The Influence of Emotion on the Neural Correlates of Episodic Memory: Linking
Encoding, Consolidation, and Retrieval Processes

by

Maureen Ritchey

Department of Psychology and Neuroscience
Duke University

Date: ________________
Approved:

____________________
Roberto Cabeza, Supervisor

____________________
Kevin S. LaBar

____________________
R. Alison Adcock

____________________
Christina L. Williams

Dissertation submitted in partial fulfillment of
the requirements for the degree of Doctor of Philosophy in the Department of
Psychology and Neuroscience in the Graduate School
of Duke University

2011
ABSTRACT

The Influence of Emotion on the Neural Correlates of Episodic Memory: Linking Encoding, Consolidation, and Retrieval Processes

by

Maureen Ritchey

Department of Psychology and Neuroscience
Duke University

Date: ________________
Approved:

____________________
Roberto Cabeza, Supervisor

____________________
Kevin S. LaBar

____________________
R. Alison Adcock

____________________
Christina L. Williams

An abstract of a dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Psychology and Neuroscience in the Graduate School of Duke University

2011
Abstract

Emotion is known to influence multiple aspects of memory formation, which may include the initial encoding of the memory trace, its consolidation over time, and the efficacy of its retrieval. However, prior investigations have tended to treat emotional modulation of episodic memory as a unitary construct, thus conflating the contributions of these different stages to emotion-mediated memory enhancements. The present thesis aims to disentangle the component processes of emotional memory formation and retrieval through a series of studies using cognitive behavioral and functional magnetic resonance imaging (fMRI) methods. In the first 2 studies, neural activity was evaluated during the initial viewing of emotionally arousing and neutral scenes and, in the 3rd study, neural activity during this initial viewing period was compared to that during a recognition memory task. The findings are compatible with the proposal that two distinct networks support successful emotional memory formation: an amygdala-medial temporal lobe (MTL) network that modulates the consolidation of memories over time and a prefrontal-MTL network that translates emotion effects on controlled elaboration into superior memory encoding. The superlative quality of emotional memories is furthermore marked by heightened similarity between neural states at encoding and retrieval, suggesting another line of evidence through which emotion effects can be observed. Taken together, the results presented here highlight the heterogeneity of processes that confer mnemonic advantages to emotionally significant information.
Dedication

To all who honor and seek knowledge for the sake of knowledge.
Contents

Abstract .......................................................................................................................... iv

List of Tables .................................................................................................................. xi

List of Figures .................................................................................................................. xii

Acknowledgements ......................................................................................................... xv

1. Introduction .................................................................................................................. 1

1.1 Overview of Emotion Effects on Memory ................................................................. 3

1.1.1 Declarative Memory Processes ............................................................................. 3

1.1.2 Neural Correlates of Emotional Arousal ............................................................ 7

1.1.3 Behavioral Effects of Emotion on Memory .......................................................... 9

1.1.4 Thesis .................................................................................................................. 11

1.2 Encoding .................................................................................................................... 12

1.2.1 General Effects .................................................................................................. 12

1.2.2 Emotion Effects ................................................................................................ 14

1.2.2.1 Perception .................................................................................................... 14

1.2.2.2 Attention ...................................................................................................... 16

1.2.2.3 Semantic processing ..................................................................................... 18

1.2.3 From Encoding to Consolidation ......................................................................... 19

1.3 Consolidation ............................................................................................................ 20

1.3.1 Arousal-Mediated Consolidation in Rodents ....................................................... 20

1.3.2 Arousal-Mediated Consolidation in Humans ....................................................... 23

1.3.2.1 Patient and pharmacological evidence ......................................................... 24
1.3.2.2 Behavioral and neuroimaging evidence...........................................25
1.3.3 Other Approaches ...........................................................................27
1.3.4 Dissociating Encoding and Consolidation.........................................29
1.4 Retrieval .............................................................................................30
  1.4.1 Overview .......................................................................................30
    1.4.1.1 General effects .......................................................................30
    1.4.1.2 Emotion effects .....................................................................31
  1.4.2 Encoding-Retrieval Overlap ..............................................................33
    1.4.2.1 General effects .......................................................................33
    1.4.2.2 Emotion effects .....................................................................35
  1.5 Key Questions .....................................................................................36
2. Passage of Time Modulates Networks Predicting Emotional Memory Success........38
  2.1 Introduction .......................................................................................38
  2.2 Methods ............................................................................................43
    2.2.1 Participants ...............................................................................43
    2.2.2 Materials ...................................................................................43
    2.2.3 Procedure ..................................................................................44
    2.2.4 Behavioral Analyses ...................................................................45
    2.2.5 FMRI Methods ...........................................................................46
  2.3 Results ...............................................................................................50
    2.3.1 Behavioral Results .....................................................................50
    2.3.2 Imaging Results .........................................................................51
2.3.2.1 Encoding activity predicting memory for emotional and neutral pictures after short versus long delays ................................................................. 51

2.3.2.2 Individual differences associated with recollection persistence for emotional stimuli ................................................................. 53

2.3.2.3 Functional connectivity distinguishing between remembered items at short versus long delays ................................................................. 55

2.4 Discussion ........................................................................................................ 59

3. Encoding Task Modulates Networks Predicting Emotional Memory Success ........ 65

3.1 Introduction ....................................................................................................... 65

3.2 Methods ............................................................................................................. 70

3.2.1 Participants .................................................................................................. 70

3.2.2 Materials ..................................................................................................... 70

3.2.3 Procedure ..................................................................................................... 71

3.2.4 Behavioral Analyses ..................................................................................... 73

3.2.5 FMRI Methods ............................................................................................ 74

3.3 Results ............................................................................................................. 78

3.3.1 Behavioral Analyses ..................................................................................... 78

3.3.1.1 Encoding response data ........................................................................... 78

3.3.1.2 Recognition memory data ........................................................................ 78

3.3.2 fMRI Analyses ........................................................................................... 80

3.3.2.1 Overall memory-related activity ............................................................... 80

3.3.2.2 Common and task-specific effects of emotional arousal on memory-related activity ................................................................. 82
5.1 Key Questions, Revisited ................................................................. 126
5.2 Methodological Issues for Consideration ................................. 129
  5.2.1 On Consolidation and Time ....................................................... 129
  5.2.2 Choice of Encoding Tasks ......................................................... 131
  5.2.3 Interactions Between Encoding and Consolidation ............... 132
  5.2.4 Better Ways of Measuring Reactivation at Retrieval .............. 133
5.3 Remaining Questions for the Future ............................................. 134
  5.3.1 Valence and Arousal Manipulations ...................................... 134
  5.3.2 MTL Specialization ............................................................... 136
  5.3.2 Links between Consolidation and Retrieval ......................... 139
5.4 Concluding Thoughts ................................................................. 141
References ....................................................................................... 143
Biography ......................................................................................... 164
List of Tables

Table 1: Encoding success activity (remembered > forgotten) collapsed over delay ........52
Table 2: Activity predicting individual differences in recollection persistence ..................54
Table 3: Regions exhibiting emotion- and delay-specific connectivity with amygdala ....56
Table 4: Behavioral Results ..................................................................................................79
Table 5: Emotion Effects ........................................................................................................80
Table 6: Overall Dm Activity ..................................................................................................81
Table 7: Influence of Emotional Arousal on Dm Activity ......................................................83
Table 8: Influence of Emotional Valence on Dm Activity ........................................................85
Table 9: All regions tested with Match x Memory ANOVA results .......................................110
Table 10: Within-subjects logistic regression of memory performance on ROI activity and encoding-retrieval similarity .........................................................................................113
Table 11: Mediation analysis linking encoding-retrieval similarity to memory ........116
Table 12: Regions showing emotional modulation of encoding-retrieval similarity ......118
List of Figures

Figure 1: Behavioral results. Memory at each delay was assessed using the corrected recognition score d’, and recollection and familiarity estimates were obtained via a dual-process ROC curve-fitting procedure (Yonelinas et al. 2002). Persistence scores for memory, recollection, and familiarity were then calculated by dividing long-delay estimates by their associated short-delay estimates (e.g., emotional memory persistence is equivalent to emotional long-delay d’ divided by emotional short-delay d’). Recollection persistence scores were significantly greater for emotional than neutral items, suggesting an emotional recollection effect. Error bars indicate standard error of the mean. *significant at p = .05 ......................................................... 51

Figure 2: Encoding success activity (ESA) for emotional items. Areas that show greater ESA for emotional (Emo) than neutral (Neut) items include (a) bilateral amygdalae and (b) left inferior frontal gyrus (IFG). Bar graphs represent functional ESA estimates, that is, group-averaged contrasts between hits at each delay (Short and Long) and short-delay misses. Error bars indicate standard error of the mean. See Table 1 for coordinates.................................53

Figure 3: Activity associated individual differences in recollection persistence for emotional stimuli. a) Left amygdala region whose activity correlates across-subjects with individual differences in recollection persistence for emotional items. See Table 2 for coordinates. b) Scatterplot depicting the relationship between individual recollection persistence scores for emotional stimuli and mean activity in the left amygdala region in response to emotional pictures. c) Scatterplot depicting the relationship between individual recollection persistence scores for neutral stimuli and mean activity in the left amygdala region in response to neutral pictures......55

Figure 4: Functional connectivity with the amygdala. a) Bilateral anterior parahippocampal regions whose connectivity with the amygdala interacts with emotion and delay, such that connectivity during long-delay hits is greater than during short-delay hits, but only for emotional items. See Table 3 for coordinates. b) Scatterplot depicting the relationship between mean single-trial activation estimates (i.e., beta weights) from the indicated right PHG region and the seed amygdala voxel, across emotional long-delay hits. These data points were extracted from an individual representative participant for display purposes. .......................................................... 57

Figure 5: Functional connectivity differences associated with emotional recollection persistence. a) In these across-subject scatterplots, the y-axis denotes the difference in connectivity between the amygdala and left or right PHG during emotional long- versus short-delay hits. The x-axis indicates individual recollection persistence scores for emotional stimuli. Note that increasing levels of emotional recollection persistence are associated with increasing disparity between connectivity supporting emotional memory after long versus short delays. b) In these across-subject scatterplots, the y-axis
denotes the difference in connectivity between the amygdala and left or right PHG during neutral long- versus short-delay hits. The x-axis indicates individual recollection persistence scores for neutral stimuli. Note that there is no relationship between connectivity differences and neutral recollection persistence. .............................................. 58

Figure 6: Schematic of the experimental design for a single trial during encoding. Separate lists of 70 negative, 70 neutral, and 70 positive pictures were assigned to deep and shallow conditions. Deep and shallow conditions were blocked across runs. .......... 72

Figure 7: Common and task-specific effects of emotional arousal on Dm activity. Activations are overlaid on a T1 template and mean contrast estimates within the activated regions are plotted for each condition to illustrate the effect. a) Left peri-amygdaloid region showing common effects. b) Right amygdala region showing shallow task-specific effects. c) Right vIPFC region showing deep task-specific effects. Error bars denote standard error. ................................................................. 84

Figure 8: a) Common effects of emotional valence on Dm activity. Retrosplenial cortex activations are overlaid on a T1 template and mean contrast estimates within this activated region are plotted for each condition to illustrate the effect. b) Deep task-specific effects of emotional valence on Dm activity. c) Scatterplot depicting the correlation between each individual’s Dm activity within the caudate nucleus during the deep positive condition, and individual scores on the consummatory subscale of the Temporal Experience of Pleasure Scale (TEPS). Error bars denote standard error. .......... 86

Figure 9: a) Schematic of the functional network and equation used in the multiple regression analyses. b) Plots of the standardized beta coefficients as a function of valence for left and right hippocampus. Results are plotted separately for the deep (top) and shallow (bottom) conditions. Asterisks denote the significance of the corresponding coefficient in each condition, p < .05. HC = hippocampus, Amyg = Amygdala, Std = Standardized................................................................. 87

Figure 10: Participants viewed emotionally negative, positive, and neutral images during scene encoding and recognition memory tasks. Beta estimates were computed for each individual trial at both encoding and recognition (a). For the full complement of encoding-retrieval pairs, including one-to-one match pairs (same picture) and condition match pairs (same valence, task and memory status, different pictures), beta patterns were extracted from 31 separate anatomical ROIs and the similarity between patterns was computed (b). ......................................................................................................... 105
Figure 11: Encoding-retrieval similarity was greatest among visual processing regions (a), such as the calcarine gyrus, within which one-to-one match pairs were more similar than condition-match pairs, regardless of memory (b). d = distance, rem = remembered, forg = forgotten.................................................................110

Figure 12: Encoding-retrieval similarity in several regions was modulated by memory success (a), characterized by either a main effect of memory (blue) or memory by match interaction (ref). The inferior frontal ROI showed greater encoding-retrieval similarity for remembered items among both the one-to-one and condition-match pairs (b). The middle occipital and middle temporal ROIs were characterized by an interaction in that memory effects were stronger among one-to-one than condition-match pairs (c). Finally, mean ROI activation and encoding-retrieval similarity independently predicted across-trial variation in memory success, demonstrating a lack of redundancy among these measures (d). Mid = middle, d = distance, rem = remembered, forg = forgotten.............112

Figure 13: Mediation analysis tested the hypothesis that the hippocampus mediates the relationship between encoding-retrieval neocortical similarity and memory success (a). Among regions showing memory-modulated encoding-retrieval similarity effects, the influence of encoding-retrieval similarity in inferior frontal, inferior parietal, and occipital ROIs on memory was significantly mediated by the hippocampus (b). E-R = encoding-retrieval, hc = hippocampus.................................................................116

Figure 14: Emotion significantly enhanced overall encoding-retrieval similarity effects in a number of posterior regions and specifically enhanced one-to-one match effects within middle occipital gyrus (a). The middle occipital gyrus showed greater encoding-retrieval similarity for negative and positive relative to neutral trials among the one-to-one match pairs (b). Encoding-retrieval similarity in middle occipital gyrus was additionally correlated across trials with retrieval activity in the amygdala; this correlation was modulated by memory success for negative but not positive or neutral trials (c). Neg = negative, pos = positive, neut = neutral, MOG = middle occipital gyrus.........................118
Acknowledgements

I thank my advisors, Roberto Cabeza and Kevin S. LaBar for giving me the opportunity to immerse myself in an environment devoted to cutting-edge research and scholarship; for acting as leaders, mentors, and collaborators along the way; and for pushing me to always be better. I would also like to thank my committee members, R. Alison Adcock and Christina L. Williams, for offering their own expert perspectives on the work presented here and for their time and involvement in this process. I owe much to all of the members of the Cabeza and LaBar labs, who have provided research support and camaraderie over the last six years. In particular, I thank Florin Dolcos, Vishnu Murty, Simon W. Davis, and Erik Wing for their insights and contributions to the work described here.

My love of psychology and neuroscience was born in my hometown public library, where my mom would let me wander the shelves for what seemed like hours. My parents, Pat and Becky Ritchey, encouraged creativity and independent thinking; they bestowed me with an abundant sense that I could do anything and go anywhere. For this I am forever grateful. I am lucky to have had their support and that of my brothers, their families, and my in-laws. For all its intermittent heartbreaks and small victories, graduate school will linger in my memory as an ideal time, thanks in large part to my friends who have been, at once, comrades, confidantes, and sources of inspiration. Finally, I thank Dan McGuire, my husband, for whom any measure of appreciation falls embarrassingly short. He is the keeper of my emotional memories.
1. Introduction

The ability to encode new experiences and retrieve those from our past facilitates not only human survival, but also the persistence of self across a lifetime. Our memories compose our personal histories, color interpretation of our selves and our experiences, and enable us to apply our knowledge of the world to new demands. These benefits become particularly compelling when the memories access emotional experiences: it is rewarding to remember our first love and potentially life-saving to remember a predator. Not surprisingly, then, memories tinged with emotional salience tend to be remembered better and with greater vividness than emotionally neutral memories. Arousal sets off a cascade of changes that influence nearly every facet of cognitive and mnemonic processing.

As an example, suppose that a snake crosses your path while you are out on a hike. You will quickly notice the snake’s presence, rapidly survey its visual features for signs of danger, target your attentional resources toward the snake’s movements, retrieve any semantic information you might have about snakes (particularly the dangerous ones), and maintain all of this information online so that you can act appropriately at any second. Meanwhile, the stress will set off physiological changes within the system, increasing neuronal transmission within the amygdala and sending a flood of stress hormones that impact the medial temporal lobes (MTL). Together, these responses result in a visually- and semantically-elaborated depiction of the scene in front of you as well as facilitations in the reception and consolidation of this information into a memory trace (for a review, see Kensinger & Schacter, 2008a; LaBar & Cabeza, 2006). A year later, when you go hiking again, the similar setting triggers your memories for this event. You remember the snake so
vividly that you begin to feel nervous again and take extra caution in monitoring your surroundings.

This example speaks to the complexity of characterizing all of the processes, cognitive, neural, and physiological, that contribute to the formation and retrieval of an emotional memory trace. With all of these events happening at once, how does one begin to disentangle one from the other in terms of its mnemonic consequences? One main way to classify these influences on emotional memory is to determine whether they primarily impact one memory phase versus the others or whether they have similar effects on multiple stages. Declarative memories can be regarded as consisting of three main stages: encoding, consolidation, and retrieval. Encoding refers the initial formation of a memory trace, whereas consolidation refers to the strengthening of this memory trace over time. Retrieval refers to the reactivation of these memories after a delay. This framework maps clearly onto cognitive models that regard memory as a feat of information coding, storage, and recovery. This division of memory into stages has proven influential in guiding research methodology (Squire, 1992; Tulving & Markowitsch, 1997), with neuroimaging studies of memory often centered on the encoding or retrieval phase alone. As described later, the consolidation phase is less frequently studied and more challenging to observe directly in humans, although it has been the emphasis of the literature on arousal-mediated memory in rodents (McGaugh, 2000).

Parsing the effects of emotion on memory by memory stage may prove useful for 2 reasons: 1) emotion may impact memory through separable neural networks that are differentially tied to each memory stage; and 2) emotion may influence cognitive processes that are common to multiple memory stages. More specifically, I will show evidence that
emotional memory formation is supported by a set of cortically-mediated networks that primarily impact encoding as well as an amygdala-MTL network that modulates consolidation. I will also show evidence that there are overlapping neurocognitive operations supporting emotional memories at both encoding and retrieval.

1.1 Overview of Emotion Effects on Memory

1.1.1 Declarative Memory Processes

Memories begin with the initial experience and its encoding into long-term storage. Encoding can be regarded as the sum of cognitive operations that generates and refines the cortical representation of an event, as well as the initial convergence of this information within the MTL. The most common neuroimaging method for studying encoding is the subsequent memory paradigm (Paller & Wagner, 2002). In this paradigm, neural responses are collected while participants view a series of stimuli one by one; memory for these stimuli is tested after some delay. Memory performance is used to sort the encoding trials into whether they were subsequently remembered or forgotten. The difference between remembered and forgotten items is taken as encoding success activity (ESA), and regions exhibiting ESA are thought to promote memory encoding. Across standard (non-emotional) memory paradigms, ESA effects have been consistently identified throughout the MTL as well as in the lateral prefrontal cortices (PFC) and perceptual processing regions (Spaniol et al., 2009). In particular, in addition to the MTL, the left ventrolateral PFC has been emphasized as important for successful encoding. This region is thought to substantiate controlled encoding processes such as organization and elaboration, and likely interacts with the MTL to generate strong memory traces (Simons & Spiers, 2003). Although PFC lesions are not as disruptive to memory as MTL lesions, they result in subtle memory
deficits consistent with the role of the PFC in strategic encoding or retrieval processes (Shimamura, 1995).

Consolidation, on the other hand, begins once the cortical inputs have converged, and consists of processes that strengthen the bound representation into an enduring memory trace. The term consolidation can itself be subdivided into synaptic consolidation versus systems consolidation, which refer to memory stabilization on different spatial and temporal scales (Sutherland & McNaughton, 2000). Synaptic (or cellular) consolidation refers to processes that operate within the cell to stabilize synapses within seconds, minutes, to hours after learning. Systems consolidation, on the other hand, refers to processes by which mnemonic information becomes less reliant on the MTL memory system and more grounded within neocortex over the course of days to years. Whereas evidence for synaptic consolidation is primarily derived from experiments in rodents, where it has been linked to long-term potentiation (LTP) and replay processes, systems consolidation can be observed indirectly in humans. One way to investigate consolidation in humans is to measure neural activity or introduce an intervention (e.g., pharmacological) immediately following encoding. Another approach is to measure changes in memory as a function of time and link them to neural activity during either encoding or retrieval. These methods are described in further detail in Chapter 2. In general, it has been shown that enhanced memory performance can be tied to activity associated with the learned event during sleep or post-encoding rest (e.g., Rudoy, Voss, Westerberg, & Paller, 2009; Tambini, Ketz, & Davachi, 2010). Furthermore, it has been argued older memories are less dependent on the MTL and more reliant on cortical networks at retrieval (Frankland & Bontempi, 2005).
Retrieval refers to the reactivation of the memory trace after some delay; in episodic memory, this is also conceptualized as the re-experiencing of the memory. This reactivation can be triggered by the representation of the memorandum itself, via an associate, or through an active search process. These pathways loosely correspond to 3 of the main methodologies for assessing memory retrieval in the laboratory: recognition, cued-recall, and free recall. One approach to identifying the neural correlates of successful retrieval is to compare brain activity during remembered versus forgotten items, called retrieval success activity (RSA). FMRI studies have identified a consistent network of regions including the MTL, lateral PFC, parietal cortices, and posterior midline regions that are engaged during retrieval success (Spaniol, et al., 2009). Activation profiles at retrieval may mark processes that operate primarily within the retrieval stage itself to promote memory success, or they may be influenced by the efficacy of initial encoding and subsequent integrity of the memory trace. Studies with lesion patients are able to dissociate these sources more effectively than neuroimaging designs and suggest that MTL participation may be less critical at retrieval than at encoding (Nadel, Samsonovich, Ryan, & Moscovitch, 2000; Squire, 1992).

As suggested above, MTL structures appear to be critical for the encoding, consolidation, and retrieval of memories. Since the report of patient HM’s massive memory deficits following a bilateral temporal lobectomy (Scoville & Milner, 1957), the MTL has been highlighted as the seat of memory processing. As reviewed by Amaral (1999), the MTL memory system includes the hippocampus and the surrounding parahippocampal gyrus. The parahippocampal gyrus consists of the entorhinal and perirhinal cortices at its anterior aspect and the parahippocampal cortex at the posterior. Aside from their anatomical
segregation, each of these MTL subregions might be further delimited by the function it supports. Consistent with this hypothesis, it has been proposed that these subregions contribute differentially to recognition memory (Eichenbaum, Yonelinas, & Ranganath, 2007).

At the center of the MTL memory system, the hippocampus is considered critical to forming associations between stimulus or event representations and, as such, episodic and relational memory. The perirhinal cortex, on the other hand, has been demonstrated to participate in single-item recognition in particular; thus, it may specifically play a role in item processing (Brown & Aggleton, 2001). The parahippocampal cortex is thought to support contextual learning, supported by its connectivity with regions devoted to visuospatial processing (Suzuki & Amaral, 1994). Finally, both the perirhinal and parahippocampal cortices project to the entorhinal cortex in parallel streams (Burwell, 2000); the entorhinal cortex then conveys this information through the perforant pathway across the entire length of the hippocampus (Amaral, 1999). Because of their close association, the hippocampus and entorhinal cortex are typically ascribed similar functions. The amygdala can also be included as part of the MTL, as it lies directly anterior the hippocampus and is enfolded by the rhinal cortices, although it is often discussed separately due to its distinct functions.

Memories and their corresponding neuroanatomy can be additionally segregated with respect to their phenomenology at retrieval. The dual-process memory theory posits that there are two processes, recollection and familiarity, that contribute to successful memory (Yonelinas, 2002). Under this theory, the hippocampus primarily supports recollection whereas the rhinal cortices primarily support familiarity. Single-process
memory theories, on the other hand, propose that memory strength is a unitary construct that can account for all of the available data (Wixted & Squire, 2011). Both of these theories can be applied to recognition memory data through the use of signal detection models and examination of receiver operating characteristic (ROC) curves. Although these phenomenological differences are based primarily on experience during retrieval, differences according to subsequent memory have been observed during encoding as well (Davachi, Mitchell, & Wagner, 2003; Ranganath et al., 2004). Thus, whether MTL specialization emerges as a function of information content, phenomenology, or memory strength, it appears to pervade both encoding and retrieval, with less known about consolidation.

1.1.2 Neural Correlates of Emotional Arousal

As reviewed elsewhere (Herman, Ostrander, Mueller, & Figueiredo, 2005; Lopez, Akil, & Watson, 1999; Vermetten & Bremner, 2002), stress, including emotional arousal, evokes a series of neurohormonal changes that impact physiological arousal and cognitive functioning. The primary mediators of these effects are the hypothalamic-pituitary-adrenal (HPA) axis, which modulates release of glucocorticoid hormones and epinephrine. Glucocorticoid receptors are prevalent within the hippocampus, making this site particularly susceptible to their activation (McEwen & Sapolsky, 1995). Autonomic changes are regulated by noradrenergic projections from the nucleus of the solitary tract and locus coerules, a system activated by increased epinephrine release from the adrenal gland. Noradrenergic cells are largely localized to these brainstem regions and project to a variety of cortical and subcortical regions including the PFC, amygdala and other parts of the brainstem. Through these projections, noradrenergic activation regulates cognitive
function, emotional processing, and autonomic arousal. Although other neurotransmitters like dopamine, serotonin, glutamate, and GABA also contribute to stress responses, glucocorticoids (cortisol in primates, corticosterone in rats) and norepinephrine are most critical to mediating the impact of arousal on memory function (as reviewed by McGaugh, 2004), and will be discussed further in the next section.

Noradrenergic activation in the amygdala seems to be particularly influential in guiding emotional responses and memory. The amygdala is a collection of distinct nuclei, including the basal nucleus, central nucleus, lateral nucleus, and accessory basal nucleus among others. In normal subjects, amygdala activity is heightened in response to biologically-salient stimuli, such as fearful faces, snakes, and mutilated bodies, and when the amygdala is lesioned, patients exhibit deficits in fear processing, emotional memory, and fear conditioning (Zald, 2003). The amygdala also has extensive connectivity with the rest of the brain, including sensory cortices, hippocampus, and hypothalamus, allowing it to influence perception, memory, and the endocrine system, respectively (Aggleton & Saunders, 2000).

In particular, the amygdala is heavily interconnected with the MTL memory system. The amygdala projects to all MTL subregions: the hippocampus and entorhinal, perirhinal, and parahippocampal cortices (Pitkanen, Pikkarainen, Nurminen, & Ylinen, 2000). Thus, the amygdala is able to send inputs both directly to the hippocampus and indirectly through the entorhinal cortex. The amygdala also facilitates impulse transmission between perirhinal and entorhinal cortices: perirhinal and entorhinal spikes are more correlated shortly after basolateral amygdala (BLA) activity (Paz, Pelletier, Bauer, & Pare, 2006). This could
represent arousal-driven enhancements in information processing within the MTL, with sensory-related cortical activity being relayed to the hippocampus more effectively.

Beyond the amygdala, the orbitofrontal and anterior cingulate cortices are known to be involved in higher-order emotional processing (LeDoux, 2000). The amygdala projects heavily to orbitofrontal cortex, which may provide a pathway for integrating emotion and cognition within the PFC (Barbas, 2000). Lesions to the orbitofrontal cortex result in personality changes, social deviance, and poor emotion regulation (Rolls, 2004). The anterior cingulate cortex is likewise thought to bridge between subcortical emotion responses and cortical control processes (Yamasaki, LaBar, & McCarthy, 2002).

1.1.3 Behavioral Effects of Emotion on Memory

Emotion influences multiple aspects of cognition, and the impact of emotion on memory processes has been particularly well studied. Emotion is known to modulate both non-declarative and declarative forms of memory (see LaBar & Cabeza, 2006 for a review). In particular, declarative memories for emotionally salient information tend to be enhanced relative to their neutral counterparts, marked by both improved memory accuracy for emotional information (Burke, Heuer, & Reisberg, 1992; Cahill et al., 1996; Dolcos, LaBar, & Cabeza, 2004a, 2004b; LaBar & Phelps, 1998) as well as increased vividness of these memories (Dolcos, Labar, & Cabeza, 2005; Ochsner, 2000; Sharot, Delgado, & Phelps, 2004; Sharot, Verfaellie, & Yonelinas, 2007). Memory enhancements can be driven by either the valence of a stimulus (how emotionally positive or negative it is) or the emotional arousal induced by the stimulus (see Kensinger, 2004 for a review). This overarching pattern has been identified for both laboratory-based and autobiographical memories (Talarico, LaBar, & Rubin, 2004).
Within the laboratory, the finding that emotion enhances memory has been replicated a number of times, using a variety of methodologies. Some of the first studies of human emotional memory used a slideshow narrative in which a few key slides were either emotional or neutral. Results from these early studies showed that healthy participants who viewed the emotional slides remembered them better than those who viewed the neutral slides (Cahill, Babinsky, Markowitsch, & McGaugh, 1995; Cahill, Prins, Weber, & McGaugh, 1994; Heuer & Reisberg, 1990). Since then, researchers have tended to use sets that have a large number of stimuli for use in more complex neuroimaging designs. These stimuli most often come from the International Affective Picture System (Lang, Bradley, & Cuthbert, 2001), a set of complex visual scenes, and the Affective Norms for English Words database (Bradley & Lang, 1999), both of which have been normed for properties including emotional valence and arousal. Other studies have used visual objects or fearful, happy, and neutral faces. After some delay between encoding and retrieval, which has ranged from immediate testing to one or more years, the participants’ memories are tested via recognition, cued-recall, or free recall. These design parameters are detailed in a recent meta-analysis of fMRI studies of emotional memory encoding (Murty, Ritchey, Adcock, & LaBar, 2010). Across these methods, memory performance tends to be higher for emotional materials than neutral materials, but this finding has not been completely uniform. For example, some studies using recognition memory designs have reported that emotional materials tend to induce greater recognition bias, leading to higher false alarm rates, but not greater accuracy (Maratos, Allan, & Rugg, 2000; Sharot, et al., 2004; Windmann & Kutas, 2001). However, increased bias does not sufficiently explain findings of higher accuracy rates within cued- or free-recall tests.
The impact of emotion on memory may also change depending on which features of the memorandum are tested. For example, it has been suggested that emotion differentially impacts the gist versus details of a memory (Burke, et al., 1992; Heuer & Reisberg, 1992; Kensinger, Garoff-Eaton, & Schacter, 2006; Kensinger, Garoff-Eaton, & Schacter, 2007a). The influence of emotion on detailed memory may be further modulated by whether details are central versus peripheral to the emotionally-salient features of the stimulus, leading to memory enhancements or impairments, respectively (Christianson & Loftus, 1991; Kensinger, Garoff-Eaton, & Schacter, 2007b; Loftus, 1979). In sum, the influence of emotion on memory is robust yet complex. Studying the neural correlates of these processes may help to illuminate the underlying mechanisms that result in these interesting patterns of behavior.

1.1.4 Thesis

Emotion exerts a robust influence on episodic memory, as measured in the laboratory and in the wild. Thus far, neuroimaging investigations have generally treated emotional memory as a unitary construct, focusing on mapping the neural patterns associated with emotional versus neutral memory at a single time-point. These investigations have provided essential insight into the whole-brain networks supporting emotional modulation of memory as well as into the replicability of key elements from the extensive rodent literature. With this strong foundation of knowledge, neuroimaging research is now poised to investigate emotional memory, deconstructed. The goal of this thesis is to interrogate the effects of emotion at multiple memory stages, comparing encoding effects to consequent consolidation and retrieval effects, and to identify specific networks and cognitive processes that are affected at each stage.
I begin by outlining the multiple stages of memory in turn, summarizing the available evidence linking emotion to specific processes within each stage. I argue that the formation of emotional memories is supported by two separable pathways: a set of cortically-mediated networks whereby emotion influences processes standard to memory encoding and an amygdala-MTL network whereby emotional arousal triggers a neurohormonal cascade that modulates consolidation of the memory trace. Importantly, I propose ways to experimentally manipulate relative reliance on these pathways during emotional memory formation, implemented in Chapters 2 and 3. Next I discuss how the neural systems involved in emotional memory retrieval may be similar and different to those involved during emotional memory formation. I propose that one can characterize the reactivation of a memory by studying the overlap between encoding and retrieval, thus enabling investigation of how emotion impacts the fidelity of memory reactivation. This is implemented in Chapter 4. Altogether, I present a summary view of emotional modulation at each stage of declarative memory and then novel data illustrating the neural correlates that span and distinguish each of these processes.

1.2 Encoding

1.2.1 General Effects

Memory encoding refers to the translation from experience to bound memory representation. It can be interpreted as the grand sum of all operations that participate along this pathway, including perception, attention, and semantic processing. Thus, encoding is sensitive to manipulations that impact each of these components, emotion being one such manipulation. First, I describe the contributions of component processes to
memory encoding in general. Then I will detail evidence of emotional modulation of these component processes and their impact on memory.

The first step of episodic memory encoding is the perception of the to-be-remembered item or event. The richness of the item or event representation likely depends on the degree of perceptual analysis. Consistent with this hypothesis, activity in visual processing regions predicts subsequent memory for pictures (Garoff, Slotnick, & Schacter, 2005; Kensinger & Schacter, 2006; Kirchhoff, Wagner, Maril, & Stern, 2000), words (Kensinger & Schacter, 2006; Otten & Rugg, 2001), and faces (Kuskowski & Pardo, 1999). Visual processing regions seem particularly important to supporting memory when the encoding task demands specialized perceptual processing (Bernstein, Beig, Siegenthaler, & Grady, 2002; Otten & Rugg, 2001). Importantly, the participation of these regions can influence the specificity of subsequent memory: for example, right fusiform gyrus predicts specific, detail-based memory for objects whereas left fusiform predicts non-specific, gist-based memory for objects (Garoff, et al., 2005).

The success of episodic memory encoding is also thought to depend on sufficient attentional allocation to the perceived items. Not surprisingly, awareness during encoding enhances explicit memory (Tulving, 1985), and disruptions in attention during encoding have deleterious consequences for episodic memory. This is most commonly seen within divided attention paradigms. Divided attention paradigms demand simultaneous participation in a primary and secondary task, typically resulting in performance decrements on each task compared to when they are given full attention. When one engages in a secondary task during encoding, memory suffers relative to the full attention condition (Craik, Govoni, Naveh-Benjamin, & Anderson, 1996). Although the terminology itself
1.2.2 Emotion Effects

1.2.2.1 Perception

Among these component processes, perception has been the most extensively studied with respect to how it may mediate the link between emotion and memory encoding. The evidence for emotional modulation of perception is strong. The amygdala appears to receive perceptual information via subcortical pathways prior to conscious awareness (Morris, DeGelder, Weiskrantz, & Dolan, 2001). Retrograde tracing studies have revealed direct feedback pathways from the amygdala to the ventral visual pathway (Amaral, Behniea, & Kelly, 2003), placing the amygdala in position to modulate the extent of visual processing. This anatomical relationship between emotional and visual processing is
bolstered by a wealth of data detailing emotion’s enhancing effect on activation in visual areas and subsequent effect on perceptual encoding (Dolan & Vuilleumier, 2003; Vuilleumier & Pourtois, 2007).

One function of the amygdala seems to be improving the likelihood that an arousing stimulus will reach conscious awareness, as observed in the attentional blink paradigm. The attentional blink is the tendency to miss detecting a target when it follows another target very closely in time. Emotional targets are more likely to be detected under conditions normally associated with an attentional blink (Anderson, 2005). Arousing stimuli also trigger heightened responses in perceptual processing areas compared to neutral stimuli (Vuilleumier & Driver, 2007), for both visual (Lane, Chua, & Dolan, 1999; Lang et al., 1998; Vuilleumier, Armony, Driver, & Dolan, 2001) and auditory (Grandjean et al., 2005) information. These changes occur as early as 100 to 200 ms post-onset (Pizzagalli et al., 2002; Schupp, Junghofer, Weiße, & Hamm, 2003).

Critically, these sensory facilitations are likely driven by amygdala feedback. During emotional and neutral picture viewing, amygdala activity covaried with activity in the inferior temporal cortex, with activity in both regions increasing with arousal (Sabatinelli, Bradley, Fitzsimmons, & Lang, 2005). More compellingly, amygdala damage eliminates the advantage of negative over neutral stimuli within the associated perceptual processing regions. Although the fusiform gyrus can be modulated by attentional manipulations in amygdala patients, it no longer responds preferentially to negative versus neutral faces (Vuilleumier, Richardson, Armony, Driver, & Dolan, 2004); resilience to the attentional blink also wanes in these patients (Anderson & Phelps, 2001). Together, this provides convincing evidence that the amygdala modulates activity related to perception, serving to bias
processing toward stimuli that are biologically salient, prioritize their access into conscious awareness, and improve the quality of information being sent to memory systems.

There are few studies that directly relate the influence of emotion on perception to its role in determining subsequent memory. Recently, this question has been addressed through both behavioral and neuroimaging analyses. In a paradigm designed to investigate memory for specific visual details, participants were asked to determine whether an object was identical or merely similar to one previously studied (Kensinger, et al., 2006; Kensinger, et al., 2007b). In both of these studies, memory for specific visual details was better for arousing negative objects than for neutral objects, as indicated by a greater ability to distinguish identical from similar objects. Neuroimaging results revealed that both the amygdala and fusiform gyrus participated in this effect (Kensinger, et al., 2007b). More specifically, whereas one subregion of the right fusiform gyrus predicted specific memory for both negative and neutral items, another better predicted specific memory for negative than neutral items. The latter fusiform subregion also showed greater functional connectivity with the amygdala during trials associated with specific remembered trials, compared to non-specific remembered or forgotten trials. These results bridge the effects of emotion on perception and memory by showing that arousal-mediated enhancements of visual processing regions during encoding result in superior visual memory for emotional items.

1.2.2.2 Attention

Attention can be construed as a limited capacity resource, such that allocating attention to one stimulus or task leaves fewer available for others (Desimone & Duncan, 1995). This model of attention posits that items in the environment compete for these
resources, and that competition is biased toward goal-relevant stimuli. Because arousing stimuli are biologically relevant, they should dominate the competition for available attentional resources (Pessoa & Ungerleider, 2004). Investigations using divided attention during emotional memory encoding have revealed that arousing stimuli tend to be more resistant to the negative consequences of divided attention than neutral stimuli: compared to neutral stimuli, memory for arousing stimuli encoding under divided attention is more comparable to that when encoded under full attention (Kensinger & Corkin, 2004; Kern, Libkuman, & Otani, 2005; Talmi, Schimmack, Paterson, & Moscovitch, 2007). These results can be interpreted as showing that since attention is preferentially allocated to the arousing stimuli, regardless of its competition, arousal mitigates the mnemonic consequences of adding a secondary task. Consistent with this interpretation, performance on an auditory primary task suffers when emotional word encoding serves as the secondary task, signifying a trade-off between the tasks (Talmi, et al., 2007). Importantly, this paper also employed a mediation analysis revealing that both arousal and attention make independent contributions to emotional memory enhancements. This underscores the claim that arousal can have direct effects on emotional memory processes, or it can act indirectly through attentional biasing to improve encoding: both mechanisms having the net result of improving long-term emotional memory relative to neutral. Neuroimaging data in support of this hypothesis highlighted a region in fusiform gyrus as being sensitive to attention as well as predictive of emotional memory enhancements, hinting at the possibility that interactions between this region and the amygdala facilitate the link between these effects (Talmi, Anderson, Riggs, Caplan, & Moscovitch, 2008).
Recently, these ideas have been formalized in accounts of how emotion supports memory for certain features or events during encoding but not others. One line of research has emphasized the idea of “trade-offs” between item and context encoding, demonstrating that arousing items tend to be better remembered at the expense of memory for neutral contextual information (Waring & Kensinger, 2009, 2011; Waring, Payne, Schacter, & Kensinger, 2010). This effect is accompanied by enhancements in temporo-parietal regions associated with attention (Waring & Kensinger, 2011). A more general theory encompassing these effects is the arousal-biased competition model, which suggests that attention during encoding is biased toward goal-relevant information (including but not limited to arousing stimuli) and this bias infiltrates subsequent consolidation and memory performance (Mather & Sutherland, 2011).

1.2.2.3 Semantic processing

Although much attention has been given to the effect of emotion on perception and how this interaction impacts emotional memory encoding (Kensinger, et al., 2007b; Vuilleumier & Driver, 2007), there has been little, if any, research on the role of semantic processing in predicting emotional versus neutral memory. Emotional stimuli are typically assumed to command more elaborate semantic processing, perhaps due to their distinctiveness or the degree to which one can relate emotional stimuli to personal experiences. There is evidence that the left ventrolateral PFC exhibits greater encoding success activity for emotional than neutral stimuli (Dolcos, et al., 2004a; Kensinger & Corkin, 2004). As mentioned above, this region is activated during deep, semantic encoding compared to shallow, perceptual encoding (Kapur, et al., 1994; Otten, et al., 2001; Otten & Rugg, 2001), suggesting it plays a role in semantic processing. Although this evidence is
intriguing, the emotional memory studies identifying these regions did not directly manipulate the type of controlled processes during encoding. This topic will be elaborated on in Chapter 3, which describes a study that sought to fill this gap in the literature by varying levels of processing during encoding of negative, positive, and neutral pictures.

1.2.3 From Encoding to Consolidation

Taken together, this evidence speaks to the breadth of encoding mechanisms that influence the quality of information sent to the MTL. Once these cortical inputs arrive, the MTL serves to bind distributed elements of a stimulus or event representation into a memory trace that can be sustained for minutes, days, weeks, or even years. Encoding can be construed as the gate to consolidation: the relevant information must be represented within the MTL before its trace can be strengthened over time. This interplay between encoding and consolidation is critical to the understanding of how these components contribute to memory for arousing events. Consolidation can act only on those memory elements that have been allocated sufficient encoding resources, rendering consolidation dependent on the efficacy of encoding. Furthermore, it has been proposed that competitive processes during consolidation magnify attentional biases observed during encoding, deepening this interaction (Mather & Sutherland, 2011; Payne, Stickgold, Swanberg, & Kensinger, 2008). The next section details how consolidation processes themselves are modulated by emotional arousal, thus providing a primary amygdala-MTL pathway for emotional modulation of memory as well as magnifying the influence of the cortically-mediated routes described above.
1.3 Consolidation

The study of declarative memory consolidation has only recently gained popularity within neuroimaging research, but consolidation has long been an important component of memory theories in behavioral neuroscience and studies of amnesic patients. As mentioned previously, consolidation can refer to both synaptic forms of consolidation as well as systems-level consolidation. Each of these forms of consolidation is important for the sustenance of memories over time and appear to be impacted by emotional arousal, although it is not currently clear whether the emotion effects emerge from common or separate mechanisms. I turn first to the study of arousal-mediated consolidation in rodents and then to the human neuroscience literature that has followed directly from this body of work.

1.3.1 Arousal-Mediated Consolidation in Rodents

There is a long history of studying arousal-enhanced consolidation within rodents using behavioral neuroscience paradigms such as inhibitory avoidance learning or the Morris water maze task. In these cases, memory is tested hours to days after learning and has been linked with LTP processes that operate at the level of the synapse. LTP refers to a period of increased excitability that follows moderately high levels of stimulation, which can ultimately result in structural changes at the synapse that enhance the coupling of the pre- and post-synaptic cells. LTP has served as a model for how memories may be stored within the hippocampus, and these structural changes provide a plausible neurobiological account for consolidation (Bliss & Collingridge, 1993; McGaugh, 2000).

Within animal models, stress hormones have been long known to influence memory consolidation (McGaugh, 1989). For example, both pre- and post-training injections of
glucocorticoid receptor antagonists disrupt performance on the Morris water maze task, suggesting that these receptors are essential to acquisition and consolidation of spatial memories (Oitzl & de Kloet, 1992). However, hormones are not alone in accounting for changes in memory; stress-induced catecholamine release also plays a role. Epinephrine release from the adrenal gland stimulates noradrenergic transmission from the brainstem to cortex and, critically, the amygdala. Noradrenergic activity in the amygdala also seems to affect memory consolidation in particular: post-training infusions of norepinephrine or beta-adrenergic agonists into basolateral amygdala (BLA) enhance memory retention (Ferry & McGaugh, 1999; Hatfield & McGaugh, 1999), whereas post-training infusion of beta-adrenergic antagonists impair memory retention (Hatfield & McGaugh, 1999).

It has been suggested that the amygdala plays an intermediary role in arousal-enhanced memory (see McGaugh, Cahill, & Roozendaal, 1996 for a review). A large body of evidence suggests that the influences of arousal on MTL structures are rendered ineffective without the amygdala’s support. Without an intact BLA exhibiting arousal responses, the memorial consequences of glucocorticoid modulations are eliminated (Roozendaal & McGaugh, 1996, 1997; Roozendaal, Okuda, De Quervain, & McGaugh, 2006; Roozendaal, PortilloMarquez, & McGaugh, 1996). These effects are specifically tied to beta-adrenergic receptors: blocking these receptors in the BLA eliminates the effects of pharmacological manipulations in the hippocampus (Quirarte, Roozendaal, & McGaugh, 1997; Roozendaal, Nguyen, Power, & Mcgaugh, 1999) and entorhinal cortex (Roesler, Roozendaal, & McGaugh, 2002). Additionally, these two mechanisms have different time-courses of action: glucocorticoids are relatively slow-acting and may exert its influence over memory at the scale of an entire learning session (1 to 2 hours), whereas norepinephrine may operate on
narrower timescale (less than 30 minutes) (Joels, Fernandez, & Roozendaal, 2011). There may be an ideal window during which peak noradrenergic responses coincide with peak glucocorticoid modulation and the impact on memory is maximized (Joels, et al., 2011). Importantly, because the timing of these mechanisms may be too coarse to be tied to individual items within a rapid series, it seems likely that consolidation effects are augmented especially for those items that received prioritized processing during encoding (Mather & Sutherland, 2011).

The importance of amygdala inputs may stem from their role in facilitating LTP induction and expression, consistent with the idea that arousal modulates synaptic consolidation processes. BLA lesions attenuate LTP induction in the dentate gyrus (Ikegaya, Saito, & Abe, 1994), whereas stimulation of the ipsilateral BLA lowers the threshold for LTP induction (Ikegaya, Saito, & Abe, 1995; Nakao, Matsuyama, Matsuki, & Ikegaya, 2004). These effects have been shown to be dependent on norepinephrine (Akirav & Richter-Levin, 2002) and are associated with improvements in hippocampal-dependent memory (Hu et al., 2007). The interaction of BLA and hippocampal activity in generating LTP induction is time-dependent: these effects are strongest when activity is simultaneous and degrade as the interval between activations increases (Hu, et al., 2007; Ikegaya, et al., 1995; Nakao, et al., 2004). Thus, the effectiveness of post-training manipulations of noradrenergic activity in the BLA falls off over time. This timeline corresponds to period during which spontaneous BLA activity remains above baseline after an arousal-inducing shock: activity levels peak either immediately or about 40 minutes after the shock and persist for up to 2 to 3 hours (Pelletier, Likhtik, Filali, & Pare, 2005). This window of opportunity suggests that these
arousal effects primarily impact memory consolidation, mediated by late LTP expression, which unfolds over this time period.

If consolidation mechanisms are the true target of amygdala-MTL interactions, then the influence of arousal should be greatest after the memory traces have been given some time to consolidate. Indeed, pharmacological manipulations of the BLA response to arousal have time-sensitive behavioral effects. Drug infusions into the amygdala impact long-term memory (24-hours), but not working memory (3-s) or intermediate memory (1-hour) performance in an inhibitory avoidance paradigm (Bianchin, Mello e Souza, Medina, & Izquierdo, 1999). The delay in behavioral impact suggests that these drugs target consolidation mechanisms in particular, since the effects of encoding manipulations are less likely to be influenced by time between learning and retrieval. This idea will be returned to in Chapter 2, which tests the hypothesis that human neural activity at the time of encoding may reflect the initiation of processes that guide consolidation, whose effects become more apparent over time.

Taken together, this evidence strongly points to the amygdala-MTL network's role in modulating memory consolidation in particular. Targeting consolidation mechanisms has the adaptive value of allowing the organism to learn about stimuli or events that predict future stress or arousal. As we will see, this animal model of arousal-mediated memory consolidation has been extraordinarily influential in guiding our understanding of arousal-enhanced memory within the human literature as well.

1.3.2 Arousal-Mediated Consolidation in Humans

Because of this clear literature linking amygdala-MTL interactions to consolidation processes, emotional memory studies have taken a unique trajectory toward studying
human memory consolidation, emphasizing paradigms and pathways similar to those described above. However, there have been largely separate attempts to characterize systems consolidation in humans emphasizing changes in MTL reliance over time, sleep processes, and reactivation mechanisms. I first detail the literature borne directly from the amygdala and MTL results described above. Then I will return briefly to describe a few preliminary attempts to unite these separate frameworks for studying consolidation.

1.3.2.1 Patient and pharmacological evidence

The amygdala has proven to be crucial to emotional memory encoding and consolidation in humans as well. Patients with selective, bilateral amygdala damage are impaired relative to controls in declarative memory for arousing pictures (Adolphs, Cahill, Schul, & Babinsky, 1997; Cahill, et al., 1995; Phelps et al., 1998) and words (Phelps, et al., 1998), but show normal memory for non-arousing stimuli. Unilateral temporal lobectomy patients, at least those with left-lateralized lesions, may suffer similar deficits (Adolphs, Tranel, & Denburg, 2000), consistent with animal work in which lesions are often given unilaterally. These data underscore the necessity of the amygdala in generating emotional memory enhancements. Furthermore, whereas controls tend to forget emotional words more slowly than neutral words, unilateral temporal lobectomy patients do not show this pattern (LaBar & Phelps, 1998). The amygdala and MTL memory structures, then, seem to be particularly critical to arousal-mediated enhancements involving memory consolidation over time.

Similar findings can be elicited via pharmacological interventions, such as the administration of drugs that upregulate noradrenergic activation, such as yohimbine, or those that block beta-adrenergic receptors, such as propranolol. In a design in which beta
blockers, placebos, and yohimbine were administered to separate groups prior to encoding, beta blockers impaired and yohimbine enhanced memory for an arousing story relative to placebo (O’Carroll, Drysdale, Cahill, Shajahan, & Ebmeier, 1999). In a separate study, propranolol was shown to impair memory for emotional but not neutral stimuli, whether it was given before or after encoding (Cahill, et al., 1994). Pharmacological manipulations of noradrenergic activity also determine amygdala participation in emotional memory formation: for example, propranolol administration prior to encoding eliminates amygdala activity relating to emotional encoding success activity (Strange & Dolan, 2004). In other words, noradrenergic activation seems to be the main contributor to amygdala activity during encoding, and without this form of activation, the amygdala fails to contribute to arousal-enhanced memory. Thus, one can interpret amygdala activations during emotional memory encoding as being representative of noradrenergic transmission within this region.

1.3.2.2 Behavioral and neuroimaging evidence

Consistent with these findings, in normal subjects amygdala activity during encoding correlates with one’s ability to retrieve emotional but not neutral memories, from recall of films (Cahill, et al., 1996) to recognition of images (Hamann, Ely, Grafton, & Kilts, 1999). Though these original findings relied on across-subject correlations of overall performance, the same pattern holds true within subjects. Subsequent memory designs reveal that amygdala activity is greater for subsequently-remembered than forgotten stimuli, a pattern specific to arousing rather than neutral stimuli (Canli, Zhao, Brewer, Gabrieli, & Cahill, 2000; Kensinger & Corkin, 2004). This effect is localized to the BLA (Dolcos, et al., 2004b), consistent with animal studies implicating this region in arousal-enhanced memory. Encoding success activity within the hippocampus and entorhinal cortex
has also been reported to be greater for emotional than neutral stimuli (Dolcos, et al., 2004b), although other studies claim that this memory-related activity is shared equally across emotional and neutral stimuli (Cahill, et al., 1996; Hamann, et al., 1999; Kensinger & Corkin, 2004).

Because consolidation, by definition, occurs after the initial encoding of a memory, it is difficult to argue that neuroimaging techniques directly assess neural activity related to consolidation. Instead, I suggest that the neural activity and connectivity seen at encoding indicate the initiation of a cascade of events that result in improvements in memory consolidation. For example, the influence of amygdala activity on LTP, which is often assumed to be the underlying process in memory consolidation, is time-dependent: amygdala activity facilitates LTP induction when it coincides with the inducing tetanus within the hippocampus, but this facilitation fades as these two events are offset in time (Hu, et al., 2007; Ikegaya, et al., 1995). Thus, the initial co-activation of the amygdala and hippocampus is critical to facilitating improvements in consolidation over time. In this way, neuroimaging at encoding can provide an indirect measure of ensuing consolidation processes.

In parallel with animal studies indicating that co-activation of the hippocampus and amygdala is critical to emotional memory formation, neuroimaging results also speak to the importance of amygdala connectivity with memory-related regions during encoding. In one of the first studies to look at this relationship, activation estimates in both the amygdala and hippocampus were correlated with individual differences in emotional memory enhancements. Across subjects, these regions were also correlated with each other during encoding of negative and positive images (Hamann, et al., 1999). Since then, functional
connectivity between the amygdala and hippocampus has been demonstrated multiple
times, through path analysis (Kilpatrick & Cahill, 2003) as well as across-subject variations
in emotional encoding success activity (Dolcos, et al., 2004b) and activity during
subsequently-remembered arousing words (Kensinger & Corkin, 2004). Emotional memory
encoding is also associated with functional connectivity between the amygdala and
parahippocampal gyrus, including both entorhinal (Dolcos, et al., 2004b) and
parahippocampal (Kilpatrick & Cahill, 2003) cortices.

As a final point, many of these results are time-sensitive, pointing to the role of
consolidation. Because consolidation is taken as a process that unfolds over hours, days, or
longer, arousal-related modulations that specifically target consolidation mechanisms
should increase in their influence on behavior as time goes on. Both behavioral and
neuroimaging evidence in support of this hypothesis are presented in detail in Chapter 2,
which describes a study designed to assess the influence of retention interval on the neural
correlates of emotional memory formation.

1.3.3 Other Approaches

The topic of memory consolidation has been pursued separately within other lines
of research, some of which have recently started to integrate emotion effects. These lines of
research have tended to emphasize the replay or reactivation of recently learned
information, thought to promote systems consolidation of memories, in which
hippocampal-dependent memories are trained and become entrenched in neocortex
(McClelland, McNaughton, & O’Reilly, 1995). The most closely related approach to those
described above involves recording neural responses during post-encoding rest periods and
linking them to the efficacy of recent learning (Carr, Jadhav, & Frank, 2011; Sutherland &
McNaughton, 2000). In rodents, this design has yielded evidence that hippocampal replay of recently learned spatial sequences is correlated with later memory and might mark early stages of consolidation (Dupret, O’Neill, Pleydell-Bouverie, & Csicsvari, 2010). This type of design was recently adapted for humans, providing supportive evidence for increased functional connectivity between hippocampus and stimulus-specific processing regions during post-encoding rest that predicted individual variability in memory (Tambini, et al., 2010).

The link between replay or reactivation and memory has been explored in more detail in the context of sleep consolidation. Sleep is known to improve memory for recently learned information and render these memories less susceptible to interference (Ellenbogen, Hulbert, Stickgold, Dinges, & Thompson-Schill, 2006). Information that is cued during sleep via auditory associates or contextual odors are remembered better than uncued information (Diekelmann, Büchel, Born, & Rasch, 2011; Rasch, Büchel, Gais, & Born, 2007; Rudoy, et al., 2009), and these cues evoke activity in the hippocampus (Diekelmann, et al., 2011; Rasch, et al., 2007). These studies suggest that artificially introducing reactivation during sleep facilitates memory consolidation, supporting the hypothesis that consolidation may be mediated by reactivation. The study of sleep consolidation has recently been expanded to include investigations into the influence of emotion. It has been shown that post-encoding sleep preferentially benefits emotional relative to neutral memories (Hu, Stylos-Allan, & Walker, 2006) and that these memory differences persist up to 4 years (Wagner, Hallschmid, Rasch, & Born, 2006). A night of sleep also exacerbates emotional memory trade-offs described above, with enhanced memory for negative items accompanied by impaired memory for their neutral contexts (Payne, et al., 2008).
Furthermore, after a 12-hour sleep versus 12-hour wake period, retrieval of emotional memories is associated with a more amygdala-dependent network (Payne & Kensinger, 2010).

1.3.4 Dissociating Encoding and Consolidation

Emotional arousal regulates many cognitive processes that support memory encoding as well as neurohormonal interactions within an amygdala-MTL network that facilitate memory formation and consolidation. Because these events happen near-simultaneously, it is difficult to tease apart the contributions of each processing cascade: for example, how can improvements in memory be traced back to semantic processing during encoding or enhanced consolidation, when both likely contributed? Much of the research on emotional memory has ignored this question, instead focusing on the role of either encoding or consolidation. For example, cognitive psychology has a rich tradition of modeling how stimulus processing at encoding influences later memory, with theories often constructed such that the representations themselves are generalizable to any yet-undiscovered neural substrates. Behavioral neuroscience techniques, on the other hand, can perturb neural function down to the gene, permitting direct assessments of the dependency of arousal-enhanced consolidation on neurohormonal interactions.

Cognitive neuroscience approaches may be reconcile these disparate traditions and allow for the simultaneous manipulation and measurement of neurocognitive functions supporting each aspect of emotional memory formation. Specifically, it is proposed that manipulating the time between encoding and retrieval will draw out those processes that are predictive of enhancements in consolidation, which become more apparent over time. This hypothesis is experimentally tested in the Chapter 2. Furthermore, it is hypothesized
that modulating the level of elaborative processing during encoding will primarily influence processes devoted to superior encoding for emotional materials, rather than consolidation per se. This hypothesis is experimentally tested in Chapter 3. Across both studies, hemodynamic responses are recorded during the encoding of emotional and neutral materials and then classified with respect to whether they resulted to successful or unsuccessful memory.

1.4 Retrieval

1.4.1 Overview

1.4.1.1 General effects

Often the last step in measuring memory, retrieval has been the focus of many studies of episodic memory. Within the context of current neuroimaging techniques, these investigations have revolved around identifying networks of neural regions that support successful versus unsuccessful retrieval using measures of RSA. The hippocampus and surrounding MTL cortex are at the center of these networks and are essential for the recovery of recent and, perhaps to a lesser extent, remote episodic memories (Frankland & Bontempi, 2005; Squire, 1992). During memory retrieval, memories can be triggered by cues in the environment (e.g., a familiar context or face) or as part of an active search process (e.g., trying to remember the name associated with the face). Once memories are detected—that is, once the representation sufficiently matches one from previous experience—the process of memory recovery begins. Neurocomputational models propose that the hippocampus guides the reactivation of cortical network ensembles to recreate the representation of prior experience; this reinstatement is referred to as pattern completion (McClelland, et al., 1995; Norman & O’Reilly, 2003). Successful memory recovery is
accompanied by the feeling of familiarity and, when specific details are retrieved, the feeling of re-living referred to as recollection (Yonelinas, 2002).

At the neural level, then, successful memory retrieval involves reactivation of brain regions associated with the original learning experience (Nyberg, Habib, McIntosh, & Tulving, 2000; Wheeler & Buckner, 2003; Wheeler, Petersen, & Buckner, 2000). In addition, dorsolateral prefrontal and parietal cortices are thought to be involved during memory search and monitoring (Fleck, Daselaar, Dobbins, & Cabeza, 2006). Ventral parietal cortex has been proposed to track spontaneous memory recovery and attention to mnemonic information (Cabeza, 2008; Cabeza, Ciaramelli, Olson, & Moscovitch, 2008). Engagement of the precuneus is thought to reflect imagery processes that operate during successful retrieval and, in the case of autobiographical memory in particular, medial prefrontal and retrosplenial cortical regions participate in the recovery of self-relevant memories (Cabeza & St Jacques, 2007). Interestingly, some of these components of the retrieval network overlap with what has been termed the default network, a set of brain regions that tend to be co-active during rest and less active during attention-demanding tasks (Daselaar et al., 2009).

1.4.1.2 Emotion effects

The literature on emotional influences during retrieval is less straightforward than the literature highlighting encoding or consolidation (Buchanan, 2007). Within behavioral neuroscience studies, it has been shown that the mnemonic impact of amygdala activation is temporally restricted to the learning period and shortly thereafter, suggesting that the amygdala modulates memory storage in other regions, but is not a storage site itself (Packard, Cahill, & McGaugh, 1994). Thus, it is not clear that the amygdala is even necessary to retrieve emotional memories: the work of arousal is already done. Complicating matters
further, stress responses at the time of retrieval have been shown to impair memory performance (de Quervain, Roozendaal, & McGaugh, 1998; Kuhlmann, Piel, & Wolf, 2005), and these impairments are dependent on the amygdala (Roozendaal, Griffith, Buranday, de Quervain, & McGaugh, 2003).

In humans, emotional retrieval has been demonstrated to elicit enhanced amygdala and hippocampal activation relative to neutral retrieval, in parallel with encoding effects. Furthermore, these regions tend to be functionally co-active during retrieval, suggesting that they interact to promote emotional memory enhancements (Dolcos, et al., 2005). These enhancements tend to be associated with higher rates of vivid recollection (Dolcos, et al., 2005; Ochsner, 2000), although it has been disputed that these feelings of recollection correspond to real increases in accuracy (Maratos, et al., 2000; Sharot, et al., 2004; Windmann & Kutas, 2001). However, the impact of manipulating noradrenergic systems has been disputed: whereas it has been reported that propranolol administration prior to retrieval fails to impact emotional memories (de Quervain, Aerni, & Roozendaal, 2007), recent data suggests that it weakens the enhancing effect of emotion on memory (Kroes, Strange, & Dolan, 2010).

Because many studies use recognition-based paradigms, where identical stimuli are presented at retrieval and encoding, it has been difficult to separate the influences of arousal on memory retrieval from its influences on perceptual processes that span both encoding and retrieval. It may be that enhanced activation patterns during retrieval reflects the same sense of heightened arousal that was experienced during encoding, but that only the encoding effects are causally related to memory strength. Alternatively, arousal at retrieval may facilitate the recovery of memories. A partial solution to this problem is to
embed neutral stimuli in emotional contexts at encoding and then test memory for the neutral memoranda alone at retrieval. In this type of design, any emotion-related response at retrieval must arise from memory of the original context, since emotional and neutral conditions appear the same at retrieval. In one study taking this approach, it was shown that neutral objects previously seen with emotional scenes elicited greater amygdala activity at retrieval, even in the absence of memory for the corresponding context (Smith, Henson, Rugg, & Dolan, 2005). Furthermore, functional connectivity between the amygdala and hippocampus was heightened during memory retrieval for these items (Smith, Stephan, Rugg, & Dolan, 2006).

1.4.2 Encoding-Retrieval Overlap

1.4.2.1 General effects

Another important topic in memory retrieval regards the overlap between encoding and retrieval processes. This has been formalized into the theory of encoding-retrieval match, which suggests that memory is a function of this overlap: greater similarity between neural and cognitive states at encoding and retrieval leads to better memory (Tulving & Thomson, 1973). The same ideas have also been applied directly to the cognitive operations present at encoding versus retrieval in the theory of transfer-appropriate processing (Morris, Bransford, & Franks, 1977). Within standard, non-emotional memory paradigms, these theories have been tested either directly or indirectly in 2 main ways: 1) by looking at the similarities and differences between ESA and RSA in the same study, and 2) by varying task, modality, or associates during encoding and looking for retrieval activity patterns consistent with the encoding condition. Among studies taking the first approach, ESA and RSA effects have been shown to partially overlap within the hippocampus (Prince, et al,
2005), although their overall response profiles in hippocampus may be somewhat different, with more anterior activations during encoding and more posterior activations during retrieval (Lepage, Habib, & Tulving, 1998; Prince, et al., 2005). ESA and RSA effects also overlap in processing-specific regions, such as the visual cortices when memory depends on visual associations between words and fonts and the left ventrolateral PFC when memory depends on semantic associations between words (Prince, et al., 2005). There are also clear differences according to memory stage, with ventrolateral PFC regions supporting encoding more than retrieval and vice versa for dorsolateral PFC regions (Prince, et al., 2005; Spaniol, et al., 2009). Perhaps the clearest dissociation between ESA and RSA profiles is the participation of the so-called default network. As mentioned above, this network, including lateral parietal and posterior midline regions, tends to track retrieval success; however, the same regions tend to be associated with encoding failure (Daselaar, et al., 2009). This may be due to differences in attention to internally-generated thoughts and mnemonic information.

Among studies taking the second approach to studying encoding-retrieval match, it has been demonstrated a number of times that RSA profiles tend to mimic processing regions associated with encoding. For example, if words are presented either visually or auditorily during encoding, then visual or auditory cortex tends to be reactivated during retrieval for words in the corresponding condition (Nyberg, et al., 2000; Wheeler & Buckner, 2003; Wheeler, et al., 2000). Similarly, if words are studied using distinct encoding tasks, then differences in these encoding tasks can be tracked during retrieval; in one study, multivariate pattern classifiers trained on encoding data successfully discriminated retrieval trials on the basis of task (Johnson, McDuff, Rugg, & Norman, 2009). Multivariate
pattern analysis (MVPA) techniques may be particularly informative in this line of questioning, since they allow for the comparison of distributed representational patterns between encoding and retrieval in a flexible, model-free way. Another study taking this approach showed that during paired-associate learning, patterns representing the previously studied associate came online during new learning (Kuhl, Rissman, Chun, & Wagner, 2011). This bespeaks the possibility of using MVPA approaches to flexibly identify instances of reactivation of previously learned information. This approach will be described in more detail in Chapter 4, which applies these methods to the study of encoding-retrieval match.

1.4.2.2 Emotion effects

Evidence regarding emotional modulation of encoding-retrieval overlap is sparse. Very few studies of emotional memory have collected fMRI data during both the encoding and retrieval phases (Murty et al., 2009; Sergerie, Lepage, & Armony, 2006). Taking these studies in addition to a long view of studies measuring only one phase (reviewed by Buchanan, 2007; e.g., Dolcos, et al., 2005; Smith, et al., 2006), it appears that enhancements in amygdala and MTL activation in response to emotional memoranda are shared between phases. Emotional modulation of memory success activity in regions devoted to perceptual processing has been reported separately during encoding, as described above, and retrieval (Botzung, Rubin, Miles, Cabeza, & Labar, 2010; Fenker, Schott, Richardson-Klavehn, Heinze, & Düzel, 2005; Smith, Henson, Dolan, & Rugg, 2004; Sterpenich et al., 2009).

Importantly, although it is reasonable to hypothesize that emotional arousal may impact the fidelity of neural reactivation during retrieval, this question has not yet been directly tested. As described above, some studies have shown reactivation of previously
encoded emotional contexts in response to associated neutral stimuli at retrieval (Smith, et al., 2005; Smith, et al., 2006). These findings show, at the very least, that emotional information from encoding can be reactivated during retrieval; it may be the case that this information is accompanied by an enhanced representation of the encoding state (Buchanan, 2007). Preliminary support for this pattern comes from a study showing enhanced activation of the fusiform face area during the recognition of words encoded with fearful versus neutral faces (Fenker, et al., 2005). It remains an open question whether reactivation during emotional retrieval would benefit memory above and beyond its benefits for neutral memory, or whether emotional retrieval would simply be more likely to elicit higher-fidelity encoding-retrieval match. This question will be tested empirically in Chapter 4, which tests for trial-to-trial variation in encoding-retrieval overlap for emotional versus neutral memoranda.

1.5 Key Questions

Strong evidence exists for emotional modulation of encoding, consolidation, and retrieval of declarative memories, but our understanding of the underlying mechanisms will be hindered without clear strategies for teasing apart these contributing factors. With this information in mind, there are several key questions for the present body of research. First, do amygdala and MTL responses during encoding support the stabilization of memories after a long- versus short-delay, consistent with a role in initiating consolidation processes? This question is tested in Chapter 2, which highlights the contribution of the amygdala-MTL network in promoting consolidation (Ritchey, Dolcos, & Cabeza, 2008). Second, can the effects of emotion on encoding be directly linked to memory benefits? This question is tested in Chapter 3, which demonstrates the participation of cortically-mediated pathways
in supporting emotional memory enhancements above and beyond the amygdala-MTL network (Ritchey, LaBar, & Cabeza, 2011). Finally, do emotional memory benefits reflect, in part, superior reactivation of the memory trace at retrieval? This question in tested in Chapter 4, which queries how emotional memories are affected by retrieval processes, in conjunction with and in addition to encoding and consolidation. Each of these questions is addressed via collection and analysis of behavioral and fMRI data, with an emphasis on identifying neural structures whose activity and co-activity vary with successful memory for emotional versus neutral materials.
2. Passage of Time Modulates Networks Predicting Emotional Memory Success

2.1 Introduction

The formation of emotional episodic memories, compared to non-emotional (neutral) memories, is characterized by at least two distinct advantages: increased resources during encoding (Dolcos, et al., 2004a; Kensinger, 2004) and arousal-driven enhancements leading to improved consolidation. According to the consolidation hypothesis, the latter effects reflect the modulatory influence of the amygdala on the medial temporal lobe (MTL) memory system, which boosts consolidation processes and the persistence of memories over time (LaBar & Cabeza, 2006; McGaugh, 2004).

These neuro-hormonal changes within the amygdala-MTL network, which constitute the “direct” route to emotional memory, are accompanied by a host of other changes during item encoding, including increased attentional and perceptual processing resources allocated to emotional stimuli (Dolan & Vuilleumier, 2003). These cognitive and perceptual encoding enhancements exert an indirect influence over emotional memory strength, and thus may be considered the “indirect” network supporting emotional memory. These “direct” and “indirect” networks are dissociable: whereas the direct network must be recruited by increased arousal, it has been suggested that components of the indirect network can be recruited by valence (whether an item is positive or negative) alone (Kensinger & Corkin, 2004). Furthermore, although both networks are activated during encoding, the impact of the direct network should become more apparent as consolidation processes unfold over time. By manipulating the time between encoding and retrieval, the
present study highlights the role of the direct network in creating and sustaining emotional memories.

Arousal enhances emotionally negative memories relative to neutral as time goes on, from 20 minutes to 1 week (Kleinsmith & Kaplan, 1963), from immediate to 1 hour (LaBar & Phelps, 1998), from 1 day to 2 weeks (Anderson, Yamaguchi, Grabski, & Lacka, 2006), and from immediate to 24 hours (Sharot & Phelps, 2004; Sharot & Yonelinas, 2008) post-encoding. Indeed, emotional memory is particularly resilient to time, with laboratory enhancements being reported up to 1 year post-encoding (Dolcos, et al., 2005). Emotional memories also tend to be accompanied by highly confident responding or a sense of re-experiencing (Dolcos, et al., 2005; Kensinger & Corkin, 2003; Ochsner, 2000; Sharot, et al., 2004), and these recollection benefits are also augmented relative to neutral over time (Anderson, Yamaguchi, et al., 2006; Sharot & Yonelinas, 2008).

These behavioral results are consistent with the claim that consolidation serves to mediate emotional memory enhancements over the course of hours to days (LaBar & Phelps, 1998). Accordingly, post-encoding consolidation manipulations influence memory after long (e.g., 24 hours) but not after short (e.g., 1.5 hours) delays (Bianchin, et al., 1999). The passage of time, then, should yield functional dissociations in the relative importance of encoding and consolidation effects to predicting subsequent retrieval of emotional memories (Hamann, 2001). One may predict that activity associated with arousal-mediated consolidation should increasingly distinguish between subsequently remembered and forgotten emotional items over time, whereas activity related to perceptual, attentional, or semantic encoding should make no improvement or even decay in its ability to make this distinction.
Although consolidation occurs after encoding, emotional arousal during encoding initiates firing rate increases within the amygdala that can persist for up to 2 hours post-encoding (Pelletier, et al., 2005), spanning the period during which consolidation manipulations are particularly effective (McGaugh, 2004). Furthermore, it has been demonstrated that amygdala activity facilitates the induction and expression of hippocampal long-term potentiation, which may be the underlying mechanism of memory consolidation (Hu, et al., 2007; Nakao, et al., 2004). These effects are time-sensitive: long-term potentiation benefits most when the amygdala and hippocampus are co-activated during acquisition or encoding. Thus, initial co-activation of these structures determines how much the memory trace will be strengthened and persist over time. These results give credence to the supposition that amygdala and MTL activity during encoding have implications for memory consolidation, consistent with previous interpretations of human data (Cahill, et al., 1996; Dolcos, et al., 2004b; Hamann, et al., 1999).

One powerful way to study how encoding activity leads to successful memory is the subsequent memory paradigm (Paller & Wagner, 2002). This paradigm involves measuring a participant’s brain activity while they encode a list of items. The results from a subsequent memory test are then applied to each participant’s encoding data, classifying each encoding trial as a subsequently remembered or forgotten trial. Greater activity for remember than forgotten trials is taken as encoding success activity (ESA), or encoding activity that leads to successful subsequent memory. Critically, this method enables the researcher to draw conclusions about within-subject, event-related activity that specifically predicts memory for that item. In comparison, correlations between an individual’s encoding activity and
overall memory score enable conclusions about across-subject, individual differences supporting later memory.

Few studies have investigated the neural correlates supporting emotional memory or recollection changes over time. In one such study, positron-emission tomography (PET) scans revealed that amygdala regional cerebral blood flow during encoding correlated with emotional recognition after a 4-week delay, but not with emotional free recall after a 10-minute delay (Hamann, et al., 1999). The authors attributed this effect to the role of consolidation, but due to limitations of the PET method, they were unable to look at event-related activity predicting subsequent memory. A later event-related functional magnetic resonance imaging (fMRI) investigation found that ventral amygdala activity during emotional picture viewing correlated with emotional memory after a 2-week delay, whereas dorsal amygdala activity correlated with emotional memory immediately after encoding (Mackiewicz, Sarinopoulos, Cleven, & Nitschke, 2006). Because this experiment did not employ a subsequent memory design, these results are again derived from across-subject correlations. It remains to be seen how the amygdala participates at the trial level to identify which items will be remembered after short versus long delays. Furthermore, neither of these studies reported a corresponding behavioral effect, with improved emotional memory relative to neutral over time. Taken together, these results suggest that individual variations during emotional memory encoding are related to how well these traces persist over time, but the role of inter-trial functional differences remains unclear.

Another key consideration in this line of research is the dynamic nature of arousal-mediated consolidation, which depends on interactions between the amygdala and the MTL memory system. Emotional memory enhancements are contingent on co-activation of the
amygdala with hippocampal (Roozendaal, et al., 1999) and parahippocampal (Roesler, et al., 2002) regions, and manipulations of either component can impact memory function (McIntyre, Power, Roozendaal, & McGaugh, 2003; Richardson, Strange, & Dolan, 2004). This interactive relationship has also been observed at the level of functional neuroimaging: correlations between memory-related activity in the amygdala and that in the hippocampus (Dolcos, et al., 2004b; Kensinger & Corkin, 2004) and parahippocampal gyrus (Dolcos, et al., 2004b; Kilpatrick & Cahill, 2003) are greater during emotional item-encoding than neutral. The dynamic process of consolidation, then, may be best captured via connectivity analyses, rather than simple contrasts.

The present study improves upon the previous literature by combining complementary methods to investigate the impact of study-test delay on encoding and consolidation-related activity supporting emotional memory. It employs a subsequent memory design to look at within-subject event-related activity and connectivity that distinguish between remembered and forgotten emotional items after short (20-minute) versus long (1-week) delays, as well as across-subject differences that correlate with emotional memory persistence. We interrogate three main hypotheses: 1) Activity in the amygdala and MTL memory system will be more predictive of long-delay emotional memory than short-delay emotional memory. 2) Individuals who display greater amygdala responses to emotional stimuli during encoding will show greater preservation of recollection for emotional stimuli over time. 3) Functional connectivity between the amygdala and MTL memory system will be greatest for those items remembered at the long delay, representing the increasing importance of dynamic consolidation processes.
2.2 Methods

2.2.1 Participants

Nineteen young adults (9 female; mean Age = 22.7, SD = 3.2) participated in the study. Participants were healthy, right-handed, native English speakers, with no disclosed history of neurological or psychiatric episodes. Participants gave written informed consent for a protocol approved by the Duke University Institutional Review Board. Due to image quality problems in their MRI scans, 2 of these participants were excluded from all analyses. Of the remaining 17 participants, 4 did not have enough trials (i.e., at least 10 per trial type) in each of the trial types of interest, and thus could not be included in the fMRI analyses. All behavioral and neuroimaging analyses were conducted on the remaining 13 participants (7 female; mean Age = 22.6, SD = 3.4).

2.2.2 Materials

Stimuli consisted of 480 pictures. These were selected from the International Affective Picture System (Lang, et al., 2001) as well as from an in-house, standardized database (Yamasaki, et al., 2002) that allowed us to equate the pictures for visual complexity and content (e.g., human presence). Pictures were assigned on the basis of normative valence scores to emotionally negative (valence: 1.4-4) and neutral (valence: 4-6) conditions. In accordance with the picture selection procedure, valence scores (1 = negative, 5 = neutral, 9 = positive) were lower for negative (M = 2.75, SD = 0.69) than neutral pictures (M = 5.04, SD = 0.52; t (478) = 41.22, p < .001). Additionally, arousal scores (1 = calm, 9 = excited) were greater for emotional (M = 5.69, SD = 0.89) than neutral pictures (M = 3.82, SD = 0.80; t (478) = 24.29, p < .001).
2.2.3 Procedure

Participants encoded pictures in the scanner and their recognition memory for these pictures was tested after two different delays. During encoding, participants viewed 160 emotionally negative and 160 neutral pictures while functional MR images were recorded. The pictures were presented in color for 1 second, followed by a noise mask for 200 ms. Trials were separated by an inter-trial fixation period which was quasi-exponentially distributed between 3 and 9 s, with a mean of 4750 ms, allowing for event-related fMRI analyses. Participants were instructed to indicate as soon as possible whether each picture was of an indoor or outdoor scene, and responses were collected until the onset of the next stimulus. The encoding session consisted of 5 functional runs, across which emotional and neutral pictures were evenly divided. To avoid the induction of long-lasting mood states, the pictures within each block where pseudo-randomized so that no more than three pictures of the same valence were consecutively presented. Block presentation order was counterbalanced across subjects.

Twenty minutes after encoding, participants completed a recognition task for half of these pictures (80 emotional negative, 80 neutral) outside of the scanner. An additional 40 emotionally negative and 40 neutral pictures were presented as distracters. These pictures were presented for 1 second, followed by a 1500-ms fixation, during which participants were instructed to respond whether the item was old or new. Then a confidence screen appeared for 1500-ms, instructing the participants to rate their confidence on a 3-point scale, from 1 meaning “not sure” to 3 meaning “very sure.” Trials were separated by a 1500-ms fixation period, and confidence responses were recorded until the onset of the next stimulus. This two-step response procedure yielded 6 possible recognition response
options (i.e., from "very sure new" to "very sure old"). All pictures were presented in grayscale in order to attenuate memory performance. One week later, participants were tested for their recognition of the remaining study items (80 emotionally negative, 80 neutral), also outside of the scanner. Study items were randomly assigned to two retrieval lists, and these lists were counterbalanced across subjects for whether they were presented at the 20-minute or 1-week delay. Recognition sessions at each delay were identical in design.

2.2.4 Behavioral Analyses

To measure overall differences in memory between conditions, d’ scores were evaluated for each trial type. Recollection and familiarity estimates were derived for each subject according to a dual-process receiver operating characteristic (ROC) curve-fitting procedure (Yonelinas, Kroll, Dobbins, Lazzara, & Knight, 1998). This model assumes that recollection and familiarity independently contribute to memory performance but are not mutually exclusive. In order to generate the ROCs, recognition data was rescaled from 1, indicating a highly-confident “new” response, to 6, indicating a highly-confident “old” response. Hit and false alarm rates were plotted according to this confidence scale, forming an ROC for each subject and condition. By fitting these data points to a function relating them to dual-process memory performance, we obtained parameter estimates of recollection and familiarity for each ROC. Estimates from each delay were then combined into a single measure by dividing the long-delay estimate by the corresponding short-delay estimate, yielding a measure of memories’ resistance to forgetting or “persistence.” For example, if a participant had a d’ of 2.4 after a short delay and a d’ of 1.2 after a long delay, the resulting “persistence score” was 0.5. A persistence score of 1 corresponds to the case when memory performance after a long delay is as high as memory performance after a
short delay. Persistence scores were calculated for memory performance overall, and separately for recollection (recollection persistence score) and for familiarity (familiarity persistence score). These three persistence scores were separately calculated for emotional and neutral pictures.

2.2.5 FMRI Methods

Images were collected using a 4T GE scanner. Stimuli were presented using liquid crystal display goggles (Resonance Technology, Northridge, CA) and behavioral responses were recorded using a four button fiber optic response box (Resonance Technology). Scanner noise was reduced with earplugs and head motion was minimized using foam pads and a headband. Anatomical scanning started with a T2-weighted sagittal localizer series. The anterior (AC) and posterior commissures (PC) were identified in the midsagittal slice, and 34 contiguous oblique slices were prescribed parallel to the AC-PC plane. High-resolution T1-weighted structural images were collected with a 500-msec repetition time (TR), a 14-msec echo time (TE), a 24-cm field of view (FOV), a 256² matrix, 68 slices, and a slice thickness of 1.9 mm. Functional images were acquired using an inverse spiral sequence with a 2-sec TR, a 31-msec TE, a 24-cm FOV, a 64² matrix, and a 60° flip angle. Thirty-four contiguous slices were acquired with the same slice prescription as the anatomical images. Slice thickness was 3.8 mm, resulting in 3.75 x 3.75 x 3.8 mm voxels.

Preprocessing and data analyses were performed using SPM2 software implemented in Matlab (www.fil.ion.ucl.ac.uk/spm/). After discarding the first 6 volumes, the functional images were slice-timing corrected and motion-corrected, and then spatially normalized to the Montreal Neurological Institute (MNI) template and spatially smoothed using an 8 mm isotropic Gaussian kernel, and resliced to a resolution 3.75 x 3.75 x 3.8 mm
voxels. For each subject, evoked hemodynamic responses to event types were modeled with a delta (stick) function corresponding to stimulus presentation convolved with a canonical hemodynamic response function (HRF) within the context of the general linear model (GLM), as implemented in SPM2. Confounding factors (head motion, magnetic field drift) were also included in the model.

The subsequent memory paradigm (Paller & Wagner, 2002) was employed to identify *encoding success activity* (ESA), which was defined as greater activity for pictures that were remembered rather than forgotten in subsequent memory tests. Eight main trial types were modeled, representing all possible combinations of arousal (emotional vs. neutral pictures), delay (short vs. long delays), and subsequent retrieval (hit vs. miss trials). Long-delay misses were disregarded in all fMRI analyses because this trial type is ambiguously related to short-delay hits and misses. That is, this trial type represents items that, had they been tested at the short delay, may have been classified as either short-delay hits or misses. However, because we did not re-test any items, it is unclear which items would have fallen which way. Thus, both short- and long-delay hits were compared to a common baseline, short-delay misses.

To find ESA regardless of delay, short- and long-delay hits were collapsed and compared to short-delay misses for each emotion type, yielding ESA for emotional and neutral pictures for each participant. A random-effects paired t-test then revealed which regions showed a greater ESA for emotional than neutral pictures. This t-test (*p* = .05, extent threshold = 5 functional voxels) was inclusively masked with ESA for emotional pictures at *p* = .05, pulling out only those regions that contribute differentially to the encoding of emotional stimuli. While probabilities are not completely independent this procedure

47
results in a threshold that approaches the joint probability estimate of \( p = .0025 \) (Fisher, Lazar, Luna, Sweeney, & Eddy, 2002).

To assess the interaction between arousal and delay, contrasts between short- and long-delay hits for each emotion type were generated for each subject. Because short- and long-delay hits share a common baseline, this is functionally equivalent to comparing the subsequent memory effect at the short delay to that at the long delay for each emotion type. Paired t-tests compared this delay effect for emotional and neutral. These t-tests (\( p = .05 \), extent threshold = 5 voxels) were inclusively masked at \( p = .05 \) with the corresponding delay effect (e.g. long-delay emotional hits > short-delay emotional hits) and subsequent memory effect (e.g. long-delay emotional hits > short-delay emotional misses) as to isolate those memory-related areas that distinguish between emotional short- and long-delay hits, but not between neutral short- and long-delay hits. Because of the triple threshold, the joint probability of these activations can be estimated as approaching \( p = .000125 \).

In order to track regions whose activity correlated with individual differences in sustained recollection, we implemented the simple regression model in SPM2. Parametric maps contrasting all emotional or neutral items versus baseline were taken as the dependent variables for each subject, and their corresponding measures of sustained recollection served as covariates. Resulting regression maps for each emotion type were thresholded at \( p = .05 \) with extent threshold = 5 voxels within the MTL and at \( p = .001 \) with extent threshold = 5 voxels outside of the MTL. The probability threshold was lower in the MTL because we can reasonably expect to see recollection-related activity within these regions. The conjunction of these maps (via inclusive masking, both at \( p = .05 \), extent
threshold = 10 voxels) was also taken to reveal general sustained recollection effects. The joint probability of this conjunction can be estimated as approaching p = .0025.

Amygdala regions identified in the previous regression analysis were further interrogated via individual trial analysis to examine the functional network of brain regions correlated with activity in this region. We created a GLM in which each individual trial was modeled by a separate covariate, yielding different parameter estimates for each individual trial and for each individual subject. The validity of the use of this design has been confirmed in previous studies (Daselaar, Fleck, & Cabeza, 2006; Rissman, Gazzaley, & D’Esposito, 2004). Parameter estimates from our peak amygdala voxel were correlated with trial-specific parameter estimates from all other voxels, generating correlation maps for each of our trial types of interest: emotional short-delay hits, emotional long-delay hits, neutral short-delay hits, and neutral long-delay hits. The correlation data was normalized via the Fisher Transform (Fisher, 1921), resulting in connectivity z-maps.

In order to assess differences in functional connectivity between our trial types, connectivity z-maps for short- and long-delay hits were statistically compared to each other for each subject. Data from the z-maps were first subtracted from each other, then divided by the standard error of the difference, $\sqrt{1(N_{\text{short}} - 3) + 1(N_{\text{long}} - 3)}$. This yielded z-maps representing the difference in connectivity associated with subsequent hits at each delay. These connectivity difference maps for emotional versus neutral were compared with a paired t-test (p = .05, extent threshold = 4 voxels within the MTL, 10 voxels elsewhere), inclusively masked with corresponding group effect (e.g. long-delay emotional hit > short-delay emotional hit connectivity) at p = .05 (approaching the joint probability of p = .0025). This is consistent with the way in which we assessed the interaction of emotion and delay in
our ESA analyses. In this way, we were able to isolate, for example, regions exhibiting
greater amygdala connectivity for subsequent long-delay hits than for short-delay hits, but
only for emotional items. Individual differences in connectivity were assessed outside of
SPM by exporting the difference map values for a specified functional ROI and correlating
them with sustained recollection measures for each subject.

2.3 Results
2.3.1 Behavioral Results

Persistence scores were calculated by dividing long-delay d’ scores by short-delay d’
 scores for each individual (see Methods). Although persistence scores did not show emotion
effects overall, $p > .1$ (Figure 1), differences were found when persistence scores were
separately calculated for recollection and familiarity. As illustrated by Figure 1, whereas
recollection persistence scores were greater for emotional than neutral pictures, $t (12) =
2.75, p = .017$, familiarity persistence scores did not differ as a function of emotion, $p > .1$
(Figure 1). These results are consistent with evidence that the memory-enhancing effect of
emotion is driven mainly by recollection rather than familiarity (Dolcos, et al., 2005;
Kensinger & Corkin, 2003; Ochsner, 2000), and expand this evidence by showing that
recollection benefits increase over time.
Behavioral results. Memory at each delay was assessed using the corrected recognition score $d'$, and recollection and familiarity estimates were obtained via a dual-process ROC curve-fitting procedure (Yonelinas et al. 2002). Persistence scores for memory, recollection, and familiarity were then calculated by dividing long-delay estimates by their associated short-delay estimates (e.g., emotional memory persistence is equivalent to emotional long-delay $d'$ divided by emotional short-delay $d'$). Recollection persistence scores were significantly greater for emotional than neutral items, suggesting an emotional recollection effect. Error bars indicate standard error of the mean. *significant at $p = .05$

2.3.2 Imaging Results

2.3.2.1 Encoding activity predicting memory for emotional and neutral pictures after short versus long delays

Analyses comparing encoding success activity (ESA, remembered > forgotten) for emotional vs. neutral pictures were first performed collapsed over delay and then as a function of delay (i.e., emotional-neutral x short-long interaction). Greater ESA for emotional than neutral stimuli collapsed over delays was found in bilateral amygdalae and the left ventrolateral prefrontal cortex (PFC; see Figure 2), among other brain regions (see Table 1). Unexpectedly, no regions survived our interaction analysis, suggesting that ESA for emotional items does not vary by delay. Thus, the results did not support our first prediction that activity in the amygdala and MTL memory system would be more predictive of memory after a long delay than after a short delay in the case of emotional pictures.
Instead, ESA for emotional pictures was comparable for short- and long-delay memory (see Figure 2).

**Table 1:** Encoding success activity (remembered > forgotten) collapsed over delay

<table>
<thead>
<tr>
<th>ESA emotional &gt; ESA neutral</th>
<th>Coordinates (T&amp;T)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BA</td>
</tr>
<tr>
<td>Amygdala/ Parahippocampal Gyrus</td>
<td>28</td>
</tr>
<tr>
<td>Amygdala/ Parahippocampal Gyrus</td>
<td>34</td>
</tr>
<tr>
<td>Inferior Frontal Gyrus</td>
<td>45</td>
</tr>
<tr>
<td>Inferior Temporal Gyrus</td>
<td>37</td>
</tr>
<tr>
<td>Angular Gyrus</td>
<td>39</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ESA neutral &gt; ESA emotional</th>
<th>Coordinates (T&amp;T)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BA</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>R</td>
</tr>
<tr>
<td>Cingulate Gyrus</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td>L</td>
</tr>
<tr>
<td>Caudate</td>
<td>L</td>
</tr>
<tr>
<td></td>
<td>R</td>
</tr>
<tr>
<td>Lentiform Nucleus</td>
<td>L</td>
</tr>
<tr>
<td>Temporal</td>
<td></td>
</tr>
<tr>
<td>Middle Temporal Gyrus</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td>R</td>
</tr>
<tr>
<td>Inferior Temporal Gyrus/Fusiform Gyrus</td>
<td>L</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>R</td>
</tr>
<tr>
<td>Occipital</td>
<td></td>
</tr>
<tr>
<td>Fusiform Gyrus</td>
<td>L</td>
</tr>
<tr>
<td>Middle Occipital Gyrus</td>
<td>R</td>
</tr>
</tbody>
</table>

Notes: BA = Brodmann Area; t = statistical t-value; Hem = hemisphere; L = left; R = right; Talairach & Tournoux (T&T) coordinates reported.
Figure 2: Encoding success activity (ESA) for emotional items. Areas that show greater ESA for emotional (Emo) than neutral (Neut) items include (a) bilateral amygdalae and (b) left inferior frontal gyrus (IFG). Bar graphs represent functional ESA estimates, that is, group-averaged contrasts between hits at each delay (Short and Long) and short-delay misses. Error bars indicate standard error of the mean. See Table 1 for coordinates.

2.3.2.2 Individual differences associated with recollection persistence for emotional stimuli.

To identify activity more directly associated with consolidation processes leading to recollection after a long delay, individual recollection persistence scores (long divided by short) were entered as a regressor in a whole brain analysis. Consistent with our second prediction, one of the brain regions showing significant correlations between encoding activity and recollection persistence scores was the amygdala (see Table 2). Moreover, left amygdala activity predicted recollection persistence scores in the case of emotional pictures.
but not in the case of neutral pictures (see Figure 3). This suggests that people with greater amygdala response to emotional items during encoding are more likely to maintain strong, recollective memory traces for these items over time. Recollection persistence scores for emotional stimuli were also correlated with activity in the left fusiform gyrus (Table 2). Recollection persistence scores for neutral stimuli were not correlated with any regions, even using a more lenient threshold (p = .005 outside MTL). The conjunction of emotional and neutral regression maps revealed two regions predictive of recollection persistence scores for both emotional and neutral stimuli: left fusiform gyrus and posterior left ventrolateral PFC. Thus, the left amygdala was involved in predicting recollection persistence scores only for emotional items.

**Table 2:** Activity predicting individual differences in recollection persistence

<table>
<thead>
<tr>
<th></th>
<th>BA</th>
<th>Hem</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>t</th>
<th>voxels</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Correlations with recollection persistence for emotional stimuli</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amygdala</td>
<td></td>
<td>L</td>
<td>-22</td>
<td>-4</td>
<td>-13</td>
<td>2.85</td>
<td>11</td>
</tr>
<tr>
<td>Fusiform Gyrus</td>
<td>19</td>
<td>L</td>
<td>-37</td>
<td>-77</td>
<td>-9</td>
<td>5.31</td>
<td>9</td>
</tr>
<tr>
<td><strong>Correlations with recollection persistence for both emotional and neutral stimuli</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferior Frontal Gyrus</td>
<td>6</td>
<td>L</td>
<td>-45</td>
<td>2</td>
<td>35</td>
<td>3.93</td>
<td>10</td>
</tr>
<tr>
<td>Fusiform Gyrus</td>
<td>19</td>
<td>L</td>
<td>-37</td>
<td>-77</td>
<td>-9</td>
<td>5.31</td>
<td>15</td>
</tr>
</tbody>
</table>

Notes: BA = Brodmann Area; t = statistical t-value; Hem = hemisphere; L = left; R = right; Talairach & Tournoux (T&T) coordinates reported
Activity associated individual differences in recollection persistence for emotional stimuli. a) Left amygdala region whose activity correlates across-subjects with individual differences in recollection persistence for emotional items. See Table 2 for coordinates. b) Scatterplot depicting the relationship between individual recollection persistence scores for emotional stimuli and mean activity in the left amygdala region in response to emotional pictures. c) Scatterplot depicting the relationship between individual recollection persistence scores for neutral stimuli and mean activity in the left amygdala region in response to neutral pictures.

2.3.2.3 Functional connectivity distinguishing between remembered items at short versus long delays.

The peak amygdala voxel identified by the preceding regression analysis (Figure 3) was taken as the seed voxel for an analysis that identified connections between the left amygdala and the rest of the brain that predicted subsequent memory as a function of emotion and delay. Consistent with our third prediction, one of the regions where amygdala connectivity modulated the persistence of emotional memory over time was found within...
MTL (see Table 3). As illustrated by Figure 4, greater connectivity between the amygdala and bilateral anterior parahippocampal regions predicted emotional memory after a long delay compared to a short delay, and this effect was specific to emotional items (Figure 4). The peak of the left parahippocampal cluster appears to fall medially within entorhinal cortex, whereas the right parahippocampal cluster is closest to the intersection of entorhinal and perirhinal cortices. No MTL regions showed the opposite pattern of connectivity, with greater connectivity predicting memory for emotional stimuli after a short rather than long delay. Outside of the MTL, greater connectivity between the amygdala and right parietal and medial frontal regions also predicted memory for emotional stimuli after a long delay to a greater extent than memory after a short delay (Table 3). In the reverse analysis, compared to memory after a long delay, memory for emotional pictures after a short delay was predicted by greater encoding connectivity between the amygdala and the left medial frontal gyrus.

Table 3: Regions exhibiting emotion- and delay-specific connectivity with amygdala

<table>
<thead>
<tr>
<th></th>
<th>BA</th>
<th>Hem</th>
<th>Coordinates (T&amp;T)</th>
<th>t</th>
<th>voxels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emotional long- vs. short-delay hits &gt; Neutral long- vs. short-delay hits</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parahippocampal Gyrus</td>
<td>28</td>
<td>R</td>
<td>30 -1 -26</td>
<td>3.49</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>28,34</td>
<td>L</td>
<td>-19 -8 -22</td>
<td>2.07</td>
<td>4</td>
</tr>
<tr>
<td>Medial Frontal Gyrus</td>
<td>8</td>
<td>R/L</td>
<td>7 38 37</td>
<td>2.54</td>
<td>30</td>
</tr>
<tr>
<td>Parietal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postcentral Gyrus</td>
<td>2</td>
<td>R</td>
<td>59 -24 36</td>
<td>4.26</td>
<td>15</td>
</tr>
<tr>
<td>Inferior Parietal Lobule</td>
<td>40</td>
<td>R</td>
<td>56 -38 37</td>
<td>2.85</td>
<td>12</td>
</tr>
</tbody>
</table>

| Emotional short- vs. long-delay hits > Neutral short- vs. long-delay hits |    |     |                   |    |        |
| Medial Frontal Gyrus | 9  | L   | -19 44 15         | 3.4 | 18     |

56
Notes: BA = Brodmann Area; t = statistical t-value; Hem = hemisphere; L = left; R = right; Talairach & Tournoux (T&T) coordinates reported

**Figure 4:** Functional connectivity with the amygdala. a) Bilateral anterior parahippocampal regions whose connectivity with the amygdala interacts with emotion and delay, such that connectivity during long-delay hits is greater than during short-delay hits, but only for emotional items. See Table 3 for coordinates. b) Scatterplot depicting the relationship between mean single-trial activation estimates (i.e., beta weights) from the indicated right PHG region and the seed amygdala voxel, across emotional long-delay hits. These data points were extracted from an individual representative participant for display purposes.

To investigate this pattern of amygdala-MTL connectivity further, z-scores representing the difference between connectivity associated with long- versus short-delay emotional hits were extracted from each identified parahippocampal region. Note that positive values indicate greater connectivity associated with long- than short-delay memory. These connectivity differences correlated across-subjects with individual differences in recollection persistence scores for emotional stimuli, but not recollection persistence scores for neutral stimuli (Figure 5). This suggests that individuals whose memory for emotional stimuli after a long delay is predicted by greater amygdala-parahippocampal connectivity during encoding show better preservation of recollection for these stimuli after a long delay. These results give further support to the prediction that greater amygdala-MTL connectivity during encoding makes memories for emotional stimuli
more resistant to forgetting, consistent with the hypothesis that emotional arousal
enhances consolidation processes.

Figure 5: Functional connectivity differences associated with emotional recollection persistence. a) In these across-subject scatterplots, the y-axis denotes the difference in connectivity between the amygdala and left or right PHG during emotional long- versus short-delay hits. The x-axis indicates individual recollection persistence scores for emotional stimuli. Note that increasing levels of emotional recollection persistence are associated with increasing disparity between connectivity supporting emotional memory after long versus short delays. b) In these across-subject scatterplots, the y-axis denotes the difference in connectivity between the amygdala and left or right PHG during neutral long- versus short-delay hits. The x-axis indicates individual recollection persistence scores for neutral stimuli. Note that there is no relationship between connectivity differences and neutral recollection persistence.
2.4 Discussion
The present study investigated how encoding activity predicting subsequent emotional memory is modulated by study-test delay. Participants were scanned while encoding emotional and neutral pictures, and recognition memory for non-overlapping sets of these items was tested 20 minutes and 1 week post-encoding. The experiment yielded three main findings. First, activity in the amygdala predicted emotional memory but not neutral memory, and this pattern was similar for emotional memory after both short and long delays. Second, corresponding to our behavioral finding of greater recollection persistence for emotional than neutral stimuli, activity in the left amygdala correlated with individual differences in the persistence of recollection over time for emotional but not neutral stimuli. Finally, greater connectivity between the left amygdala and bilateral anterior MTL memory regions during encoding predicted memory for emotional stimuli after a long delay to a greater extent than memory after a short delay. We discuss these three main results in turn.

When collapsed over delay, ESA for emotional pictures revealed a network of regions including bilateral amygdalae and left ventrolateral PFC. This finding is consistent with extensive evidence that the amygdala is critical to the formation of emotional memories (Cahill, et al., 1996; Canli, et al., 2000; Dolcos, et al., 2004b; Hamann, et al., 1999; LaBar & Phelps, 1998), and that the left PFC contributes to superior encoding for emotional stimuli (Dolcos, et al., 2004a; Kensinger & Corkin, 2004). Contrary to our predictions, however, we did not find any differences in ESA for short-delay versus long-delay memory that was unique to emotional stimuli. This suggests that our emotional memory network contributes equally well during encoding to recognition memory shortly after encoding as well as 1 week later. In other words, basic activity estimates do not reveal any functional differences corresponding to our behavioral finding that recollection for emotional items is relatively preserved over time.
We had originally expected that long-delay hits would be the more targeted product of consolidation than short-delay hits, and that there would be greater ESA associated with ensuing consolidation for long- than short-delay hits. It is possible that we did not find any such regions because of consolidation’s dynamic nature: arousal-mediated consolidation is the product of interactions between the amygdala and MTL memory system (McGaugh, 2004), and might not be captured sufficiently by basic activity estimates. This idea will be addressed further in our discussion of functional connectivity results.

Activity in the left amygdala in response to viewing emotional pictures was significantly correlated with individual differences in recollection persistence for emotional stimuli, our most behaviorally-salient measure of temporal changes in emotional memory. This relationship was unique to emotional items; in fact, no MTL regions were significantly correlated with the persistence of recollection for neutral stimuli. Because our recollection persistence scores divide long-delay recollection by short-delay recollection, baseline memory variability across subjects is ameliorated, such that this measure corresponds most truly to differences that develop across the 1-week delay. Thus, our results imply that individuals who exhibit relatively strong amygdala activation in response to emotional items are less likely to forget these items after a 1-week delay. This finding is consistent with the finding that patients lacking functional amygdalae do not show enhancements in the emotional memory effect over time (LaBar & Phelps, 1998).

These results successfully replicate and improve upon previous investigations into the interaction of emotion and delay in determining ESA. Across-subject correlations between amygdala activity and long- but not short-delay emotional memory are consistent with the results of previous studies (Hamann, et al., 1999; Mackiewicz, et al., 2006), but until now, these correlations have not been linked to behavioral changes in emotional memory over time. The present study is the first to pinpoint encoding activity in the left amygdala as specifically
predictive of emotional recollection, in particular, the degree to which recollection for emotional stimuli persists over time. Thus, our results more strongly argue for amygdala activity as the catalyst for the temporal persistence of emotional memory, an interpretation compatible with the consolidation hypothesis (McGaugh, 2004).

   Functional connectivity analyses revealed that the degree to which connectivity between the left amygdala and bilateral anterior MTL memory regions predicted subsequent memory was determined by both emotion and delay. Specifically, connectivity between these regions during encoding predicted memory for emotional pictures after a long delay rather than after a short delay, and this effect was greater for emotional than for neutral items. Although previous neuroimaging studies have shown that amygdala-MTL connectivity during encoding is associated with successful emotional memory encoding (Dolcos, et al., 2004b; Hamann, et al., 1999; Kensinger & Corkin, 2004; Kilpatrick & Cahill, 2003), this is the first study to demonstrate that the beneficial influence of this connectivity heightens over time. Furthermore, the enhancing effect of amygdala-MTL connectivity on memory for emotional stimuli after a long delay was significantly correlated with individual differences in recollection persistence scores for emotional stimuli. This finding directly links connectivity findings at the group level to individual differences in emotional memory performance.

   Taken together, these connectivity results can also be interpreted under the consolidation hypothesis, which posits that emotional memories benefit from arousal-mediated interactions between the amygdala and MTL memory system that act to improve memory consolidation (McGaugh, 2004). Because consolidation unfolds across time, its role in predicting emotional memory should grow stronger over time, echoing the pattern of connectivity observed here.

   The present results fit well with findings from animal studies of consolidation, although it should be noted that the latter typically investigate consolidation via post-training behavioral or
pharmacological manipulations. In the present study, we examined consolidation processes as they began during the encoding phase and distinguished these processes from other encoding processes by measuring the persistence of memory traces over time. However, it is possible that the present results could be attributed to differences in memory strength established during encoding itself. For example, emotional stimuli evoked greater ESA than neutral stimuli in left ventrolateral PFC, a region often associated with semantic encoding (Gabrieli, Poldrack, & Desmond, 1998). This encoding benefit and others may have resulted in superior memory strength for emotional items, causing the emotional memories to decay more slowly than neutral memories over time. Thus, although we frame the present results in terms of consolidation, we acknowledge that memory strength differences could influence ESA and connectivity contributing to emotional memory changes over time.

Interestingly, the MTL memory regions showing emotion- and delay-specific connectivity with the amygdala are bilaterally located within the anterior parahippocampal gyrus, not within the hippocampus proper. In particular, these regions appear to be centered either within entorhinal cortex or near the border between entorhinal and perirhinal cortices. Although its connectivity with the hippocampus has been emphasized within the literature, the amygdala interacts with the hippocampus via its projections to entorhinal cortex (Pare, Dong, & Gaudreau, 1995). These regions are likewise involved in arousal-mediated consolidation (McGaugh, McIntyre, & Power, 2002; McIntyre, et al., 2003; Roesler, et al., 2002). In particular, the anterior parahippocampal gyrus is a site of information transfer from neocortex to the hippocampus, and amygdala activity facilitates correspondence between perirhinal and entorhinal cortex, an improvement associated with learning (Paz, et al., 2006). Moreover, our finding is consistent with previous functional neuroimaging evidence that correlations between amygdala and entorhinal activity during encoding predict subsequent emotional memory compared to neutral memory (Dolcos, et al.,
An interesting question for future research is whether the specific MTL subregions modulated by amygdala connectivity vary depending on the particular type of episodic memory investigated. For example, there is evidence that encoding activity in the hippocampus predicts better subsequent recollection whereas encoding activity in anterior parahippocampal regions predicts greater subsequent familiarity (Ranganath, et al., 2004). A similar dissociation exists within the emotional memory literature, with hippocampal ESA corresponding to incidental source memory and anterior parahippocampal and amygdala ESA for item-only memory (Kensinger & Schacter, 2006). Although the present finding that amygdala connectivity with anterior parahippocampal regions is associated with individual differences in emotional recollection may seem inconsistent with these findings, it is important to note that the anterior parahippocampal region most strongly associated with item encoding is the perirhinal cortex rather than the entorhinal cortex (Davachi, et al., 2003). In contrast, the entorhinal cortex is assumed to have memory functions intimately related to the hippocampus (Aggleton & Brown, 1999), and it is assumed to support the encoding of contextual information (Eichenbaum, et al., 2007).

The present results should be treated with two main caveats. First, because we chose to simplify the design by employing only negative and neutral stimuli, we cannot distinguish between the contributions of valence and arousal to the present results. However, previous research has shown that the amygdala responds primarily to arousal (Anderson et al., 2003; Dolcos, et al., 2004b; Kensinger & Corkin, 2004), a dimension shared by both positive and negative stimuli. Furthermore, the amygdala-MTL network predicts memory for both emotionally negative and positive stimuli (Hamann, et al., 1999). Therefore, we predict that the inclusion of positive pictures would not qualitatively change the results in the amygdala.
and MTL or their interpretation, and that these results are generalizable to both emotionally negative and positive memories.

Second, the present results do not address the issue of sex differences in emotional memory. Previous evidence indicates that emotional memory effects are lateralized by sex, with the left amygdala predicting emotional memory enhancements for females and the right amygdala for males (see Cahill, 2003 for a review). Preliminary analyses have failed to reveal any influence of sex on the present results (data not reported). However, because sex differences were not of primary interest in the present study, this null result should be treated with caution; it could be ascribed to low statistical power due to relatively small sample sizes for males and females. Future investigations should attempt to verify whether or not sex plays a role in determining patterns of amygdala-MTL connectivity in support of emotional memory.

The present study investigated how encoding activity and functional connectivity differentially predicts emotional memory after short versus long delays. We report three main findings: 1) ESA for emotional items is similar for short- and long-delay memory; 2) activity in the left amygdala predicts individual differences in emotional recollection persistence; and 3) functional connectivity between the left amygdala and bilateral anterior PHG is greater for emotional items remembered after 1 week than those remembered after 20 minutes. These results suggest that amygdala activity, along with its connectivity with the MTL memory system, sustain emotional memory enhancements over time. This interpretation is consistent with the consolidation hypothesis, which emphasizes the role of amygdala-MTL interactions in promoting emotional memory consolidation.
3. Encoding Task Modulates Networks Predicting Emotional Memory Success

3.1 Introduction

As described above, previous studies of emotional memory have tended to emphasize the role of consolidation processes in mediating these enhancements, driven by neurohormonal interactions between the amygdala and medial temporal lobe (MTL) memory system (McGaugh, 2004). Human neuroimaging has likewise demonstrated the importance of the amygdala and MTL memory system in promoting emotional memory formation (Cahill, et al., 1996; Canli, et al., 2000; Dolcos, et al., 2004b; Hamann, et al., 1999; Kensinger & Corkin, 2004; Richardson, et al., 2004).

Despite this emphasis on consolidation processes, there is also human behavioral and neuroimaging evidence that emotion influences other processes during memory encoding, including perceptual, attentional, or semantic processes (Kensinger, 2004; LaBar & Cabeza, 2006). In this way, emotion operates on memory not only through a direct pathway from the amygdala, but also via other regions in the brain that participate in memory encoding. However, the contributions of these alternative mechanisms to emotional memory formation remain underspecified. Exploration into alternative emotional memory pathways thus far has been limited, focusing primarily on the influence of emotion on perception (Vuilleumier & Pourtois, 2007) and how this interaction impacts emotional memory encoding (Kensinger, et al., 2007b).

Another candidate mechanism for emotion-driven encoding benefits is elaborative or semantic processing, thought to be mediated in part by the lateral prefrontal cortices (PFC). Elaborative processing is known to promote successful memory encoding: items
encoded with a deep, semantic strategy will tend to be remembered better, under most
testing conditions, than those encoded with a shallow, perceptual strategy, a hypothesis
known as “levels of processing” theory (Craik & Lockhart, 1972). Within the emotional
memory literature, it has been suggested that rapid, preattentive processing of emotional
stimuli culminates in increased allocation of controlled resources, and that consequent
increases in poststimulus elaboration contribute to enhanced memory for emotional stimuli
(Christianson, 1992). According to this hypothesis, under limited encoding resources,
emotion confers relatively automatic benefits to memory encoding, and when encoding
resources are bountiful, these automatic benefits are compounded with the advantages of
deep, elaborative encoding, which may extend to both emotional and neutral material.
Behavioral studies using a levels-of-processing approach during emotional and neutral
word encoding have supported this hypothesis, finding that emotional memory
enhancements were greatest when words were encoded under a shallow versus deep
condition (Jay, Caldwell-Harris, & King, 2008; Reber, Perrig, Flammer, & Walther, 1994).
These findings indicate that shallow processing amplifies the difference between emotional
and neutral words, likely due to automatic arousal mechanisms that distinguish emotional
from neutral stimuli in this condition, as well as relative benefits in elaborative processing
for neutral stimuli in the deep condition. These findings echo behavioral evidence that
dividing attention during encoding impacts memory for arousing stimuli less than for
neutral stimuli (Kensinger & Corkin, 2004; Kern, et al., 2005).

Although this evidence is intriguing, the link between deep elaborative processing
during encoding and emotional memory effects in the brain has not yet been explicitly
tested. Of particular interest is the ventrolateral PFC (vPFC), which has a known role in
semantic retrieval and elaborative encoding (Prince, Tsukiura, & Cabeza, 2007). If emotional memory encoding recruits deep semantic encoding processes more than neutral memory, one should expect to see greater activity in this region during emotional relative to neutral memory encoding. Consistent with this hypothesis, the left vIPFC has been shown to selectively promote emotional memory (Dolcos, et al., 2004a; Kensinger & Corkin, 2004), an effect that can be driven by emotional valence (how positive or negative a stimulus is) alone. With the hippocampus, the vIPFC may constitute an alternative functional network that supports memory encoding and is modulated by emotion. However, these neuroimaging studies have not manipulated encoding demands to vary reliance on prefrontal mechanisms. Thus, the link between prefrontal activations and increased elaborative encoding of emotional stimuli remains speculative.

Although emotion effects on memory have typically been reported in the left vIPFC, right vIPFC is known to participate in successful memory encoding of visual scenes (Brewer, Zhao, Glover, & Gabrieli, 1998; Kirchhoff, et al., 2000). Outside of the memory domain, there is additional evidence that the right vIPFC and amygdala are modulated by the interaction of emotion with levels of processing. For instance, some studies have investigated the perception of angry and fearful faces during affect labeling versus perceptual matching (Hariri, Bookheimer, & Mazziotta, 2000; Lieberman et al., 2007). In these studies, amygdala activity was greatest during the shallow perceptual matching condition, as well as other control conditions, whereas activity in the right vIPFC was greatest in the relatively deep affect labeling condition. Both studies furthermore identified a negative relationship between the amygdala and right vIPFC activations (Hariri, et al., 2000; Lieberman, et al., 2007), suggesting that the right vIPFC plays a role in dampening the amygdala response
during affect labeling. Lieberman et al. (2007) interpreted these results as reflecting, in part, the right vlPFC’s participation in complex evaluation of emotional stimuli (Cunningham, Johnson, Gatenby, Gore, & Banaji, 2003). This interpretation is consistent with the hypothesis that right vlPFC may contribute to enhanced elaborative processing of emotional stimuli during memory encoding. Furthermore, arousal-driven responses in the amygdala are strongest when these elaborative processes are absent, suggesting that either shallow processing accentuates the influence of emotional arousal or deep processing promotes inhibitory mechanisms that dampen arousal, or both. Thus, we propose that a levels-of-processing manipulation may reveal two distinct pathways to emotional memory formation: an amygdalar pathway that predicts emotional memory benefits during shallow processing, and a prefrontal pathway that provides additional benefits during deep processing. To our knowledge, however, no neuroimaging studies have tested this hypothesis by varying elaborative encoding demands within a subsequent emotional memory design.

In addition to the general influence of emotional arousal, emotional valence may further modulate the effects of levels of processing during memory formation. It has recently been suggested that negative stimuli tend to benefit from perceptual processing during encoding, whereas positive stimuli tend to benefit from semantic processing (Kensinger & Schacter, 2008b; Mickley & Kensinger, 2008). Positive moods may be associated with an expansion of attentional breadth, which serves to diminish attentional selection while increasing access to remote semantic associations (Rowe, Hirsh, & Anderson, 2007). Positive compared to negative words also tend to evoke greater semantic priming effects (Rossell & Nobre, 2004). Consistent with these ideas, negative memory
encoding tends to be associated with activations in the temporal and occipital lobes, whereas positive memory encoding tends to recruit prefrontal regions including left and right vlPFC (Mickley & Kensinger, 2008). Thus, we expect that the neural underpinnings of deep emotional encoding may drive memory for positive information more so than negative information. These effects may be furthermore modulated by individual differences in sensitivity to positive information—it has been hypothesized that valence effects on subsequent memory are driven by an individual’s tendency to prioritize positive versus negative information, and that these valence effects are dependent on controlled processing (Mather & Knight, 2005). We address this issue by relating valence effects on memory-related activity to individual trait differences in the experience of pleasure.

The present study seeks to fill these gaps in the literature by varying levels of processing during encoding of negative, positive, and neutral pictures. One condition employed a shallow, perceptually-focused encoding strategy and the other condition employed a deep, semantic-focused strategy (Figure 6). Recognition memory was tested 2 days later, and was used to identify regions whose activity during encoding varied with subsequent memory as a function of task and emotion.

Taken together, this study has 3 main goals. First, we aim to uncover the influence of emotional arousal on deep versus shallow memory encoding. We expect that emotional memory enhancements will be most pronounced in the shallow condition, when arousal is the main determinant of memory, and that likewise the amygdala will be the strongest predictor of memory during shallow encoding. We predict that, during deep encoding, additional regions will distinguish emotional memory encoding from neutral, including those that support elaborative processes associated with our deep encoding task, such as
the vlPFC. Second, we aim to identify the influence of emotional valence on deep versus shallow memory encoding. Consistent with the hypothesis that positive material evokes enhanced elaborative processing, it is predicted that emotional memory-related regions in PFC will be preferentially recruited for positive stimuli. We additionally explore the possibility that individual differences in sensitivity to positive information support valence effects on memory-related activity. Finally, we aim to characterize distinct functional networks linking key regions of interest, including amygdala and vlPFC, with the hippocampus. In particular, we examine how these functional networks may be differentially recruited during the encoding of positive versus negative stimuli.

### 3.2 Methods

#### 3.2.1 Participants

Twenty-one young adults (10 female; mean Age = 23.0, $SD = 3.1$) participated in the study. Participants were healthy, right-handed, native English speakers, with no disclosed history of neurological or psychiatric episodes. Participants gave written informed consent for a protocol approved by the Duke University Institutional Review Board. Due to excessive head movement, 1 of these participants was excluded from all analyses, and all behavioral and neuroimaging analyses were conducted on the remaining 20 participants (10 female; mean Age = 23.2, $SD = 3.1$).

#### 3.2.2 Materials

Stimuli consisted of 630 pictures. These were selected from the International Affective Picture System (Lang, et al., 2001) as well as from an in-house, standardized database that allowed us to better equate the pictures for visual complexity and content (e.g., human presence). Pictures were assigned on the basis of a 9-point...
normative valence scale to emotionally negative (valence: 1-4), neutral (valence: 4-6), and positive (valence: 6-9) conditions. In accordance with the picture selection procedure, standardized valence scores were lower for negative ($M = 2.85$, $SD = .62$) than neutral pictures ($M = 5.14$, $SD = .43$; $t(418) = 43.98$, $p < .001$), and higher for positive ($M = 7.02$, $SD = .54$) than neutral pictures ($t(418) = 39.85$, $p < .001$). Additionally, arousal scores ($1 = calm$, $9 = excited$) were greater for negative ($M = 5.72$, $SD = 0.49$) than neutral pictures ($M = 3.51$, $SD = .49$; $t(418) = 45.95$, $p < .001$), greater for positive ($M = 5.68$, $SD = .59$) than neutral pictures ($t(418) = 40.91$, $p < .001$), and did not significantly differ between negative and positive pictures ($t(418) = .62$, $p = .54$).

3.2.3 Procedure

Participants encoded pictures in the scanner and their recognition memory for these pictures was tested after 2 days. During encoding, participants viewed 140 negative, 140 positive, and 140 neutral pictures while functional MR images were recorded. The encoding session consisted of 10 functional runs, across which negative, positive, and neutral pictures were evenly divided. Runs alternated between two distinct tasks, deep and shallow, described below. To avoid the induction of long-lasting mood states, the pictures within each block where pseudo-randomized so that no more than three pictures of the same valence were consecutively presented. The assignment of encoding stimulus lists to the deep versus shallow task was counterbalanced across participants.

In the deep task, participants were instructed to carefully analyze each picture for its meaning and interpretation, so that after the picture was taken away, they could choose between two possible descriptions of the picture. In the shallow task, participants were instructed to carefully analyze each picture for its perceptual features, particularly colors.
and lines, so that after the picture was taken away, they could decide whether there was, for example, more red versus green or more horizontal versus vertical lines in the picture. Critically, participants were cued before each run as to which task was next, so that they were able to tailor their processing of each picture to the current task.

![Diagram](image)

**Figure 6: Schematic of the experimental design for a single trial during encoding.** Separate lists of 70 negative, 70 neutral, and 70 positive pictures were assigned to deep and shallow conditions. Deep and shallow conditions were blocked across runs.

Trial structure was similar between tasks (Figure 6). For each trial a picture was presented for 2 seconds. A jittered fixation interval followed each picture presentation, drawn from an exponential distribution with a mean of 2 seconds. After this interval the participant was instructed to rate the picture for its emotional arousal or intensity on a 4-point scale (1 = *calm*, 4 = *excited*). The rating screen remained on-screen for 1 second and was immediately followed by a question screen, which varied by task. In the deep task, the question screen said, "Which word best describes the picture?" Two possible options were
presented on-screen, both of which were written for each picture such that both could be related to the picture but only one described the true meaning of the picture. In the shallow task, the question screen said, “Which feature are there more of?” Two possible options were presented on-screen: either two color names or the words horizontal and vertical. The question screen remained for 1 second, followed by another jittered fixation interval (mean = 2 s) before the next trial. Responses were collected until the next picture appeared.

Two days after encoding, participants completed a recognition task for the pictures. An additional 70 emotionally negative, 70 positive, and 70 neutral pictures were presented as distracters. Pictures were each presented for 2 seconds, followed by a jittered fixation interval (mean = 2 s). Participants indicated whether the item was old or new using a 5-point scale, with 1 = definitely new, 2 = maybe new, 3 = maybe old, 4 = definitely old, and 5 = remember. Participants were instructed that a remember response indicated the recollection of a specific detail from when they saw that picture during the encoding period, whereas a definitely old response did not include any specific details. After the retrieval session, participants completed the Temporal Experience of Pleasure Scale (TEPS) (Gard, Gard, Kring, & John, 2006), which includes anticipatory and consummatory subscales, the latter of which indexes trait appreciation of positive stimuli and experiential pleasure. They also completed the Behavioral Inhibition System-Behavioral Activation System (BIS-BAS) scale (Carver & White, 1994), which measures individual differences in aversive and appetitive motivation (results not reported).

### 3.2.4 Behavioral Analyses

Average arousal ratings and question accuracy were calculated separately for each trial type. To measure differences in memory responding between conditions, hit rates,
false alarm rates, and d’ scores were evaluated for each trial type. The d’ statistic accounts for both hit rates and false alarm rates, thus providing a measure of true accuracy. Because the effect of emotion on memory tends to be strongest when only highly confident responses or recollection estimates are considered (Dolcos, et al., 2005; Ochsner, 2000), d’ was evaluated with its criterion between 3 (‘maybe old’) and 4 (‘definitely old’). That is, responses of 4 and R were taken as ‘old’ and the rest were taken as ‘new’ responses. Encoding response data and d’ scores were entered into separate repeated-measures ANOVAs with emotion (negative, neutral, positive) and task (deep, shallow) as factors. Subsequent post-hoc statistics consisted of repeated-measures ANOVAs with the corresponding factors and variables of interest.

### 3.2.5 FMRI Methods

Images were collected using a 4T GE scanner. Stimuli were presented using liquid crystal display goggles (Resonance Technology, Northridge, CA), and behavioral responses were recorded using a four button fiber optic response box (Resonance Technology). Scanner noise was reduced with earplugs and head motion was minimized using foam pads and a headband. Anatomical scanning started with a T2-weighted sagittal localizer series. The anterior (AC) and posterior commissures (PC) were identified in the midsagittal slice, and 34 contiguous oblique slices were prescribed parallel to the AC-PC plane. High-resolution T1-weighted structural images were collected with a 24-cm field of view (FOV), a 256² matrix, 68 slices, and a slice thickness of 1.9 mm. Functional images were acquired using an inverse spiral sequence with a 2-sec TR, a 31-msec TE, a 24-cm FOV, a 64² matrix, and a 60° flip angle. Thirty-four contiguous slices were acquired with the same slice
prescription as the anatomical images. Slice thickness was 3.8 mm, resulting in 3.75 x 3.75 x 3.8 mm voxels.

Preprocessing and data analyses were performed using SPM5 software implemented in Matlab (www.fil.ion.ucl.ac.uk/spm/). After discarding the first 6 volumes, the functional images were slice-timing corrected and motion-corrected, spatially normalized to the Montreal Neurological Institute (MNI) template, spatially smoothed using an 8 mm isotropic Gaussian kernel, and resliced to a resolution of 3.75 x 3.75 x 3.8 mm voxels. For each subject, evoked hemodynamic responses to event types were modeled with a delta (stick) function corresponding to stimulus presentation convolved with a canonical hemodynamic response function within the context of the general linear model, as implemented in SPM5. Six main event types were modeled, representing all possible combinations of emotion (negative, neutral, positive) and encoding task (deep, shallow). An additional regressor modeled the separate effects of the arousal rating and question period, but this regressor was not included in any analyses. Thus, all effects reflect activity during the picture period only. Confounding factors (head motion, magnetic field drift) were also included in the model.

The subsequent memory paradigm (Paller & Wagner, 2002) was adapted to identify regions reflecting parametric difference in memory (Dm) effects; that is, regions whose activity increased as a function of recognition response. Linear parametric regressors indexing the subsequent recognition response \(1 = \text{definitely new}, 2 = \text{maybe new}, 3 = \text{maybe old}, 4 = \text{definitely old}, \text{and} \ 5 = \text{remember}\) were included for each of the six main trial types. Estimates for the Dm regressors were generated for each participant, and then entered into a group-level, repeated-measures ANOVA with factors for emotion (negative, neutral,
positive) and task (deep, shallow). The main effect of Dm was evaluated by contrasting all Dm regressors versus implicit baseline at \( p < .0025 \), extent threshold = 5 voxels. This analysis was conducted solely to characterize the network associated with encoding overall, prior to interrogating the effects of emotion and task. Planned contrasts were used to evaluate main effects and interactions within the ANOVA framework, with an emphasis on the effects of arousal (negative and positive > neutral) and valence (negative > positive and positive > negative). Main effects of emotion on Dm were taken as the conjunction of each task effect (e.g., negative and positive > neutral for deep inclusively masked with negative and positive > neutral for shallow), with a joint probability < .0025, extent threshold = 5 voxels, to ensure the presence of a significant effect within each task. Interactions were evaluated within the ANOVA framework via interaction contrasts (e.g., negative and positive > neutral for deep and neutral > negative and positive for shallow) at \( p < .005 \), extent threshold = 5. To verify the directionality of the effect, these interactions were inclusively masked with the corresponding within-task effect (e.g., negative and positive > neutral for deep) at \( p < .05 \). In this way, the interactions allowed us to isolate those regions that predicted arousal or valence benefits to subsequent memory for one task more than the other. Effects within the amygdala, our \textit{a priori} region of interest, were taken at \( p < .05 \), extent threshold = 5. Although this within-ROI threshold is liberal, there is a wealth of evidence supporting the important role of the amygdala in predicting emotional memory benefits (see LaBar & Cabeza, 2006 for a review) and strong \textit{a priori} predictions for its role in the present study. To verify the presence of emotion effects in each task independent of subsequent memory, one-sample t-tests evaluating overall effects of emotion (negative and
positive > neutral) were conducted for each task. These results are presented in Table 2 and will not be discussed further.

Across-subject multiple regressions were used to evaluate the relationships among the amygdala, right vIPFC, and hippocampus under each task condition. Anatomical ROIs were derived from the Anatomical Automatic Labeling atlas, as implemented in the WFU Pickatlas, for left and right amygdala, left and right hippocampus, and right inferior frontal gyrus (pars triangularis), the portion of vIPFC that most closely approximated the region identified by the SPM analyses. For each subject, contrast estimates corresponding to the negative deep, positive deep, negative shallow, and positive shallow Dm regressors were extracted from these four ROIs, and their means were entered into separate linear regressions for each condition with right or left hippocampus regressing on the contralateral amygdala and right vIPFC. Because amygdala and vIPFC were included in the same model, beta coefficients reflect the amount of unique variance explained by each. Amygdala regions were chosen to be contralateral rather than ipsilateral to the hippocampus to minimize inflation of the amygdala-hippocampal relationship as a byproduct of spatial smoothing. Thus, each regression measured the degree to which memory-related activity in the hippocampus could be predicted as a function of memory-related activity in the amygdala and right vIPFC, separately for each of the 4 trial types of interest. Because ROIs were derived on an anatomical rather than functional basis, results from the regression analysis provide novel information regarding the relationships between these ROIs, above and beyond the SPM results. Linear regressions were evaluated within SPSS version 15.0 (SPSS Inc., Chicago IL), and standardized beta coefficients and p-values are reported.
3.3 Results

3.3.1 Behavioral Analyses

3.3.1.1 Encoding response data

Average arousal ratings and question accuracy scores were entered into separate repeated-measures ANOVAs with emotion (negative, neutral, positive) and task (deep, shallow) as factors (Table 4). For the arousal ratings, there was a significant main effect of emotion, $F(2, 38) = 206.31, p < .001, \eta^2_p = .92$. Follow-up tests revealed that negative pictures were rated as more arousing than neutral, $F(1, 19) = 335.38, p < .001$, or positive, $F(1, 19) = 37.63, p < .001$, pictures. Positive pictures were also rated as more arousing than neutral pictures, $F(1, 19) = 185.47, p < .001$. Critically, there was no main effect of task, $F(1, 19) < 1, p > .1, \eta^2_p = .02$, or interaction of emotion and task, $F(2, 38) < 1, p > .1, \eta^2_p = .04$, indicating that our task manipulation did not alter the participants' perceived emotional responses to the stimuli. For the question accuracy scores, there were main effects of task, $F(1, 19) = 317.42, p < .001, \eta^2_p = .94$, and emotion, $F(2, 38) = 10.45, p < .001, \eta^2_p = .36$, but only a marginally significant interaction, $F(2, 38) = 2.64, p = .08, \eta^2_p = .12$. Main effects reflected that encoding accuracy was higher for the deep than shallow task, and for positive than negative, $F(1, 19) = 21.22, p < .001$, or neutral stimuli, $F(1, 19) = 13.80, p = .001$.

Encoding accuracy in each condition was significantly above chance.

3.3.1.2 Recognition memory data

Hit rates, false alarm rates, and $d'$ scores were evaluated for each participant (Table 4). $d'$ scores were entered into separate repeated-measures ANOVAs with emotion (negative, neutral, positive) and task (deep, shallow) as factors. There was a main effect of emotion, $F(2, 38) = 14.63, p < .001, \eta^2_p = .44$, indicating that negative pictures were better
remembered than neutral, $F(1, 19) = 19.52, p < .001$, and positive, $F(1, 19) = 33.93, p < .001$, pictures. There was no difference between positive and neutral pictures, $p > .05$. There was also a main effect of task, demonstrating the LOP effect, with deeply-encoded pictures being better remembered than shallowly-encoding pictures, $F(1, 19) = 87.10, p < .001, \eta^2_p = .82$. Critically, the interaction between emotion and task was also significant, $F(2, 38) = 4.52, p = .02, \eta^2_p = .19$, reflecting a greater difference between emotional and neutral pictures in the shallow task than in the deep task. Although positive memory did not differ from neutral memory, further inspection of the results reveals that this effect may be driven by a trend toward a higher false alarm rate to positive pictures than neutral pictures, $F(2, 38) = 2.91, p = .07, \eta^2_p = .13$. Indeed, positive hit rates are significantly higher than neutral hit rates in the shallow condition, $F(1, 19) = 18.45, p < .001$. Thus, when considering only those items represented in the encoding session (i.e., hits and misses), emotion enhanced subsequent memory for both negative and positive pictures.

**Table 4: Behavioral Results**

<table>
<thead>
<tr>
<th>Task</th>
<th>Emotion Type</th>
<th>Arousal</th>
<th>Hit Rate</th>
<th>FA Rate</th>
<th>$d'$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep</td>
<td>Negative</td>
<td>2.79 (.38)</td>
<td>0.64 (0.20)</td>
<td>0.03 (0.03)</td>
<td>2.47 (0.53)</td>
</tr>
<tr>
<td></td>
<td>Neutral</td>
<td>1.39 (.20)</td>
<td>0.55 (0.22)</td>
<td>0.03 (0.02)</td>
<td>2.15 (0.55)</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>2.43 (.42)</td>
<td>0.58 (0.16)</td>
<td>0.04 (0.04)</td>
<td>2.04 (0.53)</td>
</tr>
<tr>
<td>Shallow</td>
<td>Negative</td>
<td>2.79 (.43)</td>
<td>0.56 (0.22)</td>
<td>0.03 (0.03)</td>
<td>2.22 (0.52)</td>
</tr>
<tr>
<td></td>
<td>Neutral</td>
<td>1.39 (.20)</td>
<td>0.41 (0.20)</td>
<td>0.03 (0.02)</td>
<td>1.74 (0.54)</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>2.39 (.44)</td>
<td>0.51 (0.17)</td>
<td>0.04 (0.04)</td>
<td>1.84 (0.55)</td>
</tr>
</tbody>
</table>

*Note.* Data are reported as mean (SD). Arousal refers to individual arousal ratings on a scale from 1 = *calm* to 4 = *excited*. FA = False Alarm. FA rates are common to both tasks.
### 3.3.2 fMRI Analyses

#### 3.3.2.1 Overall memory-related activity

Parametric regressors indexing subsequent memory performance were entered into a group-level ANOVA with emotion and task as factors, and planned contrasts were evaluated within this ANOVA framework. To validate the sensitivity of our design to elucidate memory effects, all trial types were first included to identify Dm effects across all conditions, regardless of emotion and task. This contrast yielded the standard memory encoding network, including bilateral MTL clusters spanning hippocampus and parahippocampal gyrus, bilateral fusiform gyrus, and bilateral vIPFC, in addition to bilateral amygdala (Table 6).

<table>
<thead>
<tr>
<th>Table 5: Emotion Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
<tr>
<td>Negative and Positive &gt; Neutral, Deep</td>
</tr>
<tr>
<td>Middle/ Inferior Temporal Gyrus</td>
</tr>
<tr>
<td>Inferior/ Middle Temporal Gyrus</td>
</tr>
<tr>
<td>Precentral Gyrus</td>
</tr>
<tr>
<td>Superior Parietal Lobule</td>
</tr>
<tr>
<td>Inferior Frontal Gyrus</td>
</tr>
<tr>
<td>Superior Parietal Lobule</td>
</tr>
<tr>
<td>Midbrain</td>
</tr>
<tr>
<td>Middle Frontal Gyrus</td>
</tr>
<tr>
<td>Medial Frontal Gyrus</td>
</tr>
<tr>
<td>Insula</td>
</tr>
<tr>
<td>Amygdala</td>
</tr>
<tr>
<td>Inferior Frontal Gyrus</td>
</tr>
<tr>
<td>Inferior Frontal Gyrus</td>
</tr>
<tr>
<td>Precuneus</td>
</tr>
<tr>
<td>Midcingulate Gyrus</td>
</tr>
<tr>
<td>Inferior Frontal Gyrus</td>
</tr>
<tr>
<td>Amygdala/ Parahippocampal Gyrus</td>
</tr>
</tbody>
</table>

80
<table>
<thead>
<tr>
<th></th>
<th>BA</th>
<th>Hem</th>
<th>Talairach Coordinates</th>
<th>t</th>
<th>voxels</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td>y</td>
<td>z</td>
</tr>
<tr>
<td>Peri-amygdala/</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hippocampus</td>
<td>37</td>
<td>L</td>
<td>-11</td>
<td>-8</td>
<td>-6</td>
</tr>
<tr>
<td>Fusiform Gyrus</td>
<td>37</td>
<td>R</td>
<td>41</td>
<td>-52</td>
<td>-17</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>R</td>
<td>37</td>
<td>-70</td>
<td>-9</td>
</tr>
<tr>
<td>Amygdala/</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parahippocampal Gyrus</td>
<td>34</td>
<td>R</td>
<td>11</td>
<td>-8</td>
<td>-9</td>
</tr>
<tr>
<td>Inferior Temporal Gyrus</td>
<td>37</td>
<td>R</td>
<td>52</td>
<td>-62</td>
<td>-3</td>
</tr>
<tr>
<td>Parahippocampal Gyrus</td>
<td>35</td>
<td>R</td>
<td>30</td>
<td>-26</td>
<td>-18</td>
</tr>
<tr>
<td>Amygdala</td>
<td>39</td>
<td>R</td>
<td>26</td>
<td>-5</td>
<td>-19</td>
</tr>
<tr>
<td>Middle Temporal Gyrus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>L</td>
<td>-37</td>
<td>-48</td>
<td>-14</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>L</td>
<td>-37</td>
<td>-66</td>
<td>-13</td>
</tr>
<tr>
<td>Superior Colliculus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-4</td>
<td></td>
<td>-29</td>
<td>-2</td>
<td>4.37</td>
</tr>
<tr>
<td>Inferior Occipital Gyrus</td>
<td>18</td>
<td>L</td>
<td>-45</td>
<td>-73</td>
<td>-6</td>
</tr>
<tr>
<td>Region</td>
<td>BA</td>
<td>Hem</td>
<td>M</td>
<td>T</td>
<td>Z</td>
</tr>
<tr>
<td>------------------------------</td>
<td>----</td>
<td>-----</td>
<td>---</td>
<td>---</td>
<td>----</td>
</tr>
<tr>
<td>Parahippocampal Gyrus</td>
<td>35</td>
<td>L</td>
<td>-19</td>
<td>-37</td>
<td>-5</td>
</tr>
<tr>
<td>Superior Frontal Gyrus</td>
<td>9</td>
<td>L</td>
<td>-7</td>
<td>56</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>L</td>
<td>-11</td>
<td>52</td>
<td>29</td>
</tr>
<tr>
<td>Medial Frontal Gyrus</td>
<td>9</td>
<td>R</td>
<td>4</td>
<td>52</td>
<td>25</td>
</tr>
<tr>
<td>Inferior Frontal Gyrus</td>
<td>45</td>
<td>R</td>
<td>48</td>
<td>37</td>
<td>2</td>
</tr>
<tr>
<td>Inferior Frontal Sulcus</td>
<td>45/46</td>
<td>R</td>
<td>48</td>
<td>30</td>
<td>13</td>
</tr>
<tr>
<td>Middle Occipital Gyrus</td>
<td>19</td>
<td>R</td>
<td>30</td>
<td>-79</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>R</td>
<td>41</td>
<td>-79</td>
<td>14</td>
</tr>
<tr>
<td>Inferior Frontal Gyrus</td>
<td>45</td>
<td>L</td>
<td>-48</td>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>L</td>
<td>-52</td>
<td>23</td>
<td>16</td>
</tr>
<tr>
<td>Medial Frontal Gyrus</td>
<td>10</td>
<td>R</td>
<td>7</td>
<td>59</td>
<td>11</td>
</tr>
<tr>
<td>Middle Temporal Gyrus</td>
<td>21</td>
<td>R</td>
<td>52</td>
<td>-1</td>
<td>-22</td>
</tr>
</tbody>
</table>

*Note. All subpeaks at least 12 mm apart are reported. BA = Brodmann Area; Hem = Hemisphere; L = Left; R = Right*

**3.3.2.2 Common and task-specific effects of emotional arousal on memory-related activity**

Effects of emotional arousal, regardless of task, were identified by evaluating the negative and positive > neutral contrast for each task and then taking their conjunction (Table 7). The left peri-amygdaloid region was the only region to show Dm effects driven by emotional arousal in both tasks (Figure 7a).

To identify task-specific effects of emotional arousal on memory-related activity, we looked for regions that predicted negative and positive versus neutral Dm more in the shallow task than in the deep task, and vice versa (Table 7). Only the right amygdala showed greater arousal-driven Dm effects in the shallow than in the deep task (Figure 7b). For the converse interaction, a network of regions including the right vlPFC, posterior cingulate, and precuneus exhibited greater arousal-driven Dm effects in the deep task than in the shallow task (Figure 7c). These results are consistent with our predictions that
emotional memory encoding in the shallow condition would be primarily supported by the amygdala, whereas deep emotional memory encoding would additionally benefit from memory-related activity in the vIPFC.

<table>
<thead>
<tr>
<th>Table 7: Influence of Emotional Arousal on Dm Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>BA</td>
</tr>
<tr>
<td>----</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Negative Dm and Positive Dm &gt; Neutral Dm, Both Deep and Shallow</td>
</tr>
<tr>
<td>Peri-Amygdaloid Region</td>
</tr>
<tr>
<td>Negative Dm and Positive Dm &gt; Neutral Dm, Shallow &gt; Deep</td>
</tr>
<tr>
<td>Amygdala</td>
</tr>
<tr>
<td>Negative Dm and Positive Dm &gt; Neutral Dm, Deep &gt; Shallow</td>
</tr>
<tr>
<td>Inferior Frontal Gyrus</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

*Note. BA = Brodmann Area; Hem = Hemisphere; L = Left; R = Right. For the conjunction, coordinates refer to the peak associated with the larger t-value.*
Figure 7: Common and task-specific effects of emotional arousal on Dm activity. Activations are overlaid on a T1 template and mean contrast estimates within the activated regions are plotted for each condition to illustrate the effect. a) Left peri-amygdaloid region showing common effects. b) Right amygdala region showing shallow task-specific effects. c) Right vIPFC region showing deep task-specific effects. Error bars denote standard error.

3.3.2.3 Common and task-specific effects of emotional valence on memory-related activity

Effects of emotional valence, regardless of task, were identified by evaluating the positive > negative Dm, and vice versa, contrast for each task and then taking their conjunction (Table 8). Several regions demonstrated stronger Dm effects for positive than negative encoding, including retrosplenial cortex, precuneus, PFC, and regions in primary visual cortex. Interestingly, many of these activations, including retrosplenial cortex, were driven by deactivations associated with memory for negative stimuli (Figure 8a). No regions were more active for negative versus positive Dm in both tasks.
To identify task-specific effects of emotional valence on memory-related activity, we looked for regions that predicted valence effects in the shallow task but not the deep task and vice versa (Table 8). The caudate nucleus and superior colliculus showed positive versus negative Dm effects in the deep task but not in the shallow task (Figure 8b). All other interactions were null. Within this region of caudate nucleus, mean Dm effects in the deep positive condition significantly correlated with individual scores on the consummatory subscale of the TEPS, indicating that the more an individual tends to appreciate positive experiences, the more that region tends to predict memory for deeply-encoded positive images (Figure 8c). Notably, this correlation was not significant for any of the other trial types.

**Table 8: Influence of Emotional Valence on Dm Activity**

<table>
<thead>
<tr>
<th></th>
<th>BA</th>
<th>Hem</th>
<th>Talairach Coordinates</th>
<th>t</th>
<th>voxels</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td>y</td>
<td>z</td>
</tr>
<tr>
<td><strong>Positive Dm &gt; Negative Dm, Both Deep and Shallow</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cuneus/ Lingual Gyrus</td>
<td>17, 18</td>
<td>L</td>
<td>-15</td>
<td>-91</td>
<td>5</td>
</tr>
<tr>
<td>Lingual Gyrus</td>
<td>19</td>
<td>L</td>
<td>-15</td>
<td>-58</td>
<td>-3</td>
</tr>
<tr>
<td>Retrosplenial Cortex</td>
<td>23</td>
<td></td>
<td>0</td>
<td>-39</td>
<td>19</td>
</tr>
<tr>
<td>Superior Frontal Gyrus</td>
<td>6</td>
<td>R</td>
<td>26</td>
<td>6</td>
<td>45</td>
</tr>
<tr>
<td>Middle Frontal Gyrus</td>
<td>8</td>
<td>L</td>
<td>-22</td>
<td>13</td>
<td>41</td>
</tr>
<tr>
<td>Precuneus</td>
<td>7</td>
<td>L</td>
<td>-11</td>
<td>-64</td>
<td>38</td>
</tr>
<tr>
<td><strong>Positive Dm &gt; Negative Dm, Deep &gt; Shallow</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superior Colliculus</td>
<td>L</td>
<td></td>
<td>-4</td>
<td>-26</td>
<td>-2</td>
</tr>
<tr>
<td>Caudate Nucleus</td>
<td>L</td>
<td></td>
<td>-15</td>
<td>8</td>
<td>10</td>
</tr>
</tbody>
</table>

*Note.* BA = Brodmann Area; Hem = Hemisphere; L = Left; R = Right. For the conjunction, coordinates refer to the peak associated with the larger $t$-value.
Figure 8: a) Common effects of emotional valence on Dm activity. Retrosplenial cortex activations are overlaid on a T1 template and mean contrast estimates within this activated region are plotted for each condition to illustrate the effect. b) Deep task-specific effects of emotional valence on Dm activity. c) Scatterplot depicting the correlation between each individual’s Dm activity within the caudate nucleus during the deep positive condition, and individual scores on the consummatory subscale of the Temporal Experience of Pleasure Scale (TEPS). Error bars denote standard error.

3.3.2.4 Multiple regression analyses

We further investigated the functional relationships between key regions of interest, focusing on interactions of the amygdala and vIPFC with the hippocampus during memory formation. In particular, we were interested in assessing whether these pathways were differentially recruited for negative versus positive information. For each of the 4 conditions of interest (negative deep, negative shallow, positive deep, and positive shallow), linear multiple regression models measured the degree to which left or right hippocampal Dm effects covaried with Dm effects in the contralateral amygdala and right vIPFC across participants (Figure 9a). Note that although amygdala and vIPFC were similarly activated
for both negative and positive Dm, these network analyses assess the degree to which each region influences memory-related activity in the hippocampus, i.e., the relative strength of the pathway. Standardized beta coefficients are presented in Figure 9b.

\[ HC_{DM} = a \cdot Amyg_{DM} + b \cdot vlPFC_{DM} + c \]

Figure 9: a) Schematic of the functional network and equation used in the multiple regression analyses. b) Plots of the standardized beta coefficients as a function of valence for left and right hippocampus. Results are plotted separately for the deep (top) and shallow (bottom) conditions. Asterisks denote the significance of the corresponding coefficient in each condition, \( p < .05 \). HC = hippocampus, Amyg = Amygdala, Std = Standardized.

For the left hippocampus, amygdala Dm predicted hippocampal Dm effects for the deep negative \( (p = .041) \) and shallow negative \( (p < .001) \) and positive \( (p = .011) \) conditions. Right vlPFC Dm, on the other hand, predicted hippocampal Dm for the deep positive \( (p = .016) \) and shallow positive \( (p < .001) \) conditions. For the right hippocampus, amygdala Dm predicted hippocampal Dm effects for the deep negative \( (p < .001) \) and shallow negative \( (p \)
< .001) conditions. Right vIPFC Dm was not a positive predictor of hippocampal Dm for any condition, but was a negative predictor in the shallow negative condition, $p = .01$. Taken together, the results indicate that, regardless of task, valence modulates the strength of these functional relationships: negative memory tends to be supported more strongly by the amygdala-hippocampal association, whereas positive memory tends to be supported more strongly by the vIPFC-hippocampal association.

### 3.4 Discussion

With respect to the previously outlined goals, the results of this study yield 3 main findings. First, the influence of emotional arousal on memory is modulated by level of processing, with the amygdala predicting emotional memory enhancements best in the shallow condition and the right vIPFC additionally supporting these enhancements in the deep condition. Second, the interaction of valence with level of processing affects memory-related activity in the caudate nucleus, but not in PFC as originally expected. Specifically, the caudate nucleus differentially supports positive memory in the deep condition, an effect related to individual differences in sensitivity to positive experiences. Finally, the amygdala and right vIPFC may participate in distinct functional networks with the hippocampus that are differentially weighted by valence.

Most neuroimaging studies of emotional memory have focused on how the amygdala predicts emotional memory enhancements, presumably by modulating memory consolidation in the MTL memory system (LaBar & Cabeza, 2006; McGaugh, 2004). Consistent with this literature, the present results indicate that the amygdala predicts memory for negative and positive stimuli better than for neutral stimuli. Whereas most previous studies have employed a single encoding task, we expand these findings to
compare the role of the amygdala during deep versus shallow encoding. Interestingly, although the results show that the left amygdala predicts emotional memory across both tasks, the right amygdala preferentially predicts emotional memory in the shallow condition. This finding maps onto the behavioral finding that emotional memory benefits are accentuated for those items encoded in the shallow condition. Taken together, these results imply that stimulus-induced arousal and corresponding amygdala activation are the critical determinants of subsequent memory during shallow encoding, when other encoding resources are minimized.

These findings are reminiscent of the results of previous studies comparing perceptual matching versus affect labeling, which can be taken as shallow and deep tasks, respectively. These studies found the amygdala response to fearful and angry faces was weakest in the affect labeling condition (Hariri, et al., 2000; Lieberman, et al., 2007). The present experiment adds the novel finding that the right amygdala likewise predicts emotional memory best in the shallow condition. Shifts in laterality from common to task-specific emotional Dm effects may additionally reflect differences in encoding demands—the left amygdala has been associated with cognitive representations of arousal, which may play a stronger role during deep encoding, whereas the right amygdala has been associated with automatic or conditioned shifts in arousal (Glascher & Adolphs, 2003; Phelps et al., 2001).

A few studies have attempted to clarify the role of the PFC in predicting emotional memory enhancements, finding that the left vIPFC promotes emotional memory better than neutral (e.g., Dolcos, et al., 2004a; Kensinger & Corkin, 2004). The present study improves upon this literature by contrasting deep versus shallow encoding, thereby isolating
emotional memory mechanisms that emerge only when encoding resources are high. The right vIPFC, in addition to regions within parietal cortex, follows this pattern, indicating its role in elaborative processes during encoding that are sensitive to emotional arousal. Although the previous literature on emotional memory has typically highlighted the left vIPFC, the right vIPFC has been shown to participate in successful memory encoding, especially for visual scenes (Brewer, et al., 1998; Kirchhoff, et al., 2000).

The right vIPFC has also been identified as being more activated during affect labeling than perceptual matching or other shallow conditions (Hariri, et al., 2000; Lieberman, et al., 2007). Because this region was inversely related to amygdala activity in these studies, the authors concluded that right vIPFC likely plays a role in dampening the amygdala response during affect labeling. One account for right vIPFC during affect labeling is that this region is involved in symbolic thought about emotional stimuli (Lieberman, et al., 2007). Supporting this idea, this region is activated during evaluative valence judgments, particularly when these judgments are ambivalent or ambiguous, increasing the complexity of the decision (Cunningham, et al., 2003; Nomura et al., 2003). Alternatively, right vIPFC activation may index inhibitory processes, which may be preferentially recruited during deep processing. Indeed, the right vIPFC has been associated with inhibitory processes across a wide variety of tasks (Aron, Robbins, & Poldrack, 2004), and this region has also been identified during tasks that require the inhibition of emotional responses (Dolcos & McCarthy, 2006). These two accounts may be compatible with each other—in the context of emotional stimuli, inhibitory processes may be supported by evaluative mechanisms, consistent with ideas regarding emotion regulation strategies such as reappraisal. Reappraisal involves re-conceptualizing emotional information, a process known to engage
right vIPFC while dampening arousal responses (Ochsner et al., 2004). Furthermore, reappraisal strategies during encoding have been shown to promote memory for emotional stimuli (Dillon, Ritchey, Johnson, & LaBar, 2007). Taken together, our finding that right vIPFC predicts emotional memory benefits in the deep condition may reflect recruitment of emotion evaluation or regulation processes that in turn promote deep memory encoding.

This account may also help reconcile the present results with previous studies of emotional arousal effects on memory encoding, which have typically found emotional Dm effects in both amygdala and vIPFC within the same task. These previous studies have traditionally employed encoding tasks consisting of simple valence ratings (e.g., Dolcos et al., 2004a,b) or binary decisions about the content of the stimulus (e.g., Kensinger & Corkin, 2004; Ritchey et al., 2008). These encoding tasks may have fallen somewhere in between the present shallow and deep tasks in terms of how much they relied on elaborative encoding processes. In the present shallow task, participants were required to conduct careful perceptual analysis of the stimuli, perhaps interfering with any meaning-based processing beyond that required for an arousal rating. In the present deep task, however, participants were required to deeply analyze the meaning of each picture so that they could answer any question about its meaning, a task more demanding of elaborative resources than a binary decision. Thus, in the present study, increased vIPFC Dm effects in the deep condition may have resulted from this condition’s heightened demands on elaborative encoding. Another consequence of these demands may have been preferential recruitment of regulatory processing, resulting in relative inhibition of the amygdala Dm effects which predominate in the shallow condition.
In addition to these main findings driven by emotional arousal, our results suggest that emotional valence also interacts with memory encoding. Across both tasks, a network of regions predicted memory for positive more than negative stimuli, although this pattern was primarily driven by inverse relationships with Dm in the negative condition. Some of these regions, including retrosplenial cortex and precuneus, are part of the default network and thought to be important for self-referential processing (Buckner, Andrews-Hanna, & Schacter, 2008). Although we did not anticipate this finding, one possible interpretation for these data is that deactivating the default network benefits memory for negative stimuli, but does not influence memory for positive stimuli. These results hint at possible differences in the kinds of processes that support each form of memory encoding. Additional research is needed to investigate how default network activity differentially impacts valenced memories, which could have important implications for understanding memory biases in psychiatric populations.

We also identified a task-specific valence effect: the caudate nucleus predicts positive versus negative memory in the deep but not shallow task. Furthermore, deep positive Dm effects in this region correlate with individual scores on the consummatory subscale of the TEPS. These results imply that the more an individual is likely to experience consummatory pleasure in response to positive stimuli, the more the caudate nucleus predicts memory for deeply-encoded positive stimuli. These results provide preliminary evidence that individual differences in valence-driven memory biases, both in the normal population and in special populations like depressed patients (Dalgleish & Watts, 1990) or older adults (Mather & Knight, 2005), might be partially underscored by individual differences in the experience of pleasure and the affiliated reward circuitry. Although there
has been increasing interest in the relationship between reward processes and memory (Adcock, Thangavel, Whitfield-Gabrieli, Knutson, & Gabrieli, 2006; Wittmann et al., 2005), little attention has been paid to how reward processes may contribute to memory for positive scenes within a standard emotional memory paradigm (but see Wittmann, Schiltz, Boehler, & Düzel, 2008). It would be worthwhile to unite these literatures by further examining the contribution of the caudate and other parts of the striatum, known to be involved in reward processing (Delgado, 2007), during emotional memory formation.

Consistent with prior suggestions that positive memory tends to be preferentially supported by elaborative encoding, we had expected to find valence interactions in vIPFC. However, these predictions emerged not as activation differences, but as network differences. Results from the multiple regression analysis indicate the presence of functional networks linking Dm activity in the hippocampus with Dm activity in the amygdala and right vIPFC. Task does not seem to influence the strength of these relationships despite task modulation of activity within right vIPFC and amygdala. This may indicate common functional pathways that simply become more or less activated in each task. However, the relative strength of these networks does vary by valence, in that the amygdala pathway tends to be strongest for negative memory and right vIPFC pathway tends to be strongest for positive memory, particularly for the left hippocampus. Although there were no activity differences according to valence within these regions, these network analyses may reflect the degree to which each pathway mediates memory-related changes in the hippocampus. That is, although memory-related activations in the amygdala and vIPFC are recruited by emotional arousal, valence determines the relative influence of these activations on memory-related activity in the hippocampus.
A few caveats are worth noting with regard to the interpretation of the present results. First, although we interpret the differences between negative and positive encoding as arising from their opposing valence, we cannot rule out the possibility that some of the present results are driven by self-reported differences in arousal between negative and positive rather than valence. Under this interpretation, the network results would be consistent with evidence linking left vIPFC to the encoding of non-arousing negative words (Kensinger & Corkin, 2004), although this previous study did not compare negative to positive stimuli. Second, because positive items tended to evoke higher false alarm rates during retrieval, indicating increased memory bias for these items, positive Dm effects may not always reflect processes supporting true memory accuracy. This may not be a problem for the present data since encoding processes such as semantic elaboration may predict subsequent memory bias as well as accuracy (Kim & Cabeza, 2007). Furthermore, it is unclear how bias could elicit task differences in encoding activity. Finally, we interpret task differences as emerging from varying degrees of deep, elaborative processing during encoding. However, we cannot rule out the possibility that these tasks may have facilitated other forms of processing that may have contributed to the present results. For example, the shallow task emphasized perceptual features of the stimuli, which may have in turn emphasized their emotionally-salient details. Similarly, the deep task may have encouraged gist-based processing of the stimuli. These possible differences are consistent with the idea that the features attended to during encoding, such as meaning, can dynamically shift the networks supporting successful memory for emotional stimuli. A fascinating question for future research is whether level of processing at encoding differentially influences gist-based versus detailed emotional memory.
Although much is known regarding the role of the amygdala in promoting emotional memory consolidation, the link between emotion, elaborative encoding, and their neural correlates has remained underexplored. By contrasting deep and shallow encoding tasks, this study isolated those components of emotional memory formation that proceed in the face of limited encoding resources, as well as those that are recruited when elaborative encoding resources are high. The present findings indicate that under shallow encoding, arousal and consequent changes in amygdala activity are the best predictors of subsequent memory, whereas under deep encoding, the right vIPFC additionally predicts subsequent emotional memory benefits. Although these activation patterns are not modulated by valence, valence does influence the relative contributions of these regions to memory-related activity in the hippocampus: amygdala-hippocampal links are strongest during negative memory encoding, whereas prefrontal-hippocampal links are strongest during positive memory encoding. The results suggest two distinct pathways to emotional memory formation: an automatic amygdalar pathway that promotes emotional memory during shallow encoding, especially for negative stimuli, and a prefrontal pathway that provides extra benefits during deep encoding, especially for positive stimuli. Through these systems, emotion influences both the quality of the information being transmitted to the MTL memory system as well as the likelihood that that information will be consolidated into a long-term memory trace.
4. Encoding-Retrieval Similarity is Associated With Emotional Memory Success

4.1 Introduction

Reactivation of memories may be precipitated by any number of events, including perceptual cues (the sight of a familiar face, the scent of honeysuckle), contextual reinstatement (getting dinner and drinks at your favorite bar), or re-engagement of familiar cognitive operations (using the FOIL method in algebra class). The result of each of these events, whether they seem spontaneous or the result of an effortful search process, is that the brain is restored to a state similar to that experienced during initial encoding. Memory strength is thought to vary as a function of encoding-retrieval match, such that stronger memories are associated with greater similarity between encoding and retrieval (Tulving & Thomson, 1973). This accounts for why high-fidelity retrieval cues are more successful memory triggers than their less faithful counterparts and why contextual manipulations like spatial or mood shifts effectively modulate memory. These ideas have also been applied specifically to cognitive operations in the theory of transfer-appropriate processing, which proposes that memory will be enhanced when the cognitive operations engaged during retrieval mimic those engaged during encoding (Morris, et al., 1977).

Prior neuroimaging studies testing the overlap between encoding and retrieval have typically taken one of two main approaches. The first has been to measure brain activity during both encoding and retrieval and look for overlaps corresponding to memory success at both phases. In this approach, one can look at overall similarities and differences in activity associated with memory success at each phase. For example, both encoding and retrieval success have been linked to activation in hippocampus as well as in neocortical
regions devoted to stimulus-specific processing (Prince, et al., 2005). The second has been to associate a specific task, context, or stimulus with each memorandum during encoding and then look for brain activity consistent with its reactivation during retrieval (reviewed by Danker & Anderson, 2010). One clear example is the finding that, even when retrieval cues are held constant, words studied with visual images elicit greater activity in visual cortex at retrieval than words studied auditorily (Nyberg, et al., 2000; Wheeler & Buckner, 2003; Wheeler, et al., 2000) or as words alone (Vaidya, Zhao, Desmond, & Gabrieli, 2002; Woodruff, Johnson, Uncapher, & Rugg, 2005). Similar encoding phase-related reactivations have been demonstrated using different cognitive tasks at encoding (Johnson, et al., 2009; Johnson & Rugg, 2007; Kahn, Davachi, & Wagner, 2004; Nyberg et al., 2001). Reactivations can also be linked to specific associations formed at the time of encoding: for example, recognition of neutral objects previously paired with emotional scenes evokes greater amygdala activity than objects paired with neutral scenes, even in the absence of an explicit retrieval attempt (Smith, et al., 2006). Studies with similar designs have shown associate-related reactivation during retrieval for words paired with fearful or neutral faces (Fenker, et al., 2005), emotional or neutral sentences (Maratos, Dolan, Morris, Henson, & Rugg, 2001), high or low reward (Kuhl, Shah, DuBrow, & Wagner, 2010), faces or spatial positions (Khader, Burke, Bien, Ranganath, & Rösler, 2005), and faces or houses (Kuhl, et al., 2011).

Combining these approaches, other studies have recorded data from both memory phases and then used the encoding data to identify activity patterns that then can be tested directly during the retrieval phase (Nyberg, et al., 2000; Vaidya, et al., 2002; Wheeler, et al., 2000). An elegant application of this strategy involves the use of multivariate pattern analysis (MVPA) techniques, which rely on spatial patterns of hemodynamic activity rather
than univariate activation estimates to compare or classify task conditions (Haynes & Rees, 2006; Norman, Polyn, Detre, & Haxby, 2006). The use of MVPA has been well established among fMRI studies of visual perception, clearly demonstrating that spatial patterns at the level of voxels can be used to decode features such as line orientation (Haynes & Rees, 2005; Kamitani & Tong, 2005) and object categories such as faces and houses (e.g., Haxby et al., 2001). Within the domain of episodic memory, MVPA has proven well-suited to the detection of brain states at retrieval that are associated with prior learning events, typically using neural networks trained on patterns from encoding to classify timepoints at retrieval. These experiments have successfully identified reinstatement of face, place, and object category patterns prior to free recall of corresponding exemplars (Polyn, Natu, Cohen, & Norman, 2005), encoding task-related patterns during word recognition (Johnson, et al., 2009), and face and place patterns linked to previously learned paired-associates during competitive associative learning (Kuhl, et al., 2011). Each of these studies demonstrated clearly that the reactivation of condition-level information can be covertly tracked during episodic memory retrieval. Furthermore, the magnitude of this condition-level reactivation was greater for remembered than forgotten items (Johnson, et al., 2009), correlated with individual differences in hippocampal response (Kuhl, et al., 2010) and predicted the amount of interference impinging on new learning (Kuhl, et al., 2011; Kuhl, et al., 2010).

The biggest limitation to any of these methods is the lack of specificity associated with the measure of reactivation. In these paradigms, reactivation is typically operationalized according to a single dimension (e.g., the encoding condition or paired associate) and measured by comparing all successful retrieval trials from one condition to the other or to unsuccessful memory trials. Even the aforementioned multivariate
techniques have been limited in the sense that classifiers can track reactivation of only the dimension that they have been trained to discriminate. This permits inquiry into a limited sense of reactivation in which only processes general to an entire condition are measured. An ideal measure of reactivation, however, would be able to flexibly track item-specific information that is recapitulated during retrieval. This study improves upon these methods by measuring the similarity between encoding and retrieval patterns for each individual trial, enabling the identification of pattern reactivations not associated with a specific experimental manipulation. Similarity measures have been proposed as an ideal method for evaluating neural activity at the level of the representation (Kriegeskorte, 2008) and thus may prove useful in comparing individual memory representations across stimuli and phases.

The recapitulation of encoding information during retrieval has been attributed to the function of two main regions: the medial temporal lobes, particularly the hippocampus, and posterior neocortex, particularly sensory regions. Neurocomputational models of memory have posited that the hippocampus initially binds cortical representations into the memory trace and then orchestrates changes in cortical networks that stabilize the memory over time (Alvarez & Squire, 1994; McClelland, et al., 1995; Nadel, et al., 2000; Norman & O’Reilly, 2003; Squire, 1992; Sutherland & McNaughton, 2000). Then, during recent memory retrieval, the hippocampus facilitates the reactivation of neocortical networks corresponding to the memory trace. These functions have been proposed to be mediated by hippocampal replay processes that occur during both sleep and awake states (Carr, et al., 2011; O’Neill, Pleydell-Bouverie, Dupret, & Csicsvari, 2010; Sutherland & McNaughton, 2000). Replay can occur spontaneously or be triggered by sensory inputs, making it an ideal
candidate mechanism for supporting memory consolidation and retrieval, respectively (Carr, et al., 2011). These theories assume that memory retrieval involves pattern completion in neocortex that is propelled by interactions with the hippocampus (McClelland, et al., 1995; Norman & O'Reilly, 2003). Thus, memory reactivation should be associated with not only enhanced similarity between encoding and retrieval states but also the coupling of reactivated neocortical networks with the hippocampus (O'Neill, et al., 2010; Sutherland & McNaughton, 2000; Wiltgen, Brown, Talton, & Silva, 2004). Although neurophysiological data have supported these ideas (Ji & Wilson, 2007; Pennartz et al., 2004; Peyrache, Khamassi, Benchenane, Wiener, & Battaglia, 2009), it has been a challenge for neuroimagers to develop appropriate methods for testing this hypothesis. In the present study, neocortical pattern completion is operationalized as the similarity between multivariate patterns during encoding versus retrieval, thus enabling analysis of how the hippocampus mediates the relationship between pattern similarity and memory retrieval on a trial-to-trial basis.

Finally, several factors are known to modulate memory strength, one of the most prominent being emotional arousal (Kensinger & Schacter, 2008a; LaBar & Cabeza, 2006). Arousing stimuli tend to be remembered with greater accuracy and vividness (Dolcos, et al., 2005; Ochsner, 2000; Ritchey, et al., 2008). These memory effects are known to be supported by noradrenergic and glucocorticoid influences on memory encoding and consolidation processes (Cahill & McGaugh, 1998; McGaugh, 2004), marked by enhanced activity in the amygdala and medial temporal lobes (Murty, et al., 2010). These regions are likewise modulated by emotion during retrieval (Dolcos, et al., 2005; Sharot, et al., 2004); however, few studies have directly compared the emotion effects on each phase (Murty, et
al., 2009; Sergerie, et al., 2006). Furthermore, because arousal upregulates processes associated with consolidation via amygdala-hippocampal interactions, it may likewise impact the frequency or fidelity of hippocampal replay, a hypothesis supported by evidence for increased replay following exposure to novel and salient environments (Foster & Wilson, 2006). If memory reactivation is mechanistically linked to these processes, one may expect arousal and concomitant amygdala activity to likewise facilitate memory-related reactivation at retrieval.

To test these hypotheses, functional magnetic resonance imaging data were collected while participants encoded a heterogeneous set of complex visual scenes that varied in emotional salience. Two days later, neuroimaging data were also collected while they completed a recognition memory task for these stimuli. Across a broad set of anatomical regions of interest, we calculated the pattern similarity between encoding and retrieval trials, matching individual trials either one-to-one (same pictures) or within condition (different pictures matched for condition and memory status). First, we tested the theory of encoding-retrieval match by measuring the neural similarity between encoding and retrieval for each individual trial and evaluating its relationship with memory success. Although the use of a recognition memory task blurs the line between perception and memory reactivation, we controlled for perceptual input by comparing remembered and forgotten items among the one-to-one match pairs; task engagement was likewise controlled by comparing successful trials from the one-to-one and condition-match pairs. Second, we sought to link findings of superior encoding-retrieval match to memory-related activity in the hippocampus on a trial-to-trial basis. Finally, we explored the idea that
emotional salience and engagement of the amygdala might modulate encoding-retrieval match and its link to memory.

4.2 Methods

4.2.1 Participants

Twenty-one participants completed the experiment. Two participants were excluded from analysis due to image quality problems. This resulted in 19 participants (9 female), ranging in age from 18 to 29 (M = 23.3, SD = 3.1). Participants were healthy, right-handed, native English speakers, with no disclosed history of neurological or psychiatric episodes. Participants gave written informed consent for a protocol approved by the Duke University Institutional Review Board.

Participants were scanned during separate memory encoding and recognition sessions, set 2 days apart. During the first session, they viewed 420 complex visual scenes for 2 seconds each. Following each scene, they made an emotional arousal rating on a 4-point scale and answered a question related to the semantic or perceptual features of the image. During the second session, participants saw all of the old scenes intermixed with 210 new scenes for 3 seconds each. For each trial, they rated whether or not the image was old or new on a 5-point scale, with response options for “definitely new,” “probably new,” “probably old,” “definitely old,” and “recollected.” The 5th response rating referred to those instances in which they were able to recall a specific detail from when they had seen that image before. For all analyses, memory success was assessed by collapsing the 4th and 5th responses, defining those items as “remembered,” and comparing them to the other responses, referred to here as “forgotten.”
The stimuli consisted of a heterogeneous set of complex visual scenes drawn from the International Affective Picture System (Lang, et al., 2001) as well as in-house sources. They included 210 emotionally negative images (low in valence and high in arousal), 210 emotionally positive images (high in valence and high in arousal), and 210 neutral images (midlevel in valence and low in arousal). Additional details about the encoding design and stimulus set are described in Chapter 3.

4.2.2 FMRI Acquisition & Pre-Processing

Images were collected using a 4T GE scanner, with separate sessions for encoding and retrieval. Data acquisition parameters are identical to those described in Chapter 3. Preprocessing and data analyses were performed using SPM5 software implemented in Matlab (www.fil.ion.ucl.ac.uk/spm). After discarding the first 6 volumes, the functional images were slice-timing corrected, motion-corrected, and spatially normalized to the Montreal Neurological Institute (MNI) template. Functional data from the retrieval session were aligned with data from the encoding session, and normalization parameters were derived from the first functional from the encoding session. Data were spatially smoothed with an 8-mm isotropic Gaussian kernel for univariate analyses and left unsmoothed for multivariate pattern analyses.

4.2.3 FMRI Analysis

4.2.3.1 General Linear Model

All multivariate pattern analyses were based on a general linear model that estimated individual trials. General linear models with regressors for each individual trial were estimated separately for encoding and retrieval, yielding one model with a beta image corresponding to encoding trial and another model with a beta image corresponding to
each retrieval trial. The post-image encoding ratings were also modeled, combined into a single regressor; thus, all analyses reflect the picture presentation time only. Regressors indexing head motion were also included in the model. The validity of modeling individual trials has been demonstrated previously (Rissman, et al., 2004), and the correspondence between these models and more traditional methods was likewise confirmed within this dataset.

Additional general linear models were estimated for functional region of interest (ROI) specification. The encoding and retrieval models were similar to that described above, but collapsed the individual trials into separate regressors for each emotion type, as in standard analysis approaches. These models also included parametric regressors indexing the 5-point subsequent memory response. The retrieval model also included a single regressor for all new items.

4.2.3.2 Multivariate encoding-retrieval similarity analysis

A series of 31 bilateral anatomical ROIs were generated from the AAL system (Tzourio-Mazoyer et al, 2002) implemented in WFU Pickatlas (Maldjian, Laurienti, Kraft, & Burdette, 2003). These ROIs included all regions comprised in the lateral prefrontal, parietal, temporal, and occipital cortices, as well as regions within the medial temporal lobe (Table 9). Two of these regions (olfactory cortex and Heschl’s gyrus) were chosen as primary sensory regions that are unlikely to be impacted in this experiment, and thus they serve as conceptual controls. Bilateral ROIs were chosen to limit the number of comparisons while observing effects across a broad set of regions.

The full pattern of voxel data from a given ROI was extracted from each beta image corresponding to each trial, yielding a vector for each trial $E_i$, at encoding and each trial $R_i$, at
retrieval. Each of the vectors was normalized with respect to the mean activity and standard deviation within each trial, thus isolating the relative pattern of activity for each trial and ROI (Figure 10). Euclidean distance was computed for all possible pair-wise combinations of encoding and retrieval target trials, resulting in a single distance value for each EiRj pair. This distance value measures the degree of dissimilarity between activity patterns at encoding and those at retrieval—literally the numerical distance between the patterns plotted in n-dimensional space, where n refers to the number of included voxels (Kriegeskorte, 2008). An alternative metric for pattern similarity is the Pearson’s correlation coefficient, which is highly anti-correlated with Euclidean distance; not surprisingly, analyses using this measure replicate the findings reported here. For ease of understanding, figures report the inverse of Euclidean distance as a similarity metric; regression analyses likewise flip the sign of distance metric z-scores to reflect similarity.

![Diagram](image)

**Figure 10:** Participants viewed emotionally negative, positive, and neutral images during scene encoding and recognition memory tasks. Beta estimates were computed for each individual trial at both encoding and recognition (a). For the full complement of encoding-retrieval pairs, including one-to-one match pairs (same picture) and condition match pairs (same valence, task and memory status, different pictures), beta patterns were extracted from 31 separate anatomical ROIs and the similarity between patterns was computed (b).
Pairwise distances were summarized according to whether or not the encoding-retrieval pair corresponded to a one-to-one match between encoding and retrieval (i.e., trial $E_i$ refers to the same picture as trial $R_j$). In comparison, condition-match pairs were matched on the basis of emotion type, encoding condition, and memory status, but excluded these one-to-one match pairs (Figure 10). These experimental factors were controlled in the condition-match condition to mitigate the influence of task engagement or success. Any differences observed between the one-to-one match and condition-match distances can be attributed to reactivation of memories or processes specific to the individual stimulus. On the other hand, any memory effects observed across both the one-to-one and condition-match distances may reflect processes general to encoding and recognizing scene stimuli.

To assess reactivation, mean distances for the one-to-one match and condition-match pairs were entered into repeated-measures ANOVA with match level (one-to-one, condition-match) and memory status (remembered, forgotten) as factors. Reported results were significant at a one-tailed family-wise error rate of $p < .05$, with a Bonferroni correction for each of the 31 tested ROIs (effective $p < .0032$). All following analyses are restricted to subsets of ROIs identified here as modulated by match, memory status, or both.

Although the pattern vectors were standardized prior to distance computation, it remained a concern that overall activation in the ROIs could be driving some of these memory-related distance effects. To rule out this possibility, we conducted a logistic regression using trial-to-trial measures of mean ROI activation and pattern similarity to predict binary memory outcomes at retrieval, within each participant and for each of the memory-sensitive regions. The activation and distance beta-coefficients were tested with one-sample $t$-tests to determine whether they significantly differed from zero across the
group. A significant result would indicate that mean retrieval activation and encoding-retrieval similarity make separable contributions to memory. All subsequent memory-related analyses were restricted to regions for which encoding-retrieval similarity remained a significant predictor of memory in this regression.

4.2.3.3 Functional connectivity

Another goal was to test the hypothesis that the link between reinstatement of neocortical patterns and memory is mediated by hippocampal activity at retrieval. To address this hypothesis, multi-level mediation analysis was conducted via the Multilevel Mediation and Moderation toolbox (Atlas, Bolger, Lindquist, & Wager, 2010; Wager et al., 2009), using encoding-retrieval similarity (from the one-to-one match condition) as the independent variable, 5-point memory responses as the dependent variable, and hippocampal activity at retrieval as the mediating variable (Figure 13a). Each of these trial-wise vectors was normalized within-participants prior to analysis. Hippocampal functional ROIs included voxels within the AAL anatomical ROI that showed parametric modulation by memory strength for old items, defined separately for each individual at the liberal threshold of $p < .05$ to ensure inclusion of all memory-sensitive voxels. Voxels were limited to left hippocampus, where stronger retrieval success effects were observed. Two participants were excluded from this analysis for not having above-threshold responses in left hippocampus. Models were estimated via bootstrapping for each participant and then participants were treated as random effects in a group model that tested the significance of each path. Significant mediation was identified by the interaction of path $a$ (similarity to hippocampal activity) and path $b$ (hippocampal activity to memory, controlling for similarity). The mediation model was specified separately for each of the 10 neocortical
ROIs showing significant match and memory effects, and statistical tests were thresholded at Bonferroni-corrected $p < .05$, one-tailed (effective $p < .01$). It should be noted that it is not feasible to ascertain directionality at the level of trial-wise estimates; thus, for the sake of completeness, the reverse mediation was also computed, with hippocampal activity as the independent variable and encoding-retrieval similarity as the mediating variable.

Finally, for ROIs showing evidence of hippocampal mediation, the correlation of pattern distance and hippocampal activity during retrieval was computed separately for remembered and forgotten items. This enabled the direct test of whether pattern similarity covaried with hippocampal activity, within successfully-remembered items only, and whether this correlation was stronger for remembered than forgotten items, using one-sample and paired t-tests, respectively, on z-transformed r-values. This technique is similar to previously reported functional connectivity analyses (Daselaar, et al., 2006; Rissman, et al., 2004), but relates activity to pattern similarity rather than activity to activity.

4.2.3.4 Emotion effects

For regions showing significant modulation by match level, the influence of emotional arousal was measured by including emotion type (negative, neutral, positive) as a factor in repeated-measures ANOVA with match level and memory status as factors and encoding-retrieval similarity as the dependent variable. Reported results were significant at a one-tailed family-wise error rate of $p < .05$, with a Bonferroni correction for each of the 19 tested ROIs (effective $p < .0053$). The sole region (middle occipital gyrus) showing a significant interaction between match and emotion was interrogated further using functional connectivity methods similar to those described above to assess its relationship with amygdala activity during retrieval. Amygdala functional ROIs included voxels within
the AAL anatomical ROI (right amygdala only) that showed modulation by emotion or the interaction of emotion and memory for old items, defined separately for each individual at the liberal threshold of $p < .05$. Both the mediation tests and memory-modulated correlation tests were implemented similarly to those described above, but with amygdala filling in the role of hippocampus.

4.3 Results

4.3.1 Behavioral

Overall memory performance was very good: old items were remembered (two most confident "old" responses) 53.7% ± 19.2% of the time whereas new items were incorrectly endorsed as such only 3.3% ± 2.4% of the time, on average. This resulted in an average $d'$ score of 2.04 ± .48, which is well above chance, $t(18) = 1127.20$, $p < .001$. Memory performance was significantly modulated by the emotional content of the images, as measured by $d'$ (negative: 2.33 ± .52, positive: 1.91 ± .52, neutral: 1.92 ± .52). Negative pictures were recognized with greater accuracy than both neutral, $t(18) = 4.18$, $p = .001$, and positive, $t(18) = 5.69$, $p < .001$, pictures.

4.3.2 Neuroimaging

4.3.2.1 Evidence for item-specific memory reactivation

Pattern similarity between encoding and retrieval was measured by calculating the pairwise distance between each retrieval trial and each encoding trial. Distances were sorted with respect to whether the paired trials corresponded to the same pictures or different pictures from the same category. As expected, many of the 31 tested ROIs showed a main effect of match, exhibiting greater encoding-retrieval similarity for one-to-one match pairs than for condition-match pairs, $p < .0032$ (Table 9). Because the same images were
presented at encoding and recognition, this finding demonstrates that these pattern
dissimilarity measures are sensitive to the visual and conceptual differences that
distinguish individual images, as previously evidenced (Kay, Naselaris, Prenger, & Gallant,
2008). Not surprisingly, item-specific encoding-retrieval similarity is highest in regions
devoted to visual perception (Figure 11); for example, the mean correlation between
encoding and retrieval vectors in calcarine gyrus was .23 (subject range: .10 to .34) for
remembered items.

Figure 11: Encoding-retrieval similarity was greatest among visual processing regions
(a), such as the calcarine gyrus, within which one-to-one match pairs were more
similar than condition-match pairs, regardless of memory (b). d = distance, rem =
remembered, forg = forgotten.

Table 9: All regions tested with Match x Memory ANOVA results

<table>
<thead>
<tr>
<th>Region</th>
<th>voxels</th>
<th>Main effect of Match</th>
<th>Main effect of Memory</th>
<th>Match x Memory Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inf Frontal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opercularis</td>
<td>10</td>
<td>39.50 .000*</td>
<td>27.64 .000*</td>
<td>2.61 .124</td>
</tr>
<tr>
<td>Region</td>
<td>Value 1</td>
<td>Value 2</td>
<td>Value 3</td>
<td>Value 4</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Inf Frontal Orbitalis</td>
<td>.03</td>
<td>1.26</td>
<td>.276</td>
<td>7.30</td>
</tr>
<tr>
<td>Inf Frontal Triangularis</td>
<td>.08</td>
<td>26.38</td>
<td>.000</td>
<td>45.36</td>
</tr>
<tr>
<td>Mid Frontal</td>
<td>.04</td>
<td>32.05</td>
<td>.000</td>
<td>18.42</td>
</tr>
<tr>
<td>Mid Frontal Orbital</td>
<td>.01</td>
<td>.43</td>
<td>.520</td>
<td>.15</td>
</tr>
<tr>
<td>Sup Frontal</td>
<td>.02</td>
<td>31.29</td>
<td>.000</td>
<td>2.26</td>
</tr>
<tr>
<td>Sup Medial Frontal</td>
<td>.02</td>
<td>17.61</td>
<td>.001</td>
<td>4.76</td>
</tr>
<tr>
<td>Sup Frontal Orbital</td>
<td>.01</td>
<td>6.04</td>
<td>.024</td>
<td>1.40</td>
</tr>
<tr>
<td>Insula</td>
<td>.02</td>
<td>.16</td>
<td>.697</td>
<td>3.74</td>
</tr>
<tr>
<td>MTL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amygdala</td>
<td>.01</td>
<td>1.59</td>
<td>.223</td>
<td>.59</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>.02</td>
<td>.00</td>
<td>.946</td>
<td>2.35</td>
</tr>
<tr>
<td>Parahippocampal Gyrus</td>
<td>.04</td>
<td>21.79</td>
<td>.000</td>
<td>3.72</td>
</tr>
<tr>
<td>Temporal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fusiform</td>
<td>.21</td>
<td>89.36</td>
<td>.000</td>
<td>1.83</td>
</tr>
<tr>
<td>Inf Temporal</td>
<td>.05</td>
<td>119.06</td>
<td>.000</td>
<td>24.66</td>
</tr>
<tr>
<td>Mid Temporal</td>
<td>.06</td>
<td>38.36</td>
<td>.000</td>
<td>26.92</td>
</tr>
<tr>
<td>Mid Temporal Pole</td>
<td>.01</td>
<td>.26</td>
<td>.619</td>
<td>2.15</td>
</tr>
<tr>
<td>Sup Temporal Pole</td>
<td>.01</td>
<td>.69</td>
<td>.418</td>
<td>.55</td>
</tr>
<tr>
<td>Sup Temporal</td>
<td>.02</td>
<td>.22</td>
<td>.646</td>
<td>14.12</td>
</tr>
<tr>
<td>Parietal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angular</td>
<td>.06</td>
<td>23.63</td>
<td>.000</td>
<td>9.68</td>
</tr>
<tr>
<td>Inf Parietal</td>
<td>.06</td>
<td>42.86</td>
<td>.000</td>
<td>28.00</td>
</tr>
<tr>
<td>Sup Parietal</td>
<td>.08</td>
<td>1.19</td>
<td>.290</td>
<td>1.23</td>
</tr>
<tr>
<td>Precuneus</td>
<td>.05</td>
<td>50.28</td>
<td>.000</td>
<td>22.54</td>
</tr>
<tr>
<td>Supramarginal</td>
<td>.03</td>
<td>17.80</td>
<td>.001</td>
<td>49.54</td>
</tr>
<tr>
<td>Occipital</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcarine</td>
<td>.23</td>
<td>176.09</td>
<td>.000</td>
<td>1.99</td>
</tr>
<tr>
<td>Cuneus</td>
<td>.12</td>
<td>52.46</td>
<td>.000</td>
<td>3.05</td>
</tr>
<tr>
<td>Lingual</td>
<td>.17</td>
<td>222.77</td>
<td>.000</td>
<td>3.86</td>
</tr>
<tr>
<td>Inf Occipital</td>
<td>.19</td>
<td>55.93</td>
<td>.000</td>
<td>11.69</td>
</tr>
<tr>
<td>Mid Occipital</td>
<td>.18</td>
<td>131.33</td>
<td>.000</td>
<td>16.95</td>
</tr>
<tr>
<td>Sup Occipital</td>
<td>.16</td>
<td>124.92</td>
<td>.000</td>
<td>21.78</td>
</tr>
<tr>
<td>Primary Sensory Controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heschl</td>
<td>.01</td>
<td>1.33</td>
<td>.263</td>
<td>2.33</td>
</tr>
<tr>
<td>Olfactory</td>
<td>.01</td>
<td>.941</td>
<td>.17</td>
<td>.684</td>
</tr>
</tbody>
</table>

*Note: Asterisks denote regions significant at Bonferroni-corrected threshold. Mean r refers to the Pearson’s correlation coefficient between encoding and retrieval patterns, averaged across the group. Inf = Inferior, Mid = Middle, Sup = Superior.*
Several regions, including inferior frontal gyrus, precuneus, inferior parietal, occipital gyri, and inferior and middle temporal gyri were characterized by a main effect of memory success such that encoding-retrieval similarity was enhanced during successful recognition regardless of match level, $p < .0032$ (Figure 12a,b). This similarity may reflect the re-engagement of processes that are beneficial to memory at both encoding and retrieval, general across all trials.

![Figure 12: Encoding-retrieval similarity in several regions was modulated by memory success (a), characterized by either a main effect of memory (blue) or memory by match interaction (ref). The inferior frontal ROI showed greater encoding-retrieval similarity for remembered items among both the one-to-one and condition-match](image-url)

112
pairs (b). The middle occipital and middle temporal ROIs were characterized by an interaction in that memory effects were stronger among one-to-one than condition-match pairs (c). Finally, mean ROI activation and encoding-retrieval similarity independently predicted across-trial variation in memory success, demonstrating a lack of redundancy among these measures (d). Mid = middle, d = distance, rem = remembered, forg = forgotten.

In the critical test of memory-related reactivation, significant interactions between match and memory status were identified in middle occipital gyrus, middle temporal gyrus, and supramarginal gyrus, \( p < .0032 \) (Figure 12a,c). A marginal effect was also noted in precuneus \( (p = .008) \). In these regions, memory success is associated with greater encoding-retrieval similarity, particularly when the retrieval trial is being compared to its identical encoding trial. This interaction supports the idea that item-specific information from encoding is being reactivated during retrieval, and that this reactivation is affiliated with successful retrieval. Across-trial logistic regression analysis confirmed that, for nearly all regions identified as memory-sensitive, encoding-retrieval pattern similarity significantly predicted memory performance even when mean retrieval activation was included in the model (Table 10; Figure 12d). This suggests that reactivation of trial-specific patterns during retrieval is associated with enhanced memory, in a manner that goes beyond the magnitude of hemodynamic response.

**Table 10: Within-subjects logistic regression of memory performance on ROI activity and encoding-retrieval similarity**

<table>
<thead>
<tr>
<th>Region</th>
<th>Activation</th>
<th>Encoding-retrieval similarity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean beta</td>
<td>( t(18) )</td>
</tr>
<tr>
<td><strong>Frontal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inf Frontal Opercularis</td>
<td>.11</td>
<td>2.61</td>
</tr>
<tr>
<td>Inf Frontal Orbitalis</td>
<td>.17</td>
<td>4.70</td>
</tr>
<tr>
<td>Inf Frontal Triangularis</td>
<td>.13</td>
<td>3.22</td>
</tr>
<tr>
<td>Region</td>
<td>.01</td>
<td>.49</td>
</tr>
<tr>
<td>------------------------</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>Mid Frontal Orbital</td>
<td>.09</td>
<td>2.84</td>
</tr>
<tr>
<td>Sup Frontal</td>
<td>.01</td>
<td>.32</td>
</tr>
<tr>
<td>Sup Medial Frontal</td>
<td>.15</td>
<td>4.83</td>
</tr>
<tr>
<td>Sup Frontal Orbital</td>
<td>.08</td>
<td>3.02</td>
</tr>
<tr>
<td>Insula</td>
<td>.07</td>
<td>3.35</td>
</tr>
</tbody>
</table>

**MTL**

<table>
<thead>
<tr>
<th>Region</th>
<th>.08</th>
<th>3.40</th>
<th>.003*</th>
<th>.01</th>
<th>.49</th>
<th>.628</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amygdala</td>
<td>.12</td>
<td>6.16</td>
<td>.000*</td>
<td>.00</td>
<td>.04</td>
<td>.970</td>
</tr>
<tr>
<td>Hippocampus Parahippocampal</td>
<td>.12</td>
<td>4.39</td>
<td>.000*</td>
<td>-.01</td>
<td>-.24</td>
<td>.814</td>
</tr>
</tbody>
</table>

**Temporal**

<table>
<thead>
<tr>
<th>Region</th>
<th>.11</th>
<th>3.67</th>
<th>.002*</th>
<th>.07</th>
<th>1.66</th>
<th>.113</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fusiform</td>
<td>.13</td>
<td>5.12</td>
<td>.000*</td>
<td>.14</td>
<td>4.51</td>
<td>.000*</td>
</tr>
<tr>
<td>Inf Temporal</td>
<td>.13</td>
<td>4.23</td>
<td>.001*</td>
<td>.16</td>
<td>4.92</td>
<td>.000*</td>
</tr>
<tr>
<td>Mid Temporal</td>
<td>-.01</td>
<td>-.23</td>
<td>.818</td>
<td>.01</td>
<td>.35</td>
<td>.730</td>
</tr>
<tr>
<td>Mid Temporal Pole</td>
<td>-.01</td>
<td>-.71</td>
<td>.484</td>
<td>.02</td>
<td>.63</td>
<td>.536</td>
</tr>
<tr>
<td>Sup Temporal</td>
<td>.05</td>
<td>1.95</td>
<td>.067</td>
<td>.07</td>
<td>3.64</td>
<td>.002*</td>
</tr>
<tr>
<td>Sup Temporal Pole</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Parietal**

<table>
<thead>
<tr>
<th>Region</th>
<th>.13</th>
<th>4.54</th>
<th>.000*</th>
<th>.12</th>
<th>3.86</th>
<th>.001*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angular</td>
<td>.03</td>
<td>.91</td>
<td>.373</td>
<td>.15</td>
<td>4.82</td>
<td>.000*</td>
</tr>
<tr>
<td>Inf Parietal</td>
<td>-.03</td>
<td>-.76</td>
<td>.456</td>
<td>.11</td>
<td>4.01</td>
<td>.001*</td>
</tr>
<tr>
<td>Sup Parietal</td>
<td>.04</td>
<td>1.80</td>
<td>.089</td>
<td>.10</td>
<td>3.76</td>
<td>.001*</td>
</tr>
<tr>
<td>Supramarginal</td>
<td>.12</td>
<td>3.99</td>
<td>.001*</td>
<td>.16</td>
<td>8.26</td>
<td>.000*</td>
</tr>
</tbody>
</table>

**Occipital**

<table>
<thead>
<tr>
<th>Region</th>
<th>.06</th>
<th>2.40</th>
<th>.028</th>
<th>.04</th>
<th>1.11</th>
<th>.281</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcarine</td>
<td>.14</td>
<td>4.06</td>
<td>.001*</td>
<td>.06</td>
<td>2.21</td>
<td>.040</td>
</tr>
<tr>
<td>Cuneus</td>
<td>.02</td>
<td>.72</td>
<td>.478</td>
<td>.05</td>
<td>1.98</td>
<td>.064</td>
</tr>
<tr>
<td>Lingual</td>
<td>.09</td>
<td>2.90</td>
<td>.009</td>
<td>.14</td>
<td>3.49</td>
<td>.003*</td>
</tr>
<tr>
<td>Inf Occipital</td>
<td>.07</td>
<td>2.13</td>
<td>.048</td>
<td>.16</td>
<td>4.02</td>
<td>.001*</td>
</tr>
<tr>
<td>Mid Occipital</td>
<td>.05</td>
<td>1.40</td>
<td>.178</td>
<td>.12</td>
<td>4.13</td>
<td>.001*</td>
</tr>
<tr>
<td>Sup Occipital</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note: Asterisks denote regions significant at Bonferroni-corrected threshold. Mean beta refers to the logistic regression beta coefficient, averaged across the group. Inf = Inferior, Mid = Middle, Sup = Superior.*

4.3.2.2 Role of the hippocampus in mediating cortical reactivation

It was hypothesized that if encoding-retrieval pattern similarity is a measure of reactivation of the memory trace, then its relationship with memory should be mediated by hippocampal activity at retrieval (Figure 13a). Indeed, mediation analysis revealed that
hippocampal activity was a significant mediator of the relationship between encoding-retrieval similarity and memory, \( p < .01 \), for occipital, inferior frontal, and inferior parietal cortices (Figure 13b). After accounting for mediation, the relationship between encoding-retrieval similarity and memory remained intact for each of these regions, providing evidence for partial mediation (Table 11). For the inferior frontal and inferior and middle occipital cortices, the reverse mediation was also marginally significant \( (p < .05) \), indicating that encoding-retrieval similarity may mediate hippocampal-memory associations (Table 11). The true directionality of this relationship cannot be discerned in the present dataset, but these findings speak to the dynamic influences of hippocampal activity and cortical reactivation patterns at retrieval on each other and on memory. Finally, for inferior frontal and occipital cortices, the correlation between pattern similarity and hippocampal activity at retrieval was significant across trials even when restricted to remembered items only, \( p < .01 \). For a subset of these regions, this correlation was marginally stronger for remembered than forgotten items, \( p < .05 \). (Table 11) Taken together, activity in the hippocampus is associated with greater fidelity between neocortical representations at encoding and retrieval, and this relationship facilitates successful memory performance.
Figure 13: Mediation analysis tested the hypothesis that the hippocampus mediates the relationship between encoding-retrieval neocortical similarity and memory success (a). Among regions showing memory-modulated encoding-retrieval similarity effects, the influence of encoding-retrieval similarity in inferior frontal, inferior parietal, and occipital ROIs on memory was significantly mediated by the hippocampus (b). E-R = encoding-retrieval, hc = hippocampus.

Table 11: Mediation analysis linking encoding-retrieval similarity to memory

<table>
<thead>
<tr>
<th></th>
<th>X-&gt;M</th>
<th>M-&gt;Y</th>
<th>mediated</th>
<th>X-&gt;Y (c')</th>
<th>X-&gt;Y</th>
<th>term</th>
<th>rem</th>
<th>forg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>unmediated</td>
<td>mediation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E-R similarity (X) to memory (Y), mediated by left HC activity at retrieval (M)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inf Frontal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opercularis</td>
<td>.089*</td>
<td>.114*</td>
<td>.060*</td>
<td>.069*</td>
<td>.008*</td>
<td>.103*</td>
<td>.055</td>
<td></td>
</tr>
<tr>
<td>Inf Frontal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triangularis</td>
<td>.095*</td>
<td>.111*</td>
<td>.077*</td>
<td>.087*</td>
<td>.008*</td>
<td>.116*</td>
<td>.061</td>
<td></td>
</tr>
<tr>
<td>Inf Occipital</td>
<td>.077*</td>
<td>.113*</td>
<td>.068*</td>
<td>.075*</td>
<td>.006*</td>
<td>.093*</td>
<td>.029</td>
<td></td>
</tr>
<tr>
<td>Mid Occipital</td>
<td>.109*</td>
<td>.111*</td>
<td>.090*</td>
<td>.101*</td>
<td>.009*</td>
<td>.139*</td>
<td>.074</td>
<td></td>
</tr>
<tr>
<td>Sup Occipital</td>
<td>.093*</td>
<td>.116*</td>
<td>.059*</td>
<td>.069*</td>
<td>.008*</td>
<td>.099*</td>
<td>.092</td>
<td></td>
</tr>
<tr>
<td>Inf Parietal</td>
<td>.048*</td>
<td>.118*</td>
<td>.081*</td>
<td>.085*</td>
<td>.004*</td>
<td>.050</td>
<td>.031</td>
<td></td>
</tr>
<tr>
<td>Precuneus</td>
<td>.000</td>
<td>.121*</td>
<td>.063*</td>
<td>.062*</td>
<td>.000</td>
<td>.014</td>
<td>-.031</td>
<td></td>
</tr>
<tr>
<td>Supramargina</td>
<td>.000</td>
<td>.120*</td>
<td>.068*</td>
<td>.068*</td>
<td>.000</td>
<td>.004</td>
<td>-.029</td>
<td></td>
</tr>
<tr>
<td>Inf Temporal</td>
<td>.046</td>
<td>.116*</td>
<td>.060*</td>
<td>.063*</td>
<td>.004</td>
<td>.055</td>
<td>.034</td>
<td></td>
</tr>
<tr>
<td>Mid Temporal</td>
<td>.020</td>
<td>.119*</td>
<td>.069*</td>
<td>.070*</td>
<td>.002</td>
<td>.028</td>
<td>.010</td>
<td></td>
</tr>
</tbody>
</table>

Left HC activity at retrieval (X) to memory (Y), mediated by E-R similarity (M) |

|                |       |       |           |           |      |       |      |
| Inf Frontal    |       |       |           |           |      |       |      |
| Opercularis    | .089* | .060* | .114*     | .120*     | .003 | -     | -    |
| Inf Frontal    | .095* | .077* | .111*     | .120*     | .005 | -     | -    |

116
Triangularis
Inf Occipital  .077*  .068*  .113*  .120*  .003  -  -
Mid Occipital  .109*  .090*  .111*  .120*  .005  -  -
Sup Occipital  .093*  .059*  .116*  .120*  .003  -  -
Inf Parietal  .048*  .081*  .118*  .120*  .001  -  -
Precuneus  .000  .063*  .121*  .120*  .000  -  -
Supramarginal  .000  .068*  .120*  .120*  .000  -  -
Inf Temporal  .046  .060*  .116*  .120*  .002  -  -
Mid Temporal  .020  .069*  .119*  .120*  .000  -  -

*E-R similarity (X) to memory (Y), mediated by right amygdala activity at retrieval (M)*
Mid Occipital  .042  .031*  .103*  .103*  .000  .072  .040

*Right amygdala activity at retrieval (X) to memory (Y), mediated by E-R similarity (M)*
Mid Occipital  .042  .103*  .031*  .034*  .002  -  -

Note: * denote regions significant at Bonferroni-corrected threshold. † denotes a marginally-significant remembered versus forgotten difference, p < .05. Inf = Inferior, Mid = Middle, Sup = Superior, rem = remembered, forg = forgotten, E-R = encoding-retrieval, HC = hippocampus.

4.3.2.3 Emotional modulation of cortical reactivation

Emotional arousal globally increased the similarity of encoding and retrieval patterns (main effect of emotion, p < .0053) in many regions including the occipital, inferior and middle temporal, and supramarginal gyri (Figure 14a; Table 12). Arousal also accentuated the effect of matching one-to-one on encoding-retrieval similarity (interaction of emotion and match, F(2, 36) = 6.31, p = .004) in middle occipital gyrus (Figure 14b), suggesting that this region is involved in recapitulating item-specific information during recognition of arousing material in particular. Memory effects on encoding-retrieval similarity were not modulated by emotion. The middle occipital region was further explored via functional connectivity analyses looking at the relationship between amygdala activity at retrieval and encoding-retrieval similarity. The correlation between amygdala activity and encoding-retrieval similarity in MOG showed a significant emotion by memory interaction, F(2,32) = 3.74, p = .035 (Figure 14c). This interaction reflected a trend toward
stronger correlations for remembered than forgotten trials among negative items, \( t(16) = 1.97, p = .067 \), but not positive or neutral items, \( ps > .2 \). Mediation analysis showed that amygdala activity did not mediate the relationship between encoding-retrieval similarity and memory, or vice versa (Table 11), indicating that the hippocampus remains the primary link between cortical reactivation effects and memory. Altogether, these findings suggest that emotional arousal is associated with heightened encoding-retrieval similarity, particularly in perceptual processing regions, which tends to engage the amygdala during successful retrieval.

Figure 14: Emotion significantly enhanced overall encoding-retrieval similarity effects in a number of posterior regions and specifically enhanced one-to-one match effects within middle occipital gyrus (a). The middle occipital gyrus showed greater encoding-retrieval similarity for negative and positive relative to neutral trials among the one-to-one match pairs (b). Encoding-retrieval similarity in middle occipital gyrus was additionally correlated across trials with retrieval activity in the amygdala; this correlation was modulated by memory success for negative but not positive or neutral trials (c). Neg = negative, pos = positive, neut = neutral, MOG = middle occipital gyrus.

Table 12: Regions showing emotional modulation of encoding-retrieval similarity

<table>
<thead>
<tr>
<th>Region</th>
<th>Match x Memory x Emotion ANOVA</th>
<th>( F(2, 36) )</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main effect of Emotion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Region</td>
<td>t</td>
<td>p</td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------</td>
<td>-----</td>
<td></td>
</tr>
<tr>
<td>Mid Occipital</td>
<td>19.45</td>
<td>0.000*</td>
<td></td>
</tr>
<tr>
<td>Inf Temporal</td>
<td>17.61</td>
<td>0.000*</td>
<td></td>
</tr>
<tr>
<td>Inf Occipital</td>
<td>16.46</td>
<td>0.000*</td>
<td></td>
</tr>
<tr>
<td>Angular</td>
<td>15.38</td>
<td>0.000*</td>
<td></td>
</tr>
<tr>
<td>Inf Parietal</td>
<td>12.43</td>
<td>0.000*</td>
<td></td>
</tr>
<tr>
<td>Supramarginal</td>
<td>9.05</td>
<td>0.001*</td>
<td></td>
</tr>
<tr>
<td>Mid Temporal</td>
<td>8.29</td>
<td>0.001*</td>
<td></td>
</tr>
<tr>
<td>Sup Occipital</td>
<td>6.51</td>
<td>0.004*</td>
<td></td>
</tr>
<tr>
<td>Sup Temporal</td>
<td>5.11</td>
<td>0.011</td>
<td></td>
</tr>
<tr>
<td>Sup Parietal</td>
<td>4.95</td>
<td>0.013</td>
<td></td>
</tr>
<tr>
<td>Inf Frontal Opercularis</td>
<td>4.92</td>
<td>0.013</td>
<td></td>
</tr>
<tr>
<td>Fusiform</td>
<td>4.26</td>
<td>0.022</td>
<td></td>
</tr>
<tr>
<td>Sup Frontal</td>
<td>4.13</td>
<td>0.024</td>
<td></td>
</tr>
<tr>
<td>Inf Frontal Triangularis</td>
<td>3.88</td>
<td>0.030</td>
<td></td>
</tr>
<tr>
<td><strong>Emotion x Match Interaction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mid Occipital</td>
<td>6.31</td>
<td>0.004*</td>
<td></td>
</tr>
<tr>
<td>Fusiform</td>
<td>3.41</td>
<td>0.044</td>
<td></td>
</tr>
<tr>
<td><strong>Emotion x DM Interaction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inf Frontal Opercularis</td>
<td>3.85</td>
<td>0.030</td>
<td></td>
</tr>
<tr>
<td><strong>Emotion x Match x DM Interaction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fusiform</td>
<td>3.52</td>
<td>0.040</td>
<td></td>
</tr>
</tbody>
</table>

*Note: Asterisks denote regions significant at Bonferroni-corrected threshold. Regions showing marginal effects (p < .05) are also shown. Main effects and interactions not involving emotion are excluded. Inf = Inferior, Mid = Middle, Sup = Superior.*

**4.4 Discussion**

This study provides novel evidence that successful memory is associated with superior match between encoding and retrieval at the level of individual representations. Furthermore, hippocampal involvement during retrieval mediates this relationship on a trial-to-trial basis, lending empirical support to theories positing dynamic interactions between hippocampal and neocortex during retrieval.

Previous studies have highlighted the reactivation of condition-level information from the initial learning episode during memory retrieval, using both traditional fMRI
analysis approaches as well as multivariate pattern analysis (MVPA) techniques (Johnson, et al., 2009; Kuhl, et al., 2011). Importantly, evidence thus far has been limited to broad categorical distinctions, such as the modality of stimulus encoding (Nyberg, et al., 2000; Wheeler & Buckner, 2003; Wheeler, et al., 2000), imagery task applied during encoding (Johnson, et al., 2009) or the object category of a paired-associate (Kuhl, et al., 2011). The present study advances this line of research by providing critical evidence that reactivation of encoding-related information during retrieval can be tracked at the level of individual items and be used to predict memory success. This item-level information may consist of cognitive or perceptual operations unique to the individual stimulus that are shared between encoding and retrieval or the reactivation of specific associations formed during the time of encoding. Both forms of information may serve to propel brain states at retrieval closer toward where they were during encoding. These measures are not restricted to category or task-related information like previous studies have been, and thus are ideal for flexibly capturing instances of encoding-retrieval match tailored to each individual person and trial. Validating the sensitivity of these methods to item-level information, cortical regions across the brain showed greater encoding-retrieval similarity when trials were matched one-to-one rather than within condition. This finding reflects the high degree of perceptual correspondence between encoding and recognition trials; indeed, the level of similarity was greatest in regions involved in low-level visual perception, consistent with prior evidence that individual visual stimuli can be decoded using voxel information from visual cortex (Kay, et al., 2008).

Critically, memory success interacts with the level of encoding-retrieval match: encoding-retrieval similarity is most sensitive to memory success when trials are matched
one-to-one. This provides direct evidence for the theory of encoding-retrieval match, in that increased match yields superior memory performance. The interaction also provides assurance that these results cannot be attributed to perceptual similarities between encoding and recognition, which should be consistent across the one-to-one match pairs, or to variation in task engagement, which should be consistent across successfully remembered items. Logistic regression furthermore clarified that the link between one-to-one encoding-retrieval similarity and memory success cannot be explained by differences in overall ROI activation; in many regions spanning frontal, parietal, and occipital cortices, encoding-retrieval similarity predicted memory success when mean activation did not. Finally, there were several additional regions that tracked memory performance regardless of match level, including inferior frontal, inferior parietal, and temporal regions. These regions may support processes that are generally beneficial to both encoding and retrieval, such that the consistent participation of these regions enriches memory across the entire set of trials. Consistent with this, frontal and parietal regions have emerged as consistent predictors of memory success at both phases (Spaniol, et al., 2009).

A couple of recent studies have used pattern similarity analysis to look at how variation across encoding trials predicts memory success, exploiting the ability of similarity measures to tap into the representational structure underlying neural activity (Kriegeskorte, 2008). One used pattern distance to measure contextual shifts during encoding and linked these shifts to successful memory formation (Jenkins & Ranganath, 2010). Another study measured the similarity between repetitions of the same encoding trial to test the hypothesis that memories benefit from consistent training, in contrast to the encoding variability hypothesis (Xue et al., 2010). This latter study presented evidence that
increased similarity between encoding repetitions, calculated separately for each individual stimulus, corresponded to greater memory success. In contrast, the present study focuses not on the similarity of identically-presented encoding trials, but on the similarities between processing the same mnemonic stimuli at two separate phases of memory—namely, the overlap between encoding and explicit recognition processes. Because a different task is required at each phase, the similarity between encoding and retrieval trials must arise from either perceptual attributes, which are common between remembered and forgotten trials, or from information that aids or arises from mnemonic recovery, which differ between remembered and forgotten trials. Thus, any differences between remembered and forgotten items in the one-to-one match pairs must reflect the reactivation of encoding-related processes during the recognition period.

Another critical advance in the present study is the use of similarity measures as a covariate for functional connectivity analyses looking at the role of the hippocampus in supporting neocortical pattern reactivation. Consistent with theories of memory positing dynamic interactions between hippocampus and neocortex during episodic retrieval (Alvarez & Squire, 1994; McClelland, et al., 1995; Nadel, et al., 2000; Norman & O’Reilly, 2003; Squire, 1992; Sutherland & McNaughton, 2000), these analyses showed that the hippocampus partially mediates the link between encoding-retrieval similarity and retrieval success across a number of neocortical ROIs. Although mediation analysis assumes theoretical directionality during model fitting, it is not feasible to discriminate causality among the neural components of the model within this dataset. These data may indicate that the overlap between encoding and retrieval representations triggers hippocampal retrieval or that hippocampal activation promotes pattern completion processes that
manifest as encoding-retrieval overlap—or some interaction of both sets of mechanisms. Interestingly, hippocampal activation did not fully account for the link between encoding-retrieval similarity and memory, implying that both components of the model are independently related to memory success, consistent with suggestions that both hippocampus and neocortical representations are essential to memory retrieval (McClelland, et al., 1995; Wiltgen, et al., 2004). Altogether these findings underscore the presence of a dynamic relationship between distributed neocortical representations and hippocampal involvement that supports successful memory retrieval.

This study also presents novel evidence for emotional modulation of encoding-retrieval match. Few studies have previously investigated the neural correlates of both encoding and retrieval within an emotional memory paradigm, but findings from the retrieval phase point to larger memory effects in the amygdala and MTL memory system (Buchanan, 2007), similar to that seen during encoding (Murty, et al., 2010). Emotional memories also tend to be accompanied by an increased sense of vividness relative to their neutral counterparts (Dolcos, et al., 2005; Ochsner, 2000; Ritchey, et al., 2008; Sharot, et al., 2004) and are marked by enhancements in consolidation (Cahill & McGaugh, 1998; McGaugh, 2004), both of which hint at memory reactivation. The present study replicates these results and extends them to show that across all trials, emotion heightens the similarity between encoding and retrieval patterns in several neocortical regions in occipital and temporal cortex. Furthermore, emotional arousal is associated with enhanced item-specific pattern similarity in middle occipital gyrus, evidenced by the interaction of emotion and match. Emotion did not interact with memory success, suggesting additive rather than interactive effects of emotion and memory. That is, emotional arousal may
impact memory retrieval by increasing the likelihood of encoding-retrieval overlap, perhaps by targeting replay mechanisms that guide propensity toward reactivation during both consolidation and retrieval. Functional connectivity analyses with the amygdala seem consistent with this proposition: activity in the amygdala covaried with encoding-retrieval similarity in occipital cortex during successfully-retrieved negative trials, but it did not mediate the link between similarity and memory. These data are compatible with the hypothesis that, rather than modulate memory themselves, amygdala responses at retrieval may be driven by the recovery and processing of item-specific details. As such, the hippocampus remains the primary route by which encoding-retrieval similarity predicts memory performance, for both emotional and neutral trials.

An interesting null result was the absence of significant pattern similarity effects in the hippocampus or amygdala. Prior evidence indicates segregation among memory representations within the hippocampus (Bonnici et al., 2011; Gelbard-Sagiv, Mukamel, Harel, Malach, & Fried, 2008; Hassabis et al., 2009) and thus we anticipated uncovering pattern effects in this region. Although it is possible that the role of these regions is more modulatory than representational, a likely explanation is the use of standard spatial resolution parameters, which may be too coarse to detect consistent voxel patterns within these small structures even when more distributed patterns can be detected across larger surfaces. Notably, the logistic regression results show clearly that overall activity in both regions predicts memory success; thus we can be sure that these regions are sensitive to memory in the present design.

Finally, an important caveat to the present results is the use of a recognition task during the retrieval phase, which re-introduces the same perceptual information at
retrieval as is present during encoding. Although this perceptual overlap is equivalent across both remembered and forgotten items, thus mitigating the possibility of its contribution to memory effects, an ideal test of memory reactivation would measure cognitive and neural responses reinstated in the absence of supporting information, as in a cued- or free-recall design. This would ensure that the similarity between encoding and retrieval patterns would be driven nearly exclusively by information arising from memory, rather than being inflated by perceptual similarities. In the present study, these concerns are assuaged by the findings that encoding-retrieval similarity varies with memory success and is related to hippocampal activation; nonetheless, this remains an essential step for future research.

In conclusion, this study presents the novel finding that episodic memory success tracks item-specific fluctuations in encoding-retrieval match, as measured by patterns of hemodynamic activity across neocortex. Importantly, this relationship is mediated by the hippocampus, providing critical evidence for hippocampal-neocortical interactions during reinstatement of memories at retrieval. We also report new evidence linking emotional arousal to enhancements in memory reactivation, a mechanism that may bridge understanding of how emotion impacts encoding, consolidation, and retrieval processes. Altogether, these findings speak to the promise of pattern similarity measures for evaluating the integrity of episodic memory traces and measuring communication between the medial temporal lobes and distributed neocortical representations.
5. Conclusion

The studies described here elucidate multiple stages in the lifetime of an emotional memory. Starting with memory formation, the first study demonstrated that amygdala activity predicts the persistence of emotional memories over time and, furthermore, that its link with the medial temporal lobe (MTL) memory system likewise tracks long-term memory success. These regions are likely to be involved in initiating consolidation processes that are enhanced by emotional arousal. The second study presented additional evidence in support of 2 distinct networks during emotional memory encoding: one including lateral prefrontal cortex (PFC) that is sensitive to depth of processing and one including the amygdala that is recruited relatively automatically. The dissociation of these networks lends support to the idea that emotion benefits memory first by influencing the efficacy of standard memory encoding processes and then by triggering a neurohormonal cascade that modulates consolidation. Finally, shifting to memory retrieval, the third study provided novel evidence that the involvement of the amygdala at retrieval may correspond to the reactivation of processes previously engaged during encoding. In particular, this study showed that memory performance can be linked to the level of encoding-retrieval match at each trial and that emotion increases the similarity between encoding and retrieval processes. I now return to each of the goals laid out in Chapter 1, and then discuss methodological issues and remaining questions that may be resolved by future research.

5.1 Key Questions, Revisited

As described in the Introduction, most neuroimaging studies of emotional memory have set out to replicate and expand upon the large literature linking neurohormonal interactions in amygdala and the MTL to improvements in memory consolidation. The study
described in Chapter 2 advanced this research one step further by demonstrating that memory enhancements associated with emotion are exacerbated by the passage of time and, similarly, neural activity in the amygdala and its relationship with the MTL tend to track the persistence of these memories. This provides support for the hypothesis that neural activity at the time of encoding can be used to assess changes in memory generally attributed to memory consolidation processes that unfold over time. Critically, this implies that retention interval manipulations can be used to increase the relative reliance of emotional memory success on consolidation mechanisms. It has been proposed both here and previously (LaBar & Cabeza, 2006) that superior memories for emotional material can be propagated both by the influence of emotion on MTL-dependent consolidation mechanisms and by modulation of encoding processes, which capitalize on existing cortical pathways that guide memory formation. Chapter 2 was primarily concerned with fleshing out the former route: consolidation is a time-dependent process whereas encoding effects may emerge immediately or interact with forgetting rates.

The study described in Chapter 3, however, was oriented toward deeper understanding of encoding effects supporting emotional memory: more specifically, how improvements in controlled semantic processing during encoding may promote richer memory traces for emotional material. This study effectively demonstrated that limiting the availability of controlled processing resources reduced the contribution of lateral PFC to emotional memory success; alternatively, encouraging controlled processing enhanced it. This gives novel evidence in support of the assumption that PFC effects reflect engagement of elaborative processes co-opted to produce emotional memory benefits, an effect that had not been clearly demonstrated before. This study also informed understanding of
interactions between the amygdala and MTL memory system, in that depleting controlled processing during encoding left intact, or even strengthened, the relationship between these regions and emotional memory. Together, the evidence presented in Chapters 2 and 3 supports the utility and validity of characterizing cortical versus amygdala-MTL networks that aid emotional memory formation, and that relative reliance on each of these networks can be shifted under certain encoding or testing conditions.

The final main goal of this thesis revolved around the role of emotion during retrieval and how this role coincides with or diverges from emotion effects during encoding or consolidation. In particular, the study described in Chapter 4 tested whether emotional memories are accompanied by superior reactivation during retrieval, indicating greater fidelity between memory traces at encoding and retrieval and perhaps relying on similar replay mechanisms that support consolidation. The data appear to support the affirmative: emotional trials are associated with greater similarity between encoding and retrieval processing, and greater similarity itself is associated with superior memory performance. Furthermore, this similarity correlates with amygdala activity during successful recognition of negative items. Thus, memories for emotional events tend to more successfully revert neural states back to the neural states initially experienced during learning, capitalizing on the memory benefits associated with high encoding-retrieval match and boosting amygdala responsiveness during retrieval. This suggests that retrieval of emotional memories does, in fact, share much in common with the encoding of emotional memories—perhaps even more in common than their neutral counterparts. I return to the relationship between retrieval and consolidation mechanisms below.
5.2 Methodological Issues for Consideration

The studies described here have motivated reflection on not only the significance of these findings for the emotional memory literature, summarized above, but also how current and future research might address these questions more effectively. I describe some of the key methodological issues pertinent to understanding the implications of these studies, others like them, and their successors.

5.2.1 On Consolidation and Time

With regard to the study described in Chapter 2, one remaining question asks whether or not consolidation can be measured satisfactorily by neuroimaging techniques. The first study took the approach of testing memory at 2 time-points separated by a week delay, with the hypothesis that activity associated with ensuing consolidation would be more predictive of long- than short-delay memory. Although the results are consistent with this interpretation and there is evidence that neural responses during encoding may initiate processes related to consolidation (Hu, et al., 2007; Nakao, et al., 2004), this is an indirect measure of consolidation at best. The most obvious way to use neuroimaging data to compare encoding and consolidation would be to image these processes separately and contrast their contributions to memory success. However, this is problematic in its own right—for example, it is not clear which time period would be used to assess consolidation nor how to identify specific instances of consolidation-related activity during this period. Furthermore, the process of consolidation spans hours to days and longer and thus, any measured period would capture only a fraction of the variance associated with consolidation. In spite of these limitations, a few recent studies have collected neuroimaging data either during post-encoding rest (Tambini, et al., 2010) or sleep (Diekelmann, et al.,
2011; Rasch, et al., 2007; Rudoy, et al., 2009), linking activity purported to reflect memory reactivation to later memory. Similar measures may be taken with emotional and neutral materials or with a post-encoding arousal manipulation; ideally, data would be collected during both the encoding and post-encoding periods to allow for comparison of these phases.

Another weakness of retention interval manipulations for measuring consolidation versus encoding is that they may overestimate the independence of their contributions to time-sensitive outcomes. Although it is reasonable to assume that enhancements that increase over time might be attributed to consolidation, one cannot completely rule out the influence of memory strength changes over time. For example, deep semantic processing during encoding results in enduring memory traces whereas shallow perceptual processing tends to result in weaker memories (Craik & Lockhart, 1972). One report suggests that the neural activity associated with each type of processing—left ventrolateral PFC for semantic and fusiform gyrus for perceptual—becomes either more or less predictive of memory over time (Uncapher & Rugg, 2005). That is, whereas fusiform activity specifically predicts recollection after 30 minutes, left ventrolateral PFC predicts recollection after a 48-hour delay, indicating dissociation between these regions. Thus temporal dissociations may conflate encoding and consolidation mechanisms. In the study presented in Chapter 2, this concern is tempered by the observation that memory differences between emotional and neutral items did not emerge until after the week delay, suggesting that these memories were not initially different in terms of memory strength. However, this caveat remains a critical point for future research.
5.2.2 Choice of Encoding Tasks

The study reported in Chapter 3 bears resemblance, both in design and in outcome, to studies using divided attention manipulations to assess the relative automaticity of the amygdala-MTL network in supporting emotional memories (Kensinger & Corkin, 2004; Kern, et al., 2005; Talmi, et al., 2007). However, whereas divided attention manipulations globally impair the efficiency of all controlled processes during encoding, the levels of processing manipulation introduced here was designed to target semantic elaboration in contrast to perceptual scrutiny during encoding. Increased process specificity improves the ability to link neural pathways with their corresponding cognitive consequences—for example, ventrolateral PFC to elaborative encoding rather than attention or task engagement. However, dividing between semantic and perceptual encoding does not effectively isolate any single cortical pathway relative to the amygdala-MTL network or vice versa, in that both forms of encoding are theoretically ascribed to cortically-mediated networks (prefrontal and occipital, respectively) affected by emotion. Whereas encoding in the deep condition bore all the benefits of emotion on cognition, encoding in the shallow condition depended heavily on perception effects while interfering with controlled processing, due to the disparity in reported task difficulty. Divided attention tasks are plagued by similar issues: because emotion effects on perception occur relatively early in processing (Pizzagalli, et al., 2002; Schupp, et al., 2003) and may rely on direct connections between amygdala and perceptual cortex (Amaral, et al., 2003), divided attention conditions may leave intact those perceptually-mediated pathways during the subordinate condition. It is clear that neither type of paradigm can isolate the amygdala-MTL network by way of encoding task selection and comparison. Thus the primary utility of these types of
paradigms is to dissect components contributing indirect advantages to emotion during encoding. One way to delineate this more carefully in a levels-of-processing design is to parametrically track semantic versus perceptual processing during encoding, so that these conditions are not yoked as baselines for each other. For example, one could vary the difficulty of semantic or perceptual processing by, for example, using stimuli that are high or low in ambiguity, semantic context, or perceptual detail. Another strategy might be to incorporate semantic and perceptual primes as implicit measures of the effect of emotion on each form of processing during encoding. Finally, a promising yet challenging approach is to separate the encoding of the memorandum from the influence of arousal on its consolidation; this idea is addressed below, although it introduces its own host of concerns.

5.2.3 Interactions Between Encoding and Consolidation

An ideal way to separate the roles of encoding and consolidation is to induce arousal separately from the memoranda, thus conferring all of the benefits of arousal-mediated consolidation while leaving encoding intact. For example, in one study, pictures of emotionally-neutral faces and houses rapidly followed by an arousing scene were remembered better than those pictures followed by neutral scenes (Anderson, Wais, & Gabrieli, 2006). This memory enhancement was limited to trials when the picture and scene are separated by a short interval (4 s) compared to a long interval (9 s), indicating that temporal proximity was critical to allowing the non-arousing stimulus in through the gate to improved consolidation. These findings, however, have been controversial: other studies have failed to obtain similar results (Hurlemann et al., 2005; Strange, Hurlemann, & Dolan, 2003). A series of behavioral studies elegantly tested possible explanations for this discrepancy and showed that the level of attention allocated to the neutral memorandum,
the delay between encoding and test, and the format of the test were critical variables (Knight & Mather, 2009).

The idea that arousal-inducing stimuli can interfere with the encoding of contemporaneous neutral memoranda is formalized in research into emotional memory “trade-offs” (Waring & Kensinger, 2009, 2011; Waring, et al., 2010) and changes in object binding and competition (Mather, 2007; Mather & Sutherland, 2011). On the one hand, arousal initiates neurohormonal interactions that benefit memory; on the other hand, arousing items capture attention and thus impede encoding of surrounding information. Also relevant to this issue is the timing of neurohormonal effects of arousal. Whereas cortisol changes tend to act slowly, noradrenaline release is relatively rapid. Thus there may be an optimal window in which both mechanisms are simultaneously acting (Joels, et al., 2011). This is supported by data showing that post-encoding stress manipulations benefit memory for only emotionally-evocative memoranda (Cahill, Gorski, & Le, 2003). Another possibility is that the impact of slow-acting neurohormonal mechanisms may be greater for items that received prioritized processing during encoding; that is, certain memories may be marked for enhanced consolidation later. The push and pull of these influences are critical elements to consider when developing future research, particularly among studies that aim to tease apart the contributions of encoding and consolidation to emotional memory.

5.2.4 Better Ways of Measuring Reactivation at Retrieval

As mentioned in the discussion of the third study, the re-presentation of stimuli retrieval complicates the interpretation of the encoding-retrieval similarity findings. Certainly the estimates of encoding-retrieval similarity were inflated by the presence of
identical visual information at each phase. Recognition paradigms have proven problematic for previous studies of emotional memory retrieval, in that it is difficult to know whether emotion effects at retrieval are due to the recovery of memory or to the (repeated) perception of the emotional stimulus. This has been addressed previously by embedding neutral items in an emotional context at encoding and then presenting only the neutral memoranda at retrieval, although this tests context rather than item retrieval. In the third study, it was heartening that differences according to memory were observed even when perceptual overlap remained equivalent and that these differences were linked with hippocampal activity. However, interpretation of the current results must remain agnostic with respect to the role of emotion and concomitant amygdala response at retrieval: improvements in encoding-retrieval similarity for emotional items may reflect their superior encoding and consolidation rather than a separate mechanism unto itself.

Likewise, amygdala activity at retrieval may be a passive beneficiary of these improvements rather than an active participant—although recent evidence has pointed to a causal role for noradrenergic amygdala response at retrieval (Kroes, et al., 2010). A critical next step in this line of research is to test memory for emotional and neutral items using a cued-recall approach in which the memoranda themselves are not re-presented at retrieval. This will more cleanly distinguish reactivation-related activity arising from memory from that arising from similarities in online processing.

5.3 Remaining Questions for the Future

5.3.1 Valence and Arousal Manipulations

The studies described above emphasized the influence of emotional arousal on episodic memory formation and retrieval. However, there is additional evidence that the
emotional valence of a stimulus can impact both the quality of the memory trace as well as relative reliance on different neural pathways during memory formation. Although memory effects in the amygdala and MTL memory system seem to be driven primarily by arousal (Hamann, et al., 1999; Kensinger & Corkin, 2004; Phelps, et al., 1998), memory effects in the PFC are influenced by emotional valence (Dolcos, et al., 2004a; Kensinger & Corkin, 2004). For example, left ventrolateral PFC predicts memory for negatively valenced stimuli, even in the absence of arousal, more than neutral stimuli (Kensinger & Corkin, 2004). These results suggest that arousal, when present, engages an amygdala-hippocampal network and that, in the absence of arousal, memory for valenced words relies primarily on controlled processing, supported by a PFC-hippocampal network. There are also findings of differential PFC effects for positive versus negative memory: regions in the medial PFC and left ventrolateral PFC exhibit greater ESA for positive versus negative stimuli, though other regions in left ventrolateral PFC seems to promote memory for both equally (Dolcos, et al., 2004a; Mickley & Kensinger, 2008). It has recently been hypothesized that reliance on controlled processes in the PFC versus perceptual processes in the visual areas during memory encoding varies by valence, with prefrontal networks predicting positive memory and visual processing-related networks predicting negative memory (Mickley Steinmetz & Kensinger, 2009).

The first study was unable to discriminate between valence and arousal effects since only highly-arousing negative stimuli were compared to emotionally neutral stimuli. The second study, however, incorporated both highly-arousing negative and positive stimuli, thus allowing for valence comparisons. Consistent with the proposed valence dissociations described above, individual differences in memory for positive stimuli tended to be
supported by a prefrontal-hippocampal network during encoding whereas negative memories tended to be supported by an amygdala-hippocampal network. This partially supports the idea that valence manipulations may provoke changes among cortically-mediated networks supporting emotional memory encoding. Because individual ratings of arousal were higher for negative than positive stimuli in the second study, it is possible that the role of amygdala-hippocampal networks in promoting negative memory reflects this arousal difference. Future research incorporating multiple levels of arousal within each valence are essential to teasing apart the roles of valence and arousal in supporting encoding versus consolidation effects, respectively. Beyond encoding, there is limited evidence with respect to how emotional valence versus arousal influence memory retrieval processes. The third study hinted at a stronger relationship between encoding-retrieval match in lateral occipital cortex and amygdala activity for negative versus positive stimuli. This may reflect increased reliance on perceptual information during the formation and retrieval of negative information. However, again, because negative valence and arousal were correlated in this study, additional evidence should be gathered to verify this preliminary finding.

5.3.2 MTL Specialization

A consistent finding in the literature is the tendency for emotional memories to be characterized by enhanced vividness (Dolcos, et al., 2005; Ochsner, 2000; Sharot, et al., 2004), implying increased reliance on recollection- versus familiarity-based mechanisms at retrieval. Each of the 3 studies reported above supports this pattern. The study described in Chapter 2 directly tested this question by using receiver operating characteristic curves to estimate the roles of recollection versus familiarity for emotional versus neutral recognition
memory, finding that time-dependent effects of emotion on memory were restricted to estimates of recollection. This suggests that the amygdala-MTL network and its influence on consolidation are particularly sensitive to this aspect of memory. The studies described in Chapters 3 and 4 were based on the same set of behavioral memory data, which demonstrated a clear effect of emotion on memory when only items remembered with high confidence were remembered. The data reported in Chapter 4 also suggest increased vividness for emotional memory retrieval, since these trials were associated with greater encoding-retrieval similarity, consistent with a recollection-like experience. Interestingly, in Chapter 4, emotion effects on encoding-retrieval similarity were identified in areas primarily devoted to visual processing, suggesting a link to the efficacy of perceptual processing. It may be that increased vividness during emotional memory retrieval partially arises from superior encoding and recovery of perceptual details. Compatible with this hypothesis, a recent study demonstrated that amygdala engagement during emotional memory retrieval tracked both subjective vividness as well as visual specificity of the memory (Kensinger, Addis, & Atapattu, 2011).

Emerging from this line of research, a remaining issue is the role of specific MTL subregions in supporting emotional memory enhancements. Although the hippocampus and parahippocampal gyrus, and their connectivity with the amygdala, have been implicated in emotional memory encoding and consolidation, it remains unclear whether they serve fundamentally distinct roles in mediating these memory effects. In neutral memory, these regions have been hypothesized to contribute to separable memory processes: the perirhinal and parahippocampal cortex support representations of items and scenes, respectively, whereas the hippocampus binds this information into a flexible memory trace
(Davachi, 2006; Eichenbaum, et al., 2007; but see Squire, Wixted, & Clark, 2007). One might expect that similar patterns underlie variations in emotional memory enhancements and may be relevant to understanding why emotion tends to result in greater feelings of recollection relative to familiarity (Dolcos, et al., 2005; Ochsner, 2000; Sharot, et al., 2004). Furthermore, the influence of emotion on encoding factors such as visual perception may bias the flow of information along separate pathways through MTL. Elucidating these pathways could aid understanding of why emotion effects on item and relational memory are so complex (Mather & Sutherland, 2011).

However, these ideas have received relatively little attention within the literature. Two studies have specifically set out to delineate between MTL subregions during emotional memory encoding. One identified activity associated with subsequent emotional memory success in both hippocampus and entorhinal cortex, with slightly stronger effects in entorhinal cortex (Dolcos, et al., 2004b). Another failed to find any systematic dissociations in MTL regions supporting relational versus item encoding for emotional words; instead, hippocampus, amygdala, and parahippocampal cortex all supported emotional item encoding, in regions distinct from those supporting neutral memory (Dougal, Phelps, & Davachi, 2007). These latter findings may be due to a restrictive definition of relational memory binding (word-color associations), which might not be affected by emotion despite its influence on other forms of binding (Mather, 2007). In a meta-analysis of emotional versus neutral encoding success effects, clusters were identified throughout the MTL, including both hippocampal and parahippocampal structures and spanning both anterior and posterior MTL (Murty, et al., 2010). However, this meta-analysis
collapsed across a variety of experimental designs and different stimuli and, thus, more subtle differences between MTL subregions may have been washed out.

The first study reported clusters in anterior parahippocampal gyrus, extending from the amygdala, that predicted emotional versus neutral subsequent memory success. Delay-dependent correlations with amygdala activity were also identified in anterior parahippocampal regions, corresponding to the perirhinal and entorhinal cortices. This is consistent with the idea that amygdala-MTL interactions may originate in not just the hippocampus, but also the rhinal cortices. Given the use of negative stimuli and a relatively shallow encoding task in this study, this result is compatible with hypotheses that these factors specifically promote item-based processing in the rhinal cortices; however, this interpretation remains speculative. In the second study, memory effects in MTL were general to both emotional and neutral stimuli and no MTL regions emerged as preferentially predictive of subsequent emotional memory. Finally, in the third study, the hippocampus and parahippocampal gyrus were treated as separate anatomical ROIs, but exhibited roughly the same profile of results; this issue was not interrogated further in these analyses. Altogether, the studies presented here provide only limited evidence with respect to MTL specialization during emotion-modulated episodic memory. In order to clarify this question, future studies should use high-resolution fMRI and better MTL-focused normalization or tracing procedures, in combination with study designs known to reveal complex interactions between emotion and item versus relational memory.

5.3.2 Links between Consolidation and Retrieval

The construct of memory reactivation spans the study of both retrieval and consolidation. At retrieval, reactivation refers to the reinstatement of processes and
pathways from the initial learning episode, which fosters greater memory success at that time. Within the domain of consolidation, reactivation processes may be involved when representations from the initial learning episode are spontaneously replayed, which is thought to promote memory stabilization and later success. These processes may be supported by the same underlying mechanism (Carr, et al., 2011), with the only differences being their timing with respect to memory assessment and, perhaps, the likelihood with which they are accompanied by explicit awareness.

This issue is interesting for a few reasons. First, the commonalities between these processes introduce the possibility that the methods used here to identify reactivation during retrieval can be adapted to study replay during consolidation. This would enable one to directly test the influence of emotion on periods of consolidation as well as facilitate comparisons between consolidation and retrieval phases. Second, if the retrieval-related reactivation and consolidation-related replay really index the same underlying mechanism, then this could add new understanding to how emotion influences retrieval processes. Third, this raises the interesting question of whether emotional responses (either neural, physiological, or both) are reinstated during consolidation-related replay, as we assume they are during retrieval-related reactivation. These ideas would be compatible with new ideas about reconsolidation, wherein memories become labile and subject to new consolidation upon retrieval (Hardt, Einarsson, & Nader, 2010; Sara, 2000; Wang & Morris, 2010). Altogether, consideration of the fidelity between initial learning and subsequent consolidation or retrieval phases could illuminate the ties that bind emotion effects at multiple stages of memory. This question deserves more careful exploration.
5.4 Concluding Thoughts

In conclusion, emotional arousal triggers a cascade of changes that influence nearly every facet of cognitive and mnemonic processing. During memory formation, emotion upregulates semantic processing and attention processes that influence memory encoding, thus capitalizing upon standard pathways for promoting memory success. At the same time, arousal triggers neurohormonal mechanisms that enhance subsequent consolidation of this information into long-term memory stores. Finally, at final test, emotional memories are associated with changes in the retrieval experience and the restoration of neural states from encoding.

The studies reported here provide evidence along all 3 routes toward emotional memory success. First, I showed that the participation of the amygdala and MTL memory system in promoting memory is modulated by the passage of time, consistent with the purported role of this network in enhancing consolidation. Second, I reported evidence that task manipulations during encoding modify the relative involvement of prefrontal and amygdala regions in tracking subsequent memory success, providing further evidence for emotion effects along both of these pathways. Third, I presented novel data linking memory success to the similarity between encoding and retrieval representations. I furthermore showed that emotional items are recapitulated with greater fidelity, indicating their superior memory quality and perhaps provoking enhancements in amygdala activity.

Because of these multiple benefits, delineating the neural origins of emotional memory is a challenging task. Encoding and consolidation mechanisms occur in tangent, making it difficult to disentangle their mutual and distinct contributions to behavioral and neuroimaging data. Furthermore, retrieval effects may reflect enhancements along each of
these lines or additional mechanisms whereby emotion impacts memory. However, as shown here, these issues can be remediated by analyzing each of these stages separately, when possible, and by taking advantage of experimental manipulations that bias one phase versus another. This line of research clearly can be applied toward understanding mnemonic disturbances among psychiatric populations. Elevated to a theoretical level, this work also aspires to inform basic memory research by dissecting the components of episodic memory into fundamental pathways, along which emotion can illuminate the probable causes and consequences of memory promotion.
References


Mickley, K., & Kensinger, E. A. (2008). Emotional Valence Influences the Neural Correlates Associated with Remembering and Knowing *Cognitive, Affective and Behavioral Neuroscience, 8*(2), 143-152.


dorsal and ventral sub-regions of the medial prefrontal cortex and heart-rate reactivity. *NeuroImage, 47*(3), 821-835.


Biography

Maureen Ritchey was born on September 28, 1983 in Columbus, Ohio. She graduated from the University of Notre Dame in May of 2005 with a Bachelor of Science in Mathematics and a Bachelor of Arts in Psychology. Since then, she has been awarded with the James B. Duke Fellowship and the National Research Service Award from the National Institute of Mental Health.

Representative publications:


