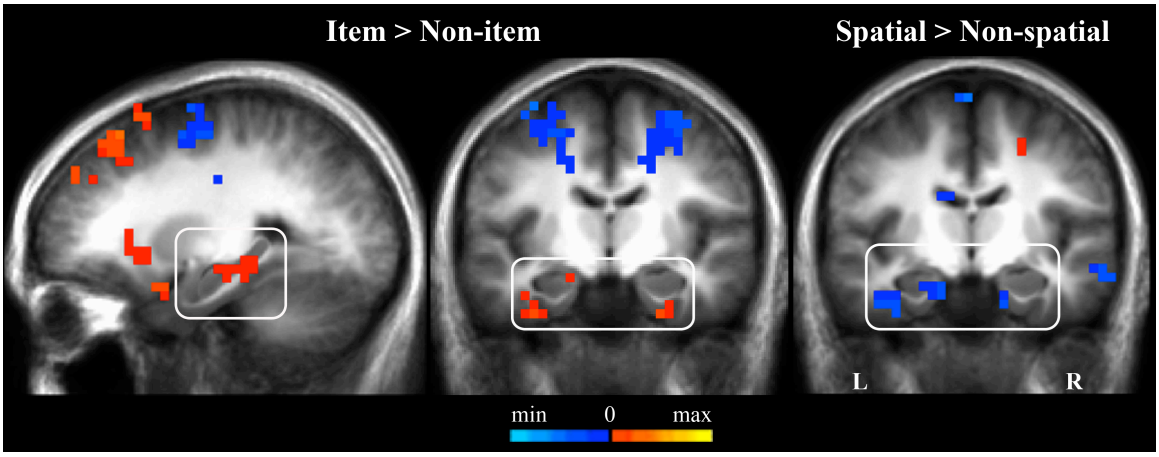

Figure 6.3: *MTL activity during item and spatial retrieval.* Activity in the left hippocampus, bilateral perirhinal cortex and left parahippocampal cortex was greater during item than spatiotemporal retrieval (left and middle). Activity in the left anterior hippocampus, bilateral entorhinal cortex and perirhinal cortex was less active during spatial than non-spatial retrieval (right). Statistical maps ($ps < 0.05$, corrected for multiple comparisons) are overlaid on a mean anatomical image of all subjects.

Multivariate fMRI

Subject-specific SVM classifiers were trained on voxel-wise activity patterns in left and right MTL subregions to distinguish spatial from non-spatial, temporal from non-temporal and item from non-item retrieval. Classification accuracies were assessed for significance with random permutation testing. Classifiers were first trained without accounting for the mean signal intensity or response times. The hemodynamic response peaked 5 seconds post-stimulus for the parahippocampal cortex, and at 7.5 seconds for the hippocampus, entorhinal cortex and perirhinal cortex. Therefore, classifiers were tested at both 5 and 7.5 seconds post-stimulus for each region. Any classifiers that performed significantly above chance when trained and tested on the untransformed data were retrained 1) after projecting out the mean signal amplitude, to evaluate classifier performance attributable to the spatial distribution of activity patterns, uncontaminated by

between-class differences in signal magnitude, and 2) after controlling for the effect of response times on signal magnitude, to evaluate classifier performance independent of task difficulty.

Classifiers trained on multivoxel activity in the right hippocampus at 7.5 seconds post-stimulus distinguished spatial from temporal and item trials (mean classification accuracy = 53.0 ± 1.5%; $t(16) = 2.03$, one-sampled t-test vs. 50%; $p < 0.05$, vs. permutation). However, classifier accuracy was no longer significant after mean projection (52.1 ± 2.7%; $t(16) = 0.77$; $p = 0.57$) or after controlling for response times (51.2 ± 1.7%; $t(16) = 0.69$; $p = 0.25$). Spatial memory classifiers trained on hippocampal activity at 5 seconds did not differ from chance (raw: $p = 0.30$; mean correction: $p = 0.59$; response time correction: $p = 0.56$). (Figure 6.4, left)

Classifiers trained on left perirhinal cortex activity patterns at 7.5 seconds distinguished item retrieval from spatial and temporal retrieval (accuracy = 54.3 ± 1.7%; $t(16) = 2.54$; $p < 0.05$). Classification accuracy remained significant after controlling for response times (54.1 ± 1.3%; $t(16) = 3.12$; $p < 0.01$), but did not differ from chance after mean projection (48.7 ± 2.3%; $t(16) = -0.57$; $p = 0.86$). Perirhinal cortex classifiers trained to distinguish item retrieval at the 5 second time-point did not differ from chance (raw: $p = 0.23$; mean correction: $p = 0.99$; response time correction: $p = 0.11$). (Figure 6.4, middle)

Classifiers trained on left parahippocampal activity patterns at 5 seconds distinguished item retrieval from spatial and temporal retrieval (accuracy = 53.5 ± 1.4%; $t(16) = 2.52$; $p < 0.05$). Classifiers remained accurate after controlling for the mean signal (55.7 ± 2.0%; $t(16) = 2.88$; $p < 0.05$) and response times (53.7 ± 1.8%; $t(16) = 2.11$; $p <$

0.05). (Figure 6.4, right) However, item retrieval classifiers trained on parahippocampal cortex activity at 7.5 seconds did not differ from chance (raw: $p = 0.51$; mean correction: $p = 0.26$; response time correction: $p = 0.63$).

Classifiers trained on entorhinal cortex activity were unable to distinguish between retrieval conditions.

It is important to note that multiple classifiers were tested to examine differences associated with temporal or spatial properties of the BOLD signal. Even with reducing comparisons by focusing on the MTL, classifier significance would not have survived correction for the 48 comparisons tested here (3 contrasts, 4 regions, 2 hemispheres, 2 time-points); thus, some caution should be taken in interpreting these results. Nonetheless, these findings align with existing models of MTL subregion function, and serve as a hypothesis generating foundation upon which to build with targeted, replication-based follow-up investigations.

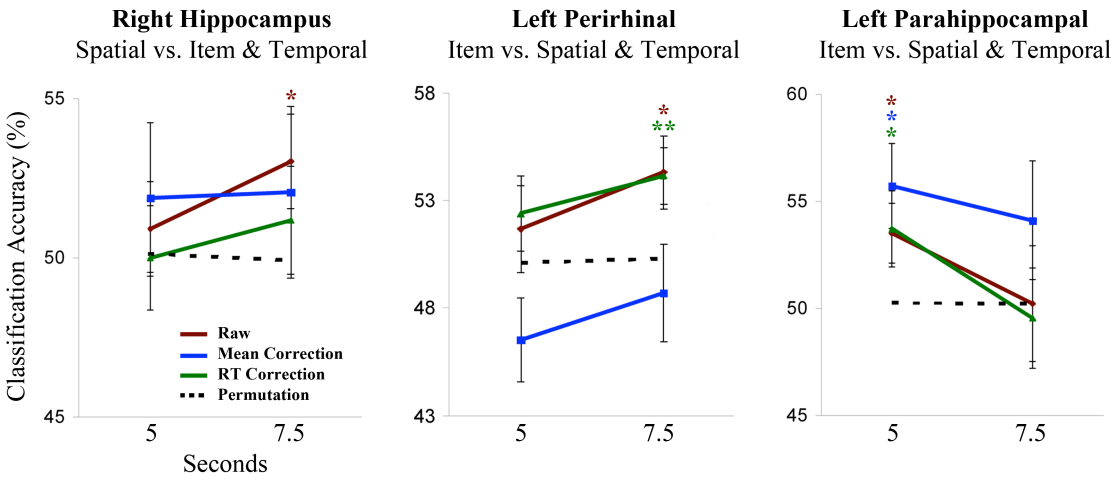

Figure 6.4: *MTL multivoxel classification accuracy.* SVM classifiers were trained on untransformed multivoxel signal estimates (red), after projecting out the mean signal amplitude (blue) or after controlling for response times (green) and were tested for significance relative to permutation testing (dotted). Multivoxel activity in the right hippocampus at 7.5 seconds distinguished spatial from non-spatial retrieval above chance when trained on raw signal, but not after controlling for the mean signal or response times (left). Left perirhinal cortex activity at 7.5 seconds distinguished item from non-item retrieval using raw signal and after controlling for response times, but not after controlling for the mean signal (middle). Left parahippocampal cortex activity at 5 seconds classified item versus non-item retrieval using raw signal and after controlling for the mean signal and response times (right). Error bars represent the standard error of the mean. * $p < .05$, ** $p < .01$

Discussion

The present study used univariate and multivariate analyses to examine both global engagement of MTL subregions and their spatially distributed activity patterns during contextual memory retrieval. Spatial and item memory signals were present in both the aggregate across-voxel response and multivoxel patterns. Critically, the SVM classifiers from MTL subregions were differentially sensitive to between-class differences in mean signal and modulation by response times, indicating that not all multivoxel effects are directly related to differences in fine-scale activity patterns.

Response-time-dependent hippocampal activity during spatial retrieval

A pattern classifier trained on BOLD signal in the right hippocampus effectively distinguished spatial from non-spatial memory retrieval. However, follow-up analyses revealed that classification accuracy was diminished when accounting for either the mean signal or trial-by-trial response times. Thus, discriminability of the hippocampus was more likely attributable to a large-scale regional response that was not detected at the group-level, rather than a small-scale spatial activity pattern specific to spatial retrieval.

The discriminating hippocampal signal was related to response times, suggesting that the between-condition signal difference covaries with task difficulty. This finding is consistent with evidence that some hippocampal activity during retrieval can be regulated by retrieval effort (for review, see Reas and Brewer, 2013b), as it is reduced during the retrieval of lower strength memories and negatively correlates with retrieval response times (Reas and Brewer, 2013a; Reas et al., 2011). Notably, only performance of the multivoxel classifier trained on the hippocampus, but not the perirhinal or parahippocampal cortex, was diminished after controlling for response times. Based on these findings, a difference in the mean signal between spatial and non-spatial retrieval might be expected from a univariate contrast. Interestingly, this analysis showed reduced activity during spatial retrieval in the left, but not the right, hippocampus. This discrepancy highlights a critical distinction between univariate group-level and multivariate subject-level approaches. While the former is exclusively sensitive to effects in which the directionality is consistent across individuals, the latter is sensitive to any difference between test conditions, regardless of their directionality. Therefore, if spatial

retrieval is inconsistently more or less difficult than non-spatial retrieval across participants, and task difficulty strongly modulates the hippocampus, an effect on hippocampal activity would emerge at the subject level (i.e. multivoxel classification) but not at the group level (i.e. univariate analysis).

Consistent with our findings, prior studies have reported hippocampal involvement in spatial location source memory for studied items (Ross and Slotnick, 2008). It is well established that spatial representations in animals are carried, at least in part, by a population-level neural code in the hippocampus (Moser et al., 2008), and emerging evidence supports a spatially distributed neural code for spatial location in humans (Hassabis et al., 2009). However, this study failed to find evidence for a multivoxel code unique to spatial, versus other contextual memory retrieval, beyond that driven by response times. Spatial memory encompasses memory for the location of experiences, objects in our external environment and our personal sense of position in relation to that environment, distinct functions subserved by different brain networks (Suzuki et al., 2005). Animal studies have shown that the hippocampus is essential for binding spatial, temporal and object details into memory (Ergorul and Eichenbaum, 2004), and that hippocampal neurons integratively code (Kraus et al., 2013), and similarly pattern separate (Azab et al., 2013), temporal and spatial information, which may suggest a patterned representation in the hippocampus that generalizes across contextual domains and where differences could be more related to response time than to particular contexts.

The perirhinal cortex in item retrieval

Univariate fMRI analyses revealed bilateral activation of the perirhinal cortex during item compared to spatiotemporal retrieval. Multivariate analyses extended this finding to suggest that multivoxel activity patterns in the left perirhinal cortex additionally distinguished between item and non-item retrieval conditions. Although the multivoxel classifier was robust to the influence of response time, its performance was largely driven by the mean BOLD signal. This is consistent with prior research showing that mean activity in the perirhinal cortex signals memory for items, unified concepts, or object familiarity (Davachi, 2006; Davachi et al., 2003; Kohler et al., 2005; Mayes et al., 2007; Staresina et al., 2012). Thus, while these findings support the regional involvement of the perirhinal cortex in object retrieval that is independent of task difficulty, they provide no evidence for a spatially distributed neural code selective for the process of item retrieval. Rather, the perirhinal cortex may be globally engaged while retrieving item information, with distinct neural representations for object identity (Hseih, et al., 2014; Naya and Suzuki, 2011).

Parahippocampal cortex activity patterns code for item retrieval

Activity patterns in the left parahippocampal cortex also effectively discriminated between item and spatiotemporal retrieval. However, in contrast to the perirhinal cortex classifier, the parahippocampal classifier was robust to effects of both the mean signal and response times. Notably, the univariate analysis also demonstrated regional activation of the left parahippocampal cortex during item retrieval. Together, these findings suggest that the parahippocampal cortex is not only globally recruited during retrieval of a paired

associate, but that the spatial distribution of its activity discriminates between an item and spatiotemporal content associated with a retrieved memory.

Although multivoxel classifiers can identify discriminative activity pattern differences, they do not inform about which class carries the more discriminating representation. Thus, in this comparison (item versus non-item), the multivoxel patterns may code for either aspect of a recalled memory's context, either its associated item or its integrated spatiotemporal features. Support for both possibilities exists. Prior research has demonstrated parahippocampal involvement in both spatial and temporal memory context (Ekstrom et al., 2011; Jenkins and Ranganath, 2010; Mullally and Maguire, 2011; St Jacques et al., 2008; Tubridy and Davachi, 2011) and activity patterns that distinguish between spatial environments (Hassabis et al., 2009). Yet, parahippocampal activity patterns were also reported to differentiate visual stimulus classes (Diana et al., 2008), together suggesting that such patterns could encode either spatiotemporal context or categorical object information. More broadly, the parahippocampal cortex is thought to subserve contextual associations (Bar et al., 2008), and could thus differentially represent the item and spatiotemporal associations in the present study. Such functional diversity may be accounted for by anatomically heterogeneity within the parahippocampal cortex, as distinct connectivity and cytoarchitectonic profiles have been identified in subregions of both the monkey (TH, TF) and human parahippocampal cortex (Baldassano et al., 2013; Suzuki and Amaral, 1994; Suzuki and Amaral, 2003). Although additional research is needed to disambiguate which precise contextual features are represented by parahippocampal activity patterns, these findings provide compelling evidence for a distributed code for episodic memory context in the parahippocampal cortex.

Conclusions

Multivoxel classifiers trained on untransformed BOLD signal estimates identified three MTL subregions in which activity patterns accurately discriminated retrieval conditions. However, follow-up analyses controlling for effects related to the mean signal intensity and task difficulty revealed that only one of the three classifiers was robust against these confounds. These findings underscore the importance of fully characterizing the signal driving multivoxel effects. Future studies should incorporate appropriate controls to dissociate information represented by regional engagement from that carried in a distributed code, which may reflect meaningfully different neural coding mechanisms.

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CHAPTER 7:

CONCLUSIONS

Together, findings from the preceding four studies reveal a finely orchestrated interplay between the neural systems directly subserving episodic memory retrieval and those supporting non-retrieval processes. They confirm prior evidence for a central role of the medial temporal lobe (MTL), and more thoroughly characterize the function of the hippocampus, in acquiring and retrieving episodic memories.

Chapter 2 examined the source of reduced hippocampal activity that is frequently observed across a range of demanding memory retrieval conditions. This study identified a negative hippocampal response that was linked to behavioral measures of memory search. Furthermore, this signal covaried with activity in the default network, a system of brain regions previously shown to deactivate with elevated task engagement and focused attention. Notably, task-negative activity associated with retrieval demands was localized to the anterior hippocampus, distinguishing it from posterior task-positive hippocampal activity. These findings established the basis for a theory, further tested in subsequent experiments, that the hippocampus is uniquely involved in mnemonic functions which fluctuate with dynamic attentional changes associated with task demands.

Chapter 3 expanded upon this preliminary evidence that the default network is modulated by the degree of search invoked during retrieval, to dissociate activity related to search from that related to memory strength. Activity in default network regions was selectively reduced with increasing retrieval search, whereas activity in distinct

prefrontal and parietal regions corresponded with the strength of recalled associations. Thus, this study supports the finding, first reported in Chapter 2, that search-driven reductions in default network activity are specifically modulated by attentional engagement, rather than mnemonic properties of the recalled target memory.

While the collective results from Chapters 2 and 3 implicate a hippocampal-neocortical system broadly sensitive to attentional load, they also prompt further questions over how such presumably task-general responses relate to specialization of the hippocampus for memory. Chapter 4 thus disentangles the concomitant effects of memory encoding, retrieval and task difficulty on hippocampal activity. Consistent with the preceding work, spatially segregated responses were observed in the anterior and posterior hippocampus to retrieval difficulty and retrieval success, respectively. But critically, the task-negative anterior hippocampal activity concurrently signaled encoding of the background environment.

Findings from these three investigations were integrated in Chapter 5, wherein I present a comprehensive theory accounting for hippocampal activity during retrieval. The reviewed evidence points strongly towards the perpetual involvement of the hippocampus in encoding novel information, and suggests that the degree to which the hippocampus remains actively engaged in memory acquisition can be regulated by simultaneous, potentially competitive, cognitive demands.

While these prior three studies helped to inform about how the hippocampus and neocortex support distinct components of a retrieval event, a final study more thoroughly examined how the MTL represents the content of a retrieved memory. This

study built upon prior evidence for MTL subregional specialization for the "what, where and when" of a memory, to identify neural representations of retrieved contextual information. Multivoxel analyses dissociated spatially distributed MTL activity patterns that coded contextual memory features from those that were redundant with large-scale regional involvement, or were broadly driven by task difficulty. Thus, these findings suggest that MTL reactivation of memory representations may manifest both as fine, spatially distributed activity and as larger-scale regional activations, and highlight the influence of non-memory behavioral parameters on retrieval-related activity.

Together, this series of investigations offers further insight into the mechanisms by which the hippocampus and surrounding neocortex support episodic memory and interact with brain systems subserving non-mnemonic functions associated with effortful retrieval.