FUNCTIONAL NEUROIMAGING INVESTIGATIONS OF HUMAN MEMORY: COMPARISONS OF SUCCESSFUL ENCODING AND RETRIEVAL FOR RELATIONAL AND ITEM INFORMATION

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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
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ABSTRACT

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Abstract

Memory is a complex and multifaceted entity. Cognitive psychology has adopted terminology to help simplify the study of memory. For example, one can consider the cognitive process the brain is engaged in, such as encoding versus retrieval. Similarly, one can consider the content of information, such as words, faces, or scenes. Content and process can also interact such as with instructions to view a face that happens to be situated next to a house (item memory) versus instructions to evaluate whether the face 'belongs' in the house (relational memory). Although neuropsychology, animal lesion studies, and cognitive neuroscience have identified brain structures that are consistently associated with memory performance, such as the medial temporal lobes (MTL) and prefrontal cortex (PFC), the specifics of when and why such regions participate in memory is still largely unexplored. Theoretical standpoints are often at odds about whether regions such as the MTL operate as a functional unit, supporting memory in general, or whether subregions within the MTL support specific types of memory (e.g. item versus relational memory). To investigate how memory processes might recruit unique and common brain regions, three functional magnetic resonance imaging (fMRI) studies were conducted. Each study involved comparisons of successful encoding (trials later remembered versus forgotten) and successful retrieval (hits versus misses). Experiment 1, using semantic and perceptual word pairs, found unique contributions

for subregions in the MTL and PFC, dependent on memory phase and stimulus class. One region in the left hippocampus was associated with memory success, regardless of either memory phase or stimulus class. Experiment 2, using faces and scenes, found unique contributions for 'stimulus sensitive' subregions of the fusiform gyrus and parahippocampal gyrus, as well as for the PFC, and MTL that were dependent on content-process interactions, or independent of content and process. Experiment 3, using faces, scenes, and face-scene pairings, found unique contributions for subregions of the MTL and PFC based on item versus relational processing and memory phase. Together, the results of the three experiments provide support for dichotomies in brain structures based on specific processes, specific content, or process-content interactions.

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Introduction

The most salient aspect of memory may be the ability to store potentially useful information for use at a later time. However, if events that occur are not associated with either an internal or external context, they may be rendered largely meaningless. For example, memory for what kind of car you just rented is not as useful if you do not remember its color, where you parked it, or where you need to drive next. The information becomes more relevant when items are integrated with the context. *Item memory* (IM) comprises the separate components of an event, while *relational memory* (RM) provides for the establishment of associations between the items. In the animal and physiological literature, the term *associative memory* has been used to describe the pairing of an old response and a new item (including classical conditioning effects or stimulus-response mappings). The term relational memory is used in this paper in order to encompass a larger set of phenomena including associations between items and their simultaneous context. Such "binding" of an item with its context may greatly contribute to the utility of retrieving stored information.

There are numerous classes of information that can be considered part of the domain of RM. In their review of source monitoring, Johnson et al. (1993) describe tasks that require spatial, temporal, perceptual, and reality judgments to be made at retrieval for information that was encoded with the relevant contextual information. In these tasks, individual items might be shown in different areas of the screen, different lists,

different colors, or read by different speakers. Memory for these relations (or sources) can be tested and additionally, a simple old/new recognition test (whether the item appeared at all) can be used to assess item memory. Johnson et al. argued that "source monitoring is based on qualities of experience resulting from combinations of perceptual and reflective processes, usually requires relatively differentiated phenomenal experience, and involves attributions varying in deliberateness." In some studies, the task requirements may shift the processes involved in RM retrieval. When subjects have to use perceptual details (size, color, pictorial content, etc.) to make their memory judgments (e.g. Johnson, Kounios, & Nolde, 1997; Ranganath, Johnson, & D'Esposito, 2000) both perceptual and reflective processes are needed. However, there are also more purely semantic RM tasks (e.g. Badgaiyan, Schacter, & Alpert, 2002; Hockley & Consoli, 1999) involving the encoding of word pairs and the assessment of recombined versus identical pairings at retrieval. Such tasks may involve perceptual details, but are more likely to rely on reflective processes. In addition to the previously mentioned classes of information, there is evidence that the specialized processing associated with faces and people may warrant a further class of RM for the information specifically associated with a face or a person. Although not an exhaustive list, the major classes of RM that will be discussed in this paper are perceptual, semantic, spatial, and face/person related.

The type of information tested in RM and IM experiments can also be thought of in terms of two distinct memory processes; recollection and familiarity (for a review, see

Yonelinas, 2002). Recollection is generally defined as retrieval that is accompanied by specific associations or contextual details whereas familiarity is defined as the feeling that one has encountered an item before, without the recovery of any specific details about the item. Over the years, these processes have been investigated using various techniques including metacognitive assessment (the remember-know procedure), task orientation (the process-dissociation procedure), and mathematical modeling (signal detection theory and receiver operating characteristics). Given that RM may be occurring in both recollection and familiarity processes, and may have different neural subregions recruited based on the class of RM tested (see list above), it is more useful to describe the experiments that will be reviewed as testing IM, RM, or both.

In addition to the basic concepts described up to this point, it is worthwhile to keep in mind that distinct brain structures may be contributing to RM processes. The frontal lobes as well as temporal and diencephalic areas are mentioned as key contributors to source monitoring abilities (Johnson et al., 1993) but not necessarily exclusively. Reviewing the brain regions that have been associated with RM and IM in patient, animal, and neuroimaging studies should help clarify the central structures involved and the areas of debate regarding functional specialization. This idea will be further refined in the next section, where the role of the prefrontal cortex (PFC) and medial temporal lobes (MTL) and their respective subregions will be fleshed out based on different theories that have ascribed specific functions to these areas. Other brain

regions are also likely to play a role in RM processes, such as the ventral visual stream (or "what" pathway) for perceptual RM and the dorsal visual stream (or "where" pathway) for spatial RM (Ungerleider, Courtney, & Haxby, 1998). Furthermore, visual and parietal regions have been shown to play a role in both IM and RM retrieval. Although these regions may be important to overall memory networks, the focus of this chapter will be on PFC and MTL regions that presumably have a more specialized and fundamental role in RM.

The size of the PFC and MTL regions of interest for RM make the task of investigating the phenomena more challenging, but subdividing these areas enables highly specific discussion of task contributions. The PFC subregions that will be discussed are dorsolateral, ventrolateral, orbitofrontal (ventromedial), and frontopolar cortices. The MTL subregions that will be discussed are entorhinal, perirhinal, hippocampal, and parahippocampal cortices. The introduction has four main sections that serve distinct purposes; Section I describes memory theories involving the functions of the MTL and its subregions and the PFC and its subregions, Section II describes lesion evidence, Section III reviews neuroimaging studies, and Section IV previews the empirical studies that comprise the later chapters.

I. Theories of MTL and PFC function

This section discusses theories regarding the MTL and PFC and the types of tasks thought to be subserved by these regions. Additionally, some theories describe the

functional and structural subdivisions thought to provide for these cognitive abilities. Components of each theory that are relevant for RM processes will be highlighted in an attempt to integrate these disparate ideas under a common framework. Later sections will review specific data from the animal, human patient, and functional neuroimaging literatures and thus the focus of this section is on the broader theoretical positions.

A. Medial Temporal Lobes

In 1953, a bilateral medial temporal lobectomy was performed on patient H.M. to alleviate epilepsy (Scoville & Milner, 1957). The surgery resulted in a profound amnesia and perhaps the most well-known human patient case in neuroscience and psychology. The unfortunately devastating results on H.M.'s memory for new information confirmed that the MTL serves a critical role in human memory. As a result of this and other cases of human amnesia, research into the structure and function of the MTL increased tremendously.

1. Squire & Zola-Morgan: Declarative Memory Theory

Based on the human amnesia findings and research using monkeys to simulate human amnesia, Squire & Zola-Morgan (1991) posited a role for the MTL in establishing long-term *declarative memory*, or memory for events and facts (also referred to as explicit memory). The hippocampus and the entorhinal, perirhinal, and parahippocampal cortices are presumed to be involved in the formation of long-term memory as a result of their reciprocal connections with the neocortex. The role of the MTL structures is to

bind into a whole memory the disparate representations of neocortical storage sites. In their view, the role of the MTL is a time limited one such that after sufficient time, memory is stored independently in the neocortex. The MTL structures are thus involved in the rapid acquisition of events and facts. On the contrary, nondeclarative memory (also referred to as implicit memory), or memory for motor sequences or skills does not seem to require the MTL at any point in time. Additionally, this model emphasizes the integration of the MTL substructures (rhinal, parahippocampal, and hippocampal), rather than the differences between their functions.

2. Eichenbaum et. al.: Relational Theory

A relational theory was proposed by Eichenbaum, Otto, and Cohen (1994), whereby the hippocampus is critical for comparing and relating items, especially as a flexible representation that can be applied to novel test situations. In this *relational theory*, short-term storage of specific information is mediated by neocortical regions, a more intermediate-term store is facilitated by the parahippocampal gyrus, and the hippocampal formation is only involved in relational processing, essentially acting on the products of prior processing. Evidence from cell recordings in monkeys and rats is discussed that suggests stimulus specific neocortical activity during DMS and DNMS tasks. Aside from such active maintenance, they make mention of a passive maintenance which could correspond to the reduced activity found after repeated exposure to a stimulus (priming). The amount of time that these regions maintain the representation is

on the order of several seconds. Additionally, similar to the conception of Squire and Zola-Morgan, the ultimate storage site for such a representation is the neocortical area that originally handles the maintenance of the representation. After neocortical maintenance, cells in the parahippocampal region (which includes the entorhinal and perirhinal cortices) exhibit passive and stimulus-specific responses.

3. Aggleton and Brown: Connectivity Model, Recollection vs. Familiarity Theory

Aggleton and Brown (1999) proposed a model that stresses the *connectivity* of the hippocampus, especially the interactions with the medial diencephalon (connections to the mamillary bodies and anterior thalamic nuclei via the fornix), as critical to the encoding and recall of episodic memory. These structures permit an episode to be set in its spatial and temporal context and they also connect to the prefrontal cortex, a more strategic processing region. The model proposes a special role for the hippocampal-diencephalic structures in allocentric (with reference to the surrounding areas within a location) spatial tasks. After lesions of these structures, performance is impaired on allocentric tasks but spared in egocentric (with reference to your viewpoint within a location) tasks. Finally, the model differentiates between recollection of an episode as being mediated by the hippocampal-anterior thalamic system and familiarity as being mediated by the perirhinal (cortical) system.

B. Prefrontal Cortex

In 1848, an accident at a railroad construction site sent a tamping bar through Phineas Gage's head, taking out a substantial portion of his frontal lobes. Initially, doctors thought he had completely recovered from the accident, but upon further investigation they found he had experienced profound behavioral changes (Mesulam, 2002). These changes were consistent with the disinhibition, or lack of inhibition of a behavior, which occurs in patients with orbital and medial frontal lobe damage. Examples included the public use of profanity (which he did not engage in prior to the incident), displaying little restraint when something conflicted with his desires, and devising numerous plans for the future which were quickly abandoned in favor of a new, temporarily more feasible one. This accident most likely initiated the formal study of the role of the human prefrontal cortex (PFC) in behavior and memory.

1. Miller & Cohen: Biasing Model/Theory

According to Miller and Cohen (Miller & Cohen, 2001), the PFC *biases* the activity of other brain structures in order to guide or "steer" activity along the neural pathways that ultimately are needed to perform a task, by properly mapping the inputs, internal states, and outputs. Based on the targeted regions, the biasing effects can be rules, goals, or attentional templates. In the *biasing model*, classical frontal lobe tests such as the Stroop task and Wisconsin card sort task (WCST) are framed in terms of the competition between multiple possible response options and top-down guidance to the task

appropriate response. By necessity, the PFC also requires tremendous flexibility in order to be able to switch between the relevant response options based on changing task demands. In novel situations, various options may be tested until the goal is achieved, and here too, the PFC is responsible for establishing an association between the circumstances, behavior and the pattern of activity.

Miller and Cohen also mention the importance of active maintenance and how it allows a behavior and a subsequent reward to be associated even though they may be separated in time (Fuster, 1985). They relate this idea to dopaminergic reward prediction which is thought to result from projections from the ventral tegmental area (VTA). These reward signals may serve to strengthen PFC representations that guide the behavior which results in the reward. Overall, the biasing theory seeks to describe how the PFC supports cognitive control, by guiding activity, maintaining information, setting the goals, establishing the activity patterns associated with reward, and linking those patterns to the likelihood of reward. Thus, the theory encompasses sensory and perceptual processes, attention, memory, decision making, etc and is intentionally integrative in nature. Structurally, the sensory inputs to the PFC are received by lateral and mid-dorsal PFC (VMPFC, DLPFC, and VLPFC) with motor outputs carried out by DLPFC (area 46) and its connections to supplementary motor areas and premotor areas. Orbital and medial PFC have direct connections to limbic structures including the hippocampus and amygdala, but other PFC regions can access the MTL regions by

virtue of their indirect connections. Finally, there are rich interconnections within PFC (especially VLPFC with DLPFC and VMPFC). This of course complicates the precise roles of the subregions, but carefully designed studies will enable progress in teasing these apart.

2. Moscovitch and Winocur: "Working-With-Memory" Theory

Moscovitch (1992) first proposed the *working with-memory (WWM)* model in 1992 and made the distinction between the automatic, obligatory role of the MTL and the intelligent, strategic role of the PFC in memory encoding and retrieval. As the title implies, one goal is to distinguish this model from the notion of working memory. The WWM framework specifies that the domain of MTL structures is in conscious, explicit memory and there is no organizing principle short of temporal contiguity. On the contrary, PFC regions operate on the products of the MTL, initiating and directing searches, monitoring and verifying memories, and placing them in the appropriate spatial-temporal context.

In their most recent description of the WWM model, Moscovitch and Winocur (2002) describe how specific PFC regions are thought to "work with" memory during retrieval. Briefly, the flow of activity is different based on the specificity of the cue, with those that are "strongly related to the information in the MTL code" able to activate MTL directly. An indirect cue elicits DLPFC, which formulates a strategy and guides the search, and then VLPFC, which specifies and describes the retrieval cues needed to

access the MTL. Within the MTL, both indirect and direct cues call on the hippocampus for ecphory to occur. In cases of certainty, the hippocampus sends the information to ventromedial PFC (VMPFC) for rapid (intuitive) rejection based on the goals of the task. In cases of uncertainty, the hippocampus and/or VMPFC send information to the frontal pole for acceptance or endorsement based on context-dependent criteria. The output of these regions is monitored (or evaluated in the case of uncertainty) by DLPFC, the same region that initially formulated the search. Finally, premotor cortex selects the response (although it may also be involved earlier in the process by helping to select from the strategies and cues that will be used to probe memory). During encoding, some of the same regions are implicated for similar types of processes; DLPFC for directing attention and encoding strategy and VLPFC for making a target distinctive and influencing how it is represented in MTL.

3. Petrides vs. Goldman-Rakic Theories on Functional subdivisions of PFC: Processes vs. Content

Petrides (1994a) describes the contribution of subregions of the frontal lobes to different aspects of guided memory search based on working memory research in nonhuman primates. According to his view, the ventrolateral cortex (VLPFC) is thought to be necessary for active or voluntary retrieval of specific information from long-term memory which the mid-dorsal lateral (DLPFC) region can then operate on. The VLPFC initiates a search in a directed manner based on the goals or intentions of the subject.

Thus, Petrides suggests a differential role for VLPFC in explicit, consciously controlled retrieval as opposed to more passive forms of retrieval such as recognition. In this model, ventromedial (VMPFC) frontal regions, based on extensive connections with the basic limbo-thalamic system, are proposed to play an important role in retrieval from long-term memory since severe deficits in visual recognition memory result from lesions of these areas (Bachevalier & Mishkin, 1986). Furthermore, when the task requires additional monitoring or control beyond the span of working memory, MTL regions, as well as DLPFC interaction with those regions, are hypothesized to facilitate this extended processing. Ultimately, the model factors in the specific cognitive process being undertaken and the pattern of connectivity between regions to assign roles to cytoarchitectonically defined PFC subregions.

Goldman-Rakic (1988) stresses the importance of the content of the information that is being processed over the specific process undertaken. Her model posits a similar role for the major substructures of the PFC; however it distinguishes those regions based on the properties of association cortex projections into those substructures. In particular, a "where" versus "what" distinction is proposed for DLPFC and VMPFC such that object location is processed by the former and object identity (or properties such as color) is processed by the latter. Tasks requiring integration of information processed by these "systems" are accomplished with parallel processing of the separate information with either a distributed network facilitating the integration or a region that receives

input from all of the involved systems coordinating the parallel processing. Rather than a PFC locus, Goldman-Rakic proposes a thalamic structure (the medial pulvinar nucleus) that may serve as a central executive, based on projections it receives from virtually all of the association cortices. In summary, the focus of this model is on distributed specialized networks that process specific kinds of information in the same way.

C. Summary and Discussion

The integration of all of these theoretical levels of description with relevant animal, human patient, and brain imaging research will certainly contribute to a more precise understanding of the PFC, the MTL, and their interactions. This section described existing theories that specifically focus on the role of these structures.

Squire & Zola-Morgan's *declarative memory theory* suggests that the MTL is needed to bind disparate neocortical representations to establish memories and has been similarly described by others (Teyler & DiScenna, 1985). Their theory describes a relatively *unitary* MTL memory system, where all the substructures perform the same declarative memory operations. There is evidence that this is too broad of a generalization. MTL substructures are arranged hierarchically, with information from sensory cortices coming to the parahippocampal and perirhinal cortices, moving to the entorhinal cortex, and finally the hippocampus. Rather than an integrative function for the entire MTL memory system, this organization may implicate "lower" structures in

IM and "higher" structures in a more integrative type of processing, or RM. The connectivity of these regions, both within and outside of the MTL may also have a strong influence on the type of processing subserved.

The *relational theory* of Eichenbaum et al. includes a hierarchical organization within the MTL and flexible representations. However, the relational theory proposes that the amount of time information is stored is what increases as the hierarchy is ascended. It is also plausible that a gradient from IM to RM operates as activity moves up the hierarchy, and this gradient may operate without time limitations. Even established memories that are stored neocortically (as suggested by the relational theory and the declarative memory theory) may still recruit hippocampus if they have a high RM demand. Finally, the connections between MTL and PFC subregions are not fully functionally delineated in this theory.

The *connectivity model/recollection familiarity theory* of Aggleton & Brown consists of a hierarchical organization and stresses the importance of MTL connections (via the anterior thalamic axis) with PFC regions. The model specifies that spatial and temporal context can be set for an episode, but does not specify the other types of RM. Furthermore, the connectivity model ascribes the processes of familiarity to the perirhinal cortex (connection to the medial dorsal nucleus of the thalamus) and recollection to the hippocampus (connection to the anterior thalamus-fornix-mamillary bodies). Once again, a gradient along the MTL hierarchy whereby IM is at the bottom

and RM is at the top may be equally as plausible. This kind of gradient does not need to factor in consciousness at encoding or strength of retrieval. It simply refers to the demand on IM and RM and what kind of processing that demand necessitates.

The PFC theories broadly described top-down influences on memory and the potential specializations of specific subregions within the PFC during encoding and retrieval. All of the PFC theories are based on the processes engaged in by these structures except for the Goldman-Rakic model, which describes the content or type of information processed as the critical factor. The process based PFC theories (working memory, biasing, and working with memory) provide candidate regions for specific tasks. These tasks frequently require more RM than IM processing and as such, each theory is relevant to RM in its own way.

The *biasing model/theory* would likely predict that information requiring more relational processing would necessitate more PFC activity. Miller and Cohen might argue that RM tasks require greater guiding of regions that facilitate RM processing and that selection of appropriate responses is generally more difficult for RM than for IM. The biasing model might suggest that the PFC as a whole would be more involved in RM, but it does not offer any ideas about whether specific regions may subserve relational processing.

Moscovitch & Winocur's "*Working With Memory" theory*, with its recent addition of regional information flow based on animal, patient, and functional neuroimaging

data, is a strong leap forward in ideas about the MTL and PFC and how they are recruited during memory. While some aspects of the model are still speculative, it offers guidelines for localization and interactions among the regions that may underlie specific cognitive processes in memory. Although specifying regions involved in context-dependent processing, the WWM model does not specifically address RM processes of binding the item and its context. It suggests that VLPFC and posterior neocortex may be called upon to supply relevant information, such as perceptual detail, but only once a rejection of information has occurred. Overall, the WWM model offers a testable framework for investigating memory and the particular regions and interactions that support it.

With the exception of Moscovitch and Winocur, few theories directly address the interaction between the MTL and PFC. In addition to the insightful WWM theory, Simons & Spiers (2003) proposed a unifying framework that outlines interactions during encoding and retrieval. Briefly, encoding interactions begin with the binding of perceptual information that has ascended the posterior cortical hierarchy, into a memory trace in the MTL. Top-down control of encoding, which can involve semantic or phonological elaborative processing of this MTL trace is facilitated by anterior and posterior VLPFC, respectively. This processing would ensure that each trace is distinct enough to enter long-term storage. A task requiring the organization or manipulation of material would additionally involve the interaction of DLPFC with the MTL trace.

During retrieval, VLPFC both specifies a cue (allowing for strategic search of MTL traces) and maintains the representation of candidate memories in working memory. These candidates are monitored by DLPFC which aids in the disambiguation of competing memories. Retrieval operations that are more complex or require internally generated information may additionally recruit anterior prefrontal (frontopolar) regions.

Simons & Spiers stress that the understanding of PFC-MTL interactions is at an early stage and requires the integration of animal, patient, and functional neuroimaging data, particularly with the use of effective connectivity measurements which can assess the influence of one region over another. The fact that these areas often display reciprocal connectivity complicates the measurement of effective connectivity, which generally requires the assumption of a unidirectional connection. However, these models are just beginning to be used and are likely to increase in complexity to account for anatomical concerns. Finally, Simons & Spiers note that the interactions may vary based on attention and strategy at encoding and the type of test or level of awareness at retrieval.

II. Animal and human lesion studies

The involvement of MTL and PFC structures in memory tasks has been well established in both animals and humans. Animal studies afford researchers the unique ability to perform selective lesions, thereby providing a more direct measure of the contribution of specific brain regions to a given task type. Human patient studies

provide evidence for the role of regions in specific tasks, but generally suffer from poor anatomical specificity. Since later chapters are based on functional neuroimaging data, this section will provide a cursory review of the evidence from human patient and animal lesion studies regarding the contributions of MTL and PFC subregions to memory processes.

A. Medial Temporal Lobes

1. Hippocampus

Although early lesion studies with rats suggested a specialized role for the hippocampus (or hippocampal system) in *spatial* working memory (O'Keefe & Nadel, 1978), more recent lesion studies using rats and monkeys have found deficits on tasks with no spatial context or cueing (Brasted, Bussey, Murray, & Wise, 2003; Fortin, Agster, & Eichenbaum, 2002; Hudon, Dore, & Goulet, 2003).

2. Perirhinal Cortex

Some lesion studies of the perirhinal cortex in monkeys suggest that it may support *visual recognition memory* (IM) (Meunier, Bachevalier, Mishkin, & Murray, 1993; Meunier, Hadfield, Bachevalier, & Murray, 1996). In contrast, other studies have found rhinal cortex to be involved in RM tasks and not merely supporting IM (Messinger, Squire, Zola, & Albright, 2001; Miyashita, Kameyama, Hasegawa, & Fukushima, 1998). These findings suggest that the perirhinal cortex may contribute to the binding of elements (this RM function may not be specific to the hippocampus) and not just simple

item familiarity (IM), calling into question aspects of both the relational theory of Eichenbaum et al. (1994) and Aggleton & Brown's theory (1999).

3. Parahippocampal Region

Results from a study by Malkova & Mishkin (2003) suggest that the parahippocampal region may be critical for allocentric memory. They tested monkeys with hippocampal only and posterior *parahippocampal* only lesions on a spatial memory task with object-place and place trials. The hippocampal group was not impaired on either trial type while the parahippocampal group was impaired on both trial types. Although Aggleton & Brown's theory proposes a special functional role for hippocampal-diencephalic structures in allocentric spatial tasks, this type of spatial memory for places and object-place associations may be critically dependent on the posterior parahippocampal region rather than the hippocampus.

4. Summary and Discussion

Overall, the evidence from these studies suggests that the MTL in general, and hippocampus in particular, are not solely involved in spatial or navigational tasks (although they are likely to contribute to spatial RM tasks). This is strongly in opposition to the cognitive map theory of O'Keefe & Nadel (1978). Moreover, there is evidence that the parahippocampal region may be differentially involved in allocentric spatial tasks.

B. Prefrontal Cortex

The common traits of the reviewed theories regarding the PFC include a) active maintenance of information, b) strategic guidance of encoding and retrieval and c) evaluation of internal/external states in relation to a current behavioral goal. If RM tasks require more of these processes than IM tasks, PFC should be more important to their performance. Furthermore, specific subregions of the PFC may be differentially recruited based on the demands of the task or the nature of the stimuli.

1. Ventrolateral PFC

According to Moscovitch and Winocur's WWM theory, the ventrolateral PFC (VLPFC) may serve to make a target distinctive at encoding, and specify a cue at retrieval. Animal studies support this role for VLPFC in encoding, or learning new information. Two studies suggest that VLPFC is involved in attending to and selecting stimuli (Rushworth, Nixon, Eacott, & Passingham, 1997) as well as cross-modal associative learning involving configurations (Whishaw, Tomie, & Kolb, 1992).

2. Medial PFC

The PFC, broadly, is thought to subserve strategic processing. Researchers have suggested that the medial PFC may specialize, in particular, in the strategic process of directing response selection (e.g. Winocur & Moscovitch, 1999). Selecting responses can also be thought of as a subset of rule learning, which in turn involves effort and often, the evaluation of reward based contingencies. In general, an animal will put in more

work for the possibility of obtaining greater rewards. In rats with medial PFC lesions however, this type of effort-based decision making is impaired, resulting in a disadvantageous criterion shift (e.g. Walton, Bannerman, & Rushworth, 2002). Thus, the medial PFC may be the structure that guides an animal to put in more work for the prospect of greater rewards.

3. Dorsolateral PFC

Studies by Petrides (1991a; , 1991b) examined the impact of lesions to the middle region of DLPFC (areas 9 and 46) compared to a more posterior region (area 8 and rostral area 6). Taken together, the results strongly suggest that mid-DLPFC is involved in monitoring of both *selected* and *sequentially displayed* items. These functions in working memory can also be thought of as temporal-order RM.

As previously discussed, the dorsal and ventral visual streams are more involved in the processing of "where" and "what", respectively. These streams project to DLPFC and VLPFC and, according to some, are involved in maintenance of the information brought in (e.g. Goldman-Rakic, 1988). However, the interconnections between these regions should allow for the *integration* of where and what information. Integration of IM "streams" into richer RM information is likely to be critical for the most common encoding and retrieval operations that support memory (Rao, Rainer, & Miller, 1997). Rainer et al. (1999) further provided evidence that the PFC processes stimuli in relation

to current behavioral demands and posit that this applies even to information brought forth from long-term memory.

4. Summary and Discussion

These studies, collectively, suggest that VLPFC serves in the selection or strategic integration of items, medial PFC helps to set a response bias involved in the selection of competing alternatives, and DLPFC supports the organization of information in time (or space). These data implicate the PFC as a highly flexible system that can accommodate behavioral demands. The PFC is much more than a temporary buffer that information passes through. In fact, the same information may pass through and be represented completely differently based on the current task demands. The idea that the PFC properly maps inputs, internal states, and outputs (Miller & Cohen, 2001), explains these findings perhaps the most thoroughly.

III. Human patient studies

Human patient studies of RM and IM typically involve individuals with damage to the MTL or PFC and tasks that are thought to tap the functions of these regions, including visuospatial navigation, working memory, recency judgments, and semantic processing, to name a few. The primary benefit of such patient studies is that they allow for strong, but not perfect, claims about the involvement of a specific region in a memory process. If a patient cannot perform a given task, the argument can be made that the region which sustained the damage supports (or is *necessary* for) performance of

that task. This section aims to review some of the major studies of patient populations and the ideas about MTL and PFC function that have emerged as a result of these studies.

A. Medial Temporal Lobes

The deficit most frequently attributed to patients with MTL damage is the failure of explicit memory for recently occurring information. On the contrary, preserved function in implicit or nondeclarative tasks has led to the conclusion that these types of memory tasks do not require the contribution of the MTL. This dichotomy has provided the foundation for the idea of multiple memory systems, with the MTL system, including all of the substructures, thought to be required specifically for conscious, declarative memory (Squire & Zola-Morgan, 1991). However, other theories (e.g. Eichenbaum et al., 1994 and Aggleton & Brown, 1998) attribute specialized functions to the substructures of the MTL system within the rubric of declarative memory, for factors such as familiarity versus recollection and the amount of time information is stored. Thus, MTL deficits should also be discussed in terms of both the strength and duration of memories.

1. RM and IM in amnesics

As described in the models of Aggleton & Brown (1999) and Eichenbaum et al. (1994), the substructures of the MTL, particularly the perirhinal cortex, entorhinal cortex, and parahippocampal gyrus may be engaged by the different demands of cognitive

tasks. Some studies involving MTL patients reveal intact IM (recognition memory, thought to be facilitated by perirhinal cortex), but impaired RM as shown by free recall or recollection based memory (Mayes, Holdstock, Isaac, Hunkin, & Roberts, 2002; Mayes et al., 2001; Vargha-Khadem et al., 1997). However, other studies have found impaired performance in IM (Manns & Squire, 1999; Reed & Squire, 1997; Stark, Bayley, & Squire, 2002; Stark & Squire, 2003) with the latter two further showing no difference between RM and IM performance.

The *declarative memory theory* assumes that IM (familiarity based recognition) is part of a more general class of declarative memory tasks, all of which depend on RM (forming associations). Thus, it would predict impaired performance on any declarative memory task for patients with MTL damage. Conversely, Vargha-Khadem et al. (1997) describe three childhood onset amnesic patients who, despite their bilateral hippocampal damage, display impaired RM (context-dependent episodic memory) but spared IM (context free recognition memory). Manns & Squire (1999) suggest that the intact recognition reported by Vargha-Khadem et al. is a result of reorganization of cortex surrounding the hippocampus in childhood onset patients, while the impaired recognition reported in their own study is due to the adult-onset of amnesia.

Yet, Mayes et al. (2002) found relatively spared item recognition and clear deficits in free recall in an adult-onset patient with bilateral hippocampal damage. Additionally, Mayes et al. (2001) found that this same patient was impaired on

associative recognition tasks that require retrieving the associations between different kinds of information (e.g. temporal order and semantic). This finding led to the conclusion that the hippocampus specifically mediates RM for different kinds of information, which are likely represented in different neocortical regions, while lower portions of the MTL hierarchy support RM for similar or "intra-item" associations which are likely to be represented in only one neocortical area.

2. Visuospatial/Navigational deficits

Studies have tested human patients with MTL damage using tasks that were designed to be human variants of the Morris water maze. Bohbot et al. (1998) measured the ability of hippocampal, parahippocampal, and control patients to find a hidden target in a room with no delay and 30 minute delay conditions. The only significant difference that was found was for the right parahippocampal group on the delayed test. The authors interpret this result as suggesting that this region, as opposed to the hippocampus, plays an important role in spatial memory. Another test involving the recall of locations of objects (in the same room) yielded impaired performance in both the right parahippocampal and hippocampal groups, compared to the epileptic controls.

Other tests of human patient memory for spatial and contextual, as well as episodic elements have been conducted using virtual reality towns (Spiers, Burgess, Hartley, Vargha-Khadem, & O'Keefe, 2001; Spiers et al., 2001). The childhood-onset patient Jon, who has bilateral hippocampal damage was impaired on recall tasks that

were context-dependent (who gave you this item, when, where, navigation and map drawing etc.) but not on simple item or scene recognition. Thus, according to the authors, the hippocampus is implicated in navigation, recall of allocentric spatial information and context-dependent episodic memory, but not visual pattern matching. Results from temporal lobectomy patients who were tested in the same environment revealed an interaction between hemisphere and test type, such that right temporal lobectomy patients were more impaired on navigation, map drawing and scene recognition, whereas left temporal lobectomy patients were more impaired on context-dependent episodic memory measures, relative to controls. Right temporal lobectomy patients were also more impaired on object recognition than left temporal lobectomy patients. The anterior nature of the removal distinctly allows for the possibility that the perirhinal and entorhinal cortices, which may have a role in recognition processes (such as visual pattern matching) were removed and therefore resulted in the performance decrement.

The findings regarding navigational tasks in patients converge somewhat, although the debate about whether the parahippocampal cortex or the hippocampus mediates spatial memory has yet to be resolved. Based on the animal literature (e.g. Malkova & Mishkin, 2003) and the water maze variant tested by Bohbot et al. (1998), there is potentially a distinct role for the parahippocampal cortex in object-place learning. In human patients, Takahashi & Kawamura (2002) used MRI scans of patients

with landmark agnosia (topographical disorientation) and found the right posterior parahippocampal cortex to be critical in the acquisition of novel information about buildings and landscapes. Taken together, the patient literature suggests that the presence of an object or episodic details within allocentric visuospatial tasks implicate the hippocampus, while the more purely spatial aspects may specifically recruit parahippocampal regions.

4. Summary and Discussion

The evidence from patient studies is not equivocal for the role of the hippocampus in RM. There are two patterns of results regarding the deficits suffered by MTL patients. One set of results support the *declarative memory theory* in finding similar deficits in RM and IM (e.g. Manns & Squire, 1999; Reed & Squire, 1997; Stark et al., 2002; Stark & Squire, 2003), while another set of results supports the *relational memory theory* in finding spared IM and impaired RM (e.g. Mayes et al., 2002; Vargha-Khadem et al., 1997), especially if the associations are for different kinds of information (Mayes et al., 2001). The specific tests that are used to measure RM and IM may explain the different patterns of results.

The MTL has also been implicated in visuospatial navigation and object-location memory based on deficits in patients with hippocampal and parahippocampal lesions. There is disagreement as to whether the hippocampus (Holdstock et al., 2000; Spiers et al., 2001; Spiers, Burgess, Maguire et al., 2001) or the parahippocampal region (Bohbot et

al., 2002; Bohbot et al., 1998) is the critical structure needed for these abilities. It is possible that the context-dependent nature of the task dictates the region and/or hemisphere recruited. More purely spatial aspects of a task may implicate the parahippocampal region whereas the inclusion of a visual object or allocentric manipulation may additionally recruit the hippocampus.

B. Prefrontal Cortex

The animal literature suggests that the PFC is a flexible, adaptive region that is capable of guiding behavior based on current task demands. While this may be an overarching feature of all PFC regions, it seems to also be the case that separate regions mediate different aspects of behavioral guidance. Perhaps due to the difficulty in finding large numbers of human frontal patients with varied lesion sites within PFC, the human patient literature, until very recently, has focused more on coarser distinctions such as left versus right frontal lesions. A common finding in the neuropsychological literature from comparisons of patients with unilateral frontal lesions is a role for the left PFC in verbal tasks and a role for the right PFC in pictorial or other nonverbal tasks (e.g. Milner, 1971).

Such hemispheric material specific roles have been found using a host of tasks, including recency judgments, frequency judgments, cued recall, and free recall. While a comprehensive review of material specific hemispheric differences is beyond the scope of this paper, neuropsychological and neuroimaging evidence from both the MTL and

PFC tend to indicate such a specialization (but see Dobbins, Kroll, Tulving, Knight, & Gazzaniga, 1998 for a material combined with task demands interpretation).

1. Semantic RM

Top-down organizational processing is a common requirement of many RM tasks. The PFC may serve an essential role in the formulation of strategies that enable successful RM processing. Tasks that place high demands on this kind of strategic, organizational processing are likely to differentially impair patients with PFC damage. For example, frontal lobe lesion patients were disproportionately impaired compared to controls on paired-associate learning tests designed to increase the amount of interference present (Shimamura, Jurica, Mangels, Gershberg, & Knight, 1995). In the first of two tests, cue words are repeated but are associated with different response words from the study list (e.g., LION-HUNTER, LION-CIRCUS). In the second test, words used in one list are recombined to form new pairs. The interference effects suggest that the on-line control of irrelevant or competing memory associations is disrupted in frontal lobe patients. The results are also framed in terms of Shimamura's *gating* hypothesis, which proposes that a general deficit in other cognitive tasks should result from the disruption of this kind of inhibitory process.

Dimitrov et al. (1999) found left frontal lobe patients to be severely impaired on cued and free recall of verbal paired associates. This was especially the case for free recall of pairs, perhaps due to more effortful demands. Similarly, patients with lateral

prefrontal lesions tested by Baldo & Shimamura (1998) generated fewer items than control patients on both letter and category fluency. There was no interaction with type of fluency test, which implied that the frontal lobes are more generally involved in verbal fluency. The authors state that along with previous results of impaired free recall and remote retrieval, these results suggest that patients with frontal lobe lesions do not efficiently *organize* and *develop* retrieval strategies.

In a comprehensive study, Alexander et al. (2003) tested patients with distinct PFC lesions (right and left anterior DLPFC, anterior MPFC, posterior MPFC, and right and left posterior DLPFC) using the California Verbal Learning Test. Although all groups displayed inefficient learning, the left posterior DLPFC group maintained this deficit across trials and this was most evident with free recall.

2. Summary and Discussion

The debate is ongoing as to whether the frontal lobes have a unitary underlying function, regardless of regional differences or specializations (e.g. orbitofrontal or medial PFC may be *guiding* or *steering*, but for emotional or goal/reward related processing). However, it is evident that the particular way PFC functions are tested in patient studies (free recall, cued recall, recognition, etc.) and the precise location of damage (DLPFC, VLPFC, MPFC, etc.) are all likely to influence the resulting pattern of deficits or sparing.

Overall, the neuropsychological evidence supports the idea of a network within the brain whose purpose is to both rapidly and flexibly encode, retrieve, and work with information from the external world, allowing us to fit events into spatiotemporal contexts which can be assessed with regards to our current goals or states. Working with such information enables us to predict causal relationships, reduce uncertainty, and ultimately navigate our way through the complexities of the everyday world.

IV. Neuroimaging studies

The advent of functional neuroimaging brought about the ability to investigate the neural correlates of human memory. The primary benefit of neuroimaging is that complex cognitive tasks with specific instructions can be administered to awake, alert human subjects. In addition to the collection of behavioral data (e.g. reaction times, accuracy, confidence), neuroimaging provides the capability to directly measure brain activity while tasks are performed. While it is not possible to say that brain regions displaying activity during a given task are *required* for that task, it is possible to say that those regions are *related* to the task.

Applying the principles of cognitive subtraction to the brain activity recorded allows for the comparison of different tasks. In blocked-design studies for example, encoding and retrieval can be separated and directly compared. This provides an advantage over lesion studies, where it may be difficult to tease apart the cause of a memory deficit as encoding-related or retrieval-related. Different manipulations at

encoding or retrieval can also be directly compared, providing a powerful tool for assessing regional involvement in various tasks. Finally, event-related designs allow for comparisons of specific event types both within and across tasks. Such fine-grained comparisons yield more precise information, allowing us to tease apart activity associated with distinct cognitive processes or directly link activity to performance.

An example of such a comparison is the investigation of subsequent memory, or the *dm effect*, where encoding trials are sorted based on the behavioral responses obtained from a later recall or recognition test. Differences in brain activity for remembered versus forgotten trials are presumably due to, or a result of, successful encoding. Several functional neuroimaging studies have used the subsequent memory paradigm, with different stimuli, designs, and goals (for a review, see Paller & Wagner, 2002). Brewer et al. (1998), Wagner et al. (1998), and Kirchhoff et al. (2000) all used incidental encoding of individually presented words and/or pictures which were later tested in a surprise recognition memory test outside of the scanner. Those studies all reported more activity in the parahippocampal gyrus and inferior prefrontal cortices for subsequently remembered versus subsequently forgotten stimuli. The authors all conclude that greater activity in these regions during encoding actually predicts successful memory.

A. Medial Temporal Lobes

1. Spatial RM

The vast majority of neuroimaging memory studies involve the visual presentation and hence, visual perception, of words or pictures. As such, it is important to make reference to the dissociation between the ventral "what" pathway and the dorsal "where" pathway of the visual system (Aguirre & D'Esposito, 1997; Kohler, Kapur, Moscovitch, Winocur, & Houle, 1995; Owen, Milner, Petrides, & Evans, 1996). Evidence for this dissociation is found in brain imaging studies as well as the animal and human patient literature. The integration of information from the dorsal and ventral visual streams presumably allows humans (and other animals) to remember where objects (or landmarks) are in the environment, where they placed objects in the past, and ultimately to successfully navigate through the world (Janzen & van Turennout, 2004).

Several studies have used complex real or virtual reality environments to examine spatial memory and navigational abilities (Aguirre, Detre, Alsop, & D'Esposito, 1996; Burgess, Maguire, Spiers, & O'Keefe, 2001; Maguire, 1997; Maguire et al., 1998). These studies all report MTL activity during either the encoding or the retrieval of spatial information within the environment. Aguirre et al. (1996) found the parahippocampus to be recruited more during learning of the virtual maze than retrieval. This region shows considerable overlaps with the lesion sites in patients displaying topographical disorientation (e.g. Takahashi & Kawamura, 2002). Burgess et al. (2001) found right hippocampal activity that they attributed to spatial navigation and left hippocampal activity that they attributed to context-dependent episodic memory.

Parahippocampal activity in the spatial task is explained as being part of the network where allocentric representations generated by the hippocampus are produced for viewing and manipulation by the precuneus. Maguire et al. (1998) found a strong association between right hippocampal activity and accurate knowledge of, and navigation to, locations in a virtual town. Left hippocampal activity was interpreted as episodic memory for specific paths that were learned or possibly maintenance of the appropriate destination. Taken together, these results suggest that the hippocampus potentially mediates the encoding and retrieval of specific locations, while parahippocampal regions support the encoding of landmark views.

2. Semantic RM tasks

Semantic RM tasks often demand that associations be made between multiple related or unrelated words. PET studies by Dolan and Fletcher (1997) and Lepage et al. (2000) reported hippocampal activity supporting the encoding of novel semantic associations. Dolan and Fletcher manipulated the novelty of category-exemplar pairs, varying one or both during the critical scans. Left hippocampal and parahippocampal activity was found in new category-new exemplar pairs compared to old category-old exemplar pairs. Interestingly, the establishment of meaningful connections between category and exemplar did not differentially recruit the MTL. Rather, an old category or exemplar paired with a new partner led to increased activity in left dorsolateral prefrontal cortex (DLPFC). Thus, they suggest that the connection between items seems

to be frontally mediated while the overall integration of those items into the context is subserved by the MTL.

Lepage et al. (2000) similarly had subjects encode category-exemplar stimuli, but they used word triads with zero, one, or two related links. Compared to a cued-recall condition (in which subjects are shown the category name and must overtly produce the two words that were shown with it), the associative encoding resulted in bilateral hippocampal activity. The right parahippocampal gyrus showed a positive linear trend (an increase in activity from zero to two links) across the encoding conditions. The main finding, however, was that the hippocampus is implicated in semantic RM encoding processes.

Henke et al. (1999) also found that semantic RM required the hippocampal formation more than IM encoding or novelty detection. Subjects either decided whether the two abstract nouns comprising a word pair fit together or they judged the words individually. This PET experiment also contrasted deep (pleasantness) versus shallow (number of vowels) processing for single item encoding, with no hippocampal activity found. Previous studies involving verbal stimuli had generally failed to elicit hippocampal activity and Henke et al. attributed this to the lack of challenge of its critical function, RM processing. In an fMRI study of word-pair encoding, Jackson & Schacter (2004) found left anterior hippocampus to be predictive of later memory success, as determined by an associative recognition test.

Davachi & Wagner (2002) and Davachi et al. (2003) conducted fMRI studies to specifically investigate the role of MTL structures in encoding and subsequent memory of relational (RM) compared to item-based (IM) information. In the earlier study, the hippocampus was found to be more active during relational processing (subjects incidentally encoded word triplets by ordering the words in terms of "desirablility") compared to item-based processing (incidental encoding by rote repetition) which yielded greater activity in entorhinal and parahippocampal regions. Additionally, the hippocampal activity displayed a *dm effect* whereby more items from the triplet were remembered when more activity occurred during encoding. The later study found a similar *dm effect* for RM in bilateral hippocampus and an additional left parahippocampal region, which supported later memory for the source of a single word (whether instructed to perform auditory imagery or simply read the adjective). In contrast, activity in the left perirhinal cortex differentiated IM (remembered versus forgotten trials), but not RM.

Giovanello et al. (2004) reported a critical role for the anterior hippocampus in RM versus IM retrieval, and attribute this to a potential reactivation of relational encoding. However, this experiment used a blocked design to compare IM and RM and subjects performed significantly better with significantly faster reaction times on the RM task. Although this experiment provides direct comparisons between IM and RM retrieval, given that memory success was not controlled for, the data may also reflect

broader performance differences. However, the finding suggests that the hippocampus may support RM retrieval and that further study is warranted.

Taken together, the results of these studies suggest a greater role for the hippocampus in successful RM compared to IM encoding (and possibly retrieval) and a greater role for rhinal cortices in IM processes. This fits very well with the hierarchical MTL arrangement and the processing differences that are predicted for lower and higher structures within the hierarchy. There may be critical effects of the type of words used (abstract vs. concrete, noun vs. adjective), the intention to remember during encoding, and the specific task supporting relational processing. Nonetheless, all the studies found that MTL activity, and more specifically hippocampal activity, was greater during RM encoding processes. fMRI studies that compare successful relational encoding *and* successful retrieval of semantic material will further clarify the contributions of the MTL substructures to RM processes in general.

3. Face/Person RM tasks

Although faces have some kind of meaning, they are generally not considered to be processed in a semantic manner and might instead be considered as classified somewhere between purely semantic and purely perceptual information. Henke et al. (1997) used PET to directly compare activity for encoding of single items, encoding interitem associations, detecting novelty, and retrieving associations previously formed. Participants encoded either the association between a face and a house (visitor or

inhabitant), or the items individually (e.g., male face, exterior of house). RM encoding differentially recruited the right hippocampus and parahippocampal gyrus. This suggested that the hippocampal formation had a role in establishing these face-house associations in memory.

Sperling et al. (2001) conducted an fMRI study of RM for face-name pairs and found activity localized in the right anterior hippocampus for the novel versus repeated pairs contrast. MTL activity was not found for the novel vs. fixation contrast, which may be a result of rehearsal during the fixation block. It could also reflect the adoption of too strict of a threshold given that MTL activity might be predicted for such a task. A similar study by Small et al. (2001) focused specifically on the hippocampus and found a unique pattern of activity for names and faces that were encoded together compared to names or faces encoded individually. This same circuit was reactivated during a cued retrieval task requiring the subject to produce the name when shown the face. Thus, memory involving face-house and face-name associations appears to rely on the hippocampus and possibly the parahippocampal region, to a greater extent than memory involving a single face, name, or house.

Preston et al. (2004) found regions within the MTL at retrieval that were differentially associated with RM for flexibly linking faces (that were related to the same house during study phase) and for basic memory of previously studied pairings. Within the hippocampus, there were examples of specialization for RM as well as general

memory success for all trial types tested. Within parahippocampal cortex, patterns were observed that were attributed to IM processing or general retrieval success.

4. Perceptual RM tasks

Using complex scenes, Montaldi et al. (1998) conducted a SPECT study in which they compared an associative encoding condition to a perceptual matching condition, with novelty held constant. Subjects were given the encoding strategy of relating the features in each scene (both positionally and functionally). The encoding condition yielded significant activations in the left hippocampus/parahippocampus whereas the perceptual matching condition yielded no MTL activations. Additionally, a regions-of-interest (ROI) analysis confirmed the left MTL encoding related activity and displayed a trend towards activation in the right MTL. Montaldi et al. concluded that associative encoding is sufficient to produce MTL activity. Pihlajamaki et al. (2003) found encoding, but not retrieval, of novel picture pairs to activate perirhinal cortex. Hippocampus and parahippocampal gyrus were elicited as well, more reliably and more anteriorly during encoding than retrieval.

5. Summary and Discussion

The MTL is implicated in tasks of spatial, semantic, face/person, and perceptual RM tasks with nearly all of the evidence involving studies of encoding. In the spatial domain, neuroimaging results suggest that the hippocampus potentially mediates the encoding and retrieval of specific locations, while parahippocampal regions support the

encoding of landmark views. In the semantic domain, the data point to a greater role for the hippocampus in RM than IM. In the face/person domain, encoding face-house and face-name associations appears to rely on the hippocampus and possibly the parahippocampal region, to a greater extent than encoding of a single face, name, or house. Finally, in the perceptual domain, hippocampal, parahippocampal, and perirhinal activity was found to be involved in the formation of various perceptual relations, such as for the details within a visual scene, picture pairings, or flexibly created face pairings.

In contrast with evidence for RM tasks recruiting the hippocampus to a greater degree than IM tasks, there is also the suggestion that both types of tasks rely on the hippocampus to the same degree. Stark and Squire (2001) compared recollective success (hits versus correct rejections) in different tasks. Subjects encoded pictures of nameable objects or words (the name of the object) and at test performed a standard old/new recognition with *either* words *or* objects resulting in a presentation modality change for one test condition (thus, the three study-test conditions were object-object, word-word, and object-word). Stark & Squire deem the critical comparison to be hits in the RM task (object-word) versus hits in the item task (object-object). Although the object-word task is described as associative, due to the modality change at retrieval, it is unclear how valid this is as an RM task. Relations for items in close temporal proximity, amongst *multiple* items at encoding, or within a scene, seem to be more representative of the type

of RM task tested in the animal and patient data and other neuroimaging tasks. In their memory tests, similar levels of hippocampal activity were found, leading Stark & Squire to conclude that RM does not increase hippocampal activity and to further suggest that all declarative memory tasks equivalently require RM (e.g. learning the relation between items and context for a subsequent recognition test). Thus, activity in the hippocampal region should benefit all declarative tasks. The majority of neuroimaging studies of RM, however, have suggested that the MTL is differentially involved.

B. Prefrontal Cortex

Clearly, memory processes are not solely mediated by the MTL (see Simons & Spiers, 2003). A review by Fernandez & Tendolkar (2001) attempted to integrate MTL functions with the connections to, and roles of, the PFC. They posit different functions for inferior PFC (comparing with internal information) and middle PFC (integrating into a coherent episode across time and modality) based on connections to and from the MTL. The types of tasks yielding PFC activity may help to provide insight into the role of these regions above and beyond the MTL and also in cooperation with the MTL. A study by Opitz and Friederici (2003) assessed the interaction of the hippocampus and PFC in the learning of an artificial grammar. Briefly, they found that as learning of the grammar progressed across blocks of their fMRI study, left posterior hippocampal activity decreased from an initially high level, while left inferior PFC (LIPC) activity increased from an initially low level. The authors attribute the shift in regions as

reflecting a transition from similarity-based learning in the MTL to language-related processing in the left PFC. The increased role of LIPC in language fits two assumptions about the PFC; 1) that PFC subserves semantic processing, and 2) that semantic processing is left lateralized. Of interest is whether this left PFC lateralization is generalized across encoding and retrieval and relational demands. Additionally, it is important to determine whether left PFC activity actually predicts later memory performance for semantic tasks, or is merely involved in the on-line processing of semantic information.

1. Semantic RM tasks

Numerous studies provide evidence that left PFC is involved in RM encoding and further, that a ventral subregion of the LIPC also appears to predict subsequent memory. Dolan & Fletcher (1997) posited a role for the left PFC in establishing meaningful connections between items. Lepage et al. (2000 found more activity in left DLPFC for associative encoding than cued recall. Achim & Lepage (2005) found left inferior PFC in their direct comparison of rearranged versus intact pairings (associative novelty). Left PFC has been associated with RM encoding and retrieval of word pairs (Fletcher, Shallice, & Dolan, 2000; Henson et al., 2002, Jackson & Schacter, 2004). Fletcher et al. (2000) found left PFC to be differentially involved when the relationship between the encoded words was more distant, compared to closely related words, while Henson et al. (2002) found reduced activity in left inferior PFC to RM retrieval with lower levels

of interference. Thus, the available evidence points to a specialized role for the left PFC in word-pair encoding that may be expanded based on high imagery content or more distant relations between words, and a bilateral PFC network for word-pair retrieval that can be strengthened in the left PFC based on low imagery content or high interference.

2. Face/Person RM tasks

In addition to MTL activity, the previously described study by Sperling et al. (2001) also exhibited highly significant activations in bilateral PFC when encoding of novel face/name pairs was contrasted with encoding of repeated pairs. In this contrast, activity was found to a greater extent in left VLPFC and DLPFC while equivalent activity was found in both hemispheres in orbitofrontal and medial PFC. Based on the findings of Kelley et al. (1998), providing a name with each novel face may be akin to encoding "nameable objects." Sperling et al. (2001) suggest that the larger extent of left PFC within the overall bilateral pattern may reflect a more extensive role in encoding associations between verbal and non-verbal stimuli. The task employed by Henke et al. (1997) required associations of faces and houses. However, no PFC activity was found during this relational encoding compared to single item encoding.

4. Perceptual RM tasks

In addition to faces, names, and houses, tests have been conducted using landscapes and indoor/outdoor scenes (e.g. Brewer & Gabrieli, 1997; Kirchhoff et al.,

2000; Rombouts et al., 1999). Due to multiple elements within scenes and landscapes, these perceptual tasks have high RM demands. The two studies involving the subsequent memory effect for scenes (Brewer et al. and Kirchhoff et al.) reported right inferior PFC (RIPC) as predicting successful recognition. Additionally, Kirchhoff et al. described a trend for a stimulus type by novelty interaction in posterior LIPC and RIPC for novel words and novel pictures, respectively. Interestingly, Rombouts et al. (1999) report an increase in RIPC with a parametric modulation of picture encoding, suggesting a role for RIPC in both successful encoding of scenes and the encoding of novel scenes when the load is high.

Finally, imaging studies of RM retrieval (or source information) have found regions that are differentially sensitive to these demands. For example, Nolde et al. (1998) found left PFC activity to be sensitive to the amount of episodic detail required at retrieval. Ranganath et al. (2000) investigated the encoding and retrieval of visually presented nameable single objects (IM). Perceptually based encoding of the objects (which were all presented at the same size) resulted in a wide network of bilateral PFC activity. The retrieval test portion varied the size of the objects, and subjects were required to make either an old/new judgment (IM) or a more specific recognition and size (RM) discrimination (old/larger, old/smaller, or new). The comparison of RM versus IM resulted in activity in left anterior middle frontal gyrus (BA 10/46) that was evident

for new pictures as well as old pictures. This suggests that the attempt to remember specific (or source) information recruits this anterior left PFC region.

5. Summary and Discussion

In summary, PFC regions have been found to be differentially involved in semantic, temporal, face/person and perceptual RM. Semantic RM encoding has been found to involve predominantly left PFC regions, while retrieval tends to involve bilateral PFC. Modulating factors for the level of activity include the imagery, relatedness, and interference of word pairs. Perceptual and face/person RM encoding and retrieval may activate a right lateralized PFC network if the tasks involve information that is not nameable. Encoding nameable objects or faces with names tends to recruit a bilateral PFC network. Encoding of scenes or complex pictures probably recruits the same bilateral network, however activity in the right PFC may influence whether it is later remembered. Finally, RM retrieval tasks may recruit a distinct left PFC region compared to IM retrieval, which may have to do with the specificity of the information sought, rather than the particular task or type of information sought.

Outline of Thesis

Although much is known about the brain regions that support memory, there are important details, heretofore unexplored, regarding the influence of content and process on memory. In specific, what role (if any) do regions that predict later memory play during the actual successful retrieval of those memories? What regions differentially

support memory for particular stimuli and what regions support memory regardless of the information content? What are the neural similarities and differences in successful encoding and successful retrieval? What are the neural similarities and differences in IM and RM encoding and retrieval?

This thesis describes three experiments that were designed to address these questions. The majority of functional neuroimaging experiments of memory focus on a particular memory phase and investigate processes such as orientation, strategy, or level (quality) of memory, within that phase. However, a fuller understanding of memory might arise from comparisons of both phases of memory. In particular, experiments that vary content and processes and the way that these interact, (e.g. item and relational memory), while holding memory success constant, have the potential to yield important insights into the neural substrates of memory.

Experiment 1 examines RM encoding and retrieval for semantic and perceptual stimuli. The results are published as a manuscript in the *Journal of Neuroscience* (Prince et al., 2005). Experiment 2 examines the influence of particular content (faces and scenes) on memory at encoding and retrieval, as well as general memory, regardless of the content of memory phase. Experiment 3 examines item versus relational memory at encoding and retrieval as well as general encoding and retrieval, regardless of the memoranda. Taken together, these experiments addressed questions of

process, content, interactions of process and content and the general nature of memory success.

2. Semantic and Perceptual relational memory success

Introduction

When we remember a past event, we typically remember not only the components of the event but also the relationships among these components. For example, when recalling a rumor heard at a party, we may recall not only the statement, but also the topic of the conversation (semantic associations), the voice of the speaker (perceptual associations), etc. (for a review, see Johnson, Hashtroudi, & Lindsay, 1993). Memory for these associations, or *relational memory* (RM), has been strongly linked to the medial temporal lobes (MTL, for a review, see Eichenbaum, Otto, & Cohen, 1994) and the prefrontal cortex (PFC, for a review, see Morris Moscovitch, 1994). In the present study, we used event-related functional MRI (fMRI) to investigate three fundamental questions regarding the neural correlates of RM.

First, *do RM encoding and RM retrieval activations differ within MTL and within PFC?* This is a controversial issue in the functional neuroimaging literature. Within MTL, one view postulates that anterior regions are more involved in encoding and posterior regions, in retrieval (Lepage, Habib, & Tulving, 1998), whereas another view proposes that anterior regions are more involved in relational memory and posterior regions, in nonrelational memory (Schacter & Wagner, 1999). Within PFC, one view postulates a hemispheric asymmetry between encoding and retrieval (Nyberg, Cabeza, & Tulving,

1996; Tulving et al., , 1994), but recent event-related fMRI studies have found left PFC activations both during RM encoding (e.g., Davachi, Mitchell, & Wagner, 2003; Davachi & Wagner, 2002) and RM retrieval (e.g., Giovanello, Schnyer, & Verfaellie, 2004; Ranganath, Johnson, & D'Esposito, 2000). It is unclear, however, whether successful encoding and retrieval activations actually differ within left PFC.

Second, *does RM involve the reactivation during retrieval of process-specific encoding regions?* This idea is predicted by the transfer-appropriate processing principle (Morris, Bransford, & Franks, 1977), which postulates that memory performance is a function of the overlap between encoding and retrieval operations and by the source monitoring framework (Johnson, Hashtroudi, & Lindsay, 1993), which proposes that cognitive operations recruited during retrieval vary depending on the nature of the target information. Although a few functional neuroimaging studies have found support for this concept, they have usually focused on sensory or motor processes (L. Nyberg, R. Habib, A. McIntosh, & E. Tulving, 2000; Nyberg et al., 2001; Wheeler, Petersen , & Buckner, 2000) and have not directly compared successful encoding and retrieval activity (Kahn, Davachi, & Wagner, 2004; Vaidya, Zhao, Desmond, & Gabrieli, 2002).

Finally, *is there a brain region critical to successful RM, regardless of memory phase (encoding vs. retrieval) and stimulus content (e.g., semantic vs. perceptual)?* The obvious candidate is the hippocampus, which is assumed to mediate the storage and recovery of memory traces (Squire, 1992; Teyler & DiScenna, 1985) and RM processes in general

(Eichenbaum, Otto, & Cohen, 1992). Although functional neuroimaging studies of RM have reported hippocampal activations in a variety of conditions, it is unclear if a common hippocampal region was activated across these different conditions.

To answer these three questions, we conducted an fMRI study crossing phase (encoding and retrieval) and content (semantic and perceptual), using successful memory activity (remembered vs. forgotten) as our critical measure. We defined *encoding success activity* (ESA) as study-phase activity for subsequently remembered vs. forgotten items, and *retrieval success activity* (RSA) as test-phase activity for hits vs. misses. To investigate encoding-retrieval differences, we compared ESA and RSA. To investigate transfer appropriate processing, we distinguished ESA-RSA overlaps for semantic vs. perceptual RM. Finally, to identify general successful RM regions, we isolated areas involved in both encoding and retrieval and in both perceptual and semantic RM.

Methods

The behavioral paradigm is illustrated in Figure 1. Participants were scanned while encoding and then retrieving associations between words (semantic condition) or between words and fonts (perceptual condition). The retrieval task was an associative recognition test that included identical and recombined pairs. In the semantic condition, recombined pairs consisted of words encoded in separate pairs, whereas in the perceptual condition, recombined pairs consisted of studied pairs written in a font

previously seen in a different pair. Thus, distinguishing between identical and recombined pairs required the retrieval of semantic associations between words in the semantic condition but the retrieval of perceptual associations between words and fonts in the perceptual condition. The processes involved in encoding and retrieving associations have been described as "associative memory" or "relational memory", and here we use the latter expression.

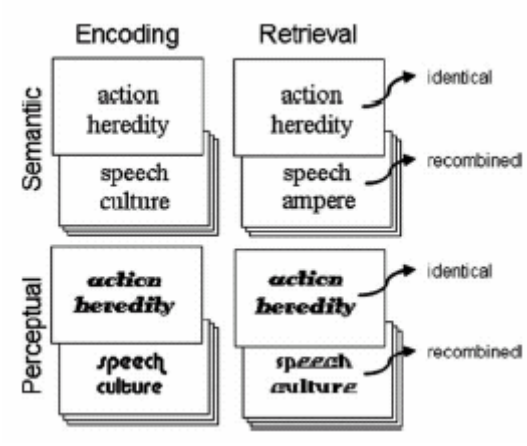

Figure 1. Behavioral Paradigm

Participants were scanned while encoding and then retrieving associations between words (semantic condition) or between words and fonts (perceptual condition). The retrieval task was an associative recognition test that included identical and recombined pairs. In the semantic condition, recombined pairs consisted of words encoded in separate pairs, whereas in the perceptual condition, recombined pairs consisted of studied pairs written in a font previously seen in a different pair.

The transfer appropriate processing (TAP) principle predicts that memory is a function of the overlap between encoding and retrieval operations. Behavioral studies investigating this idea typically include two encoding conditions (A

and B) emphasizing different forms of processing (e.g., semantic vs. perceptual) and two retrieval conditions (A' and B') also differing regarding these processes. In this situation, TAP predicts that memory performance should be better when study and test conditions match (A-A' and B-B') than when they mismatch (A-B' and B-A'). Event-related fMRI allows a different way of investigating the TAP principle, which we used in the present study. If one assumes that different forms of processing recruit different brain regions (process-specific regions), then the TAP principle predicts that successful memory performance should be associated with the reactivation during retrieval of process-specific regions that were also activated during encoding. More concretely, we tested the prediction that differences in activity between successful and unsuccessful trials would involve encoding-retrieval overlaps (ESA $\cap$ RSA) differing for semantic vs. perceptual processing.

Unlike functional neuroimaging studies that compared relational and nonrelational memory conditions (e.g. Davachi & Wagner, 2002), we investigated the neural correlates of RM by comparing successful vs. unsuccessful RM activity, both during encoding and during retrieval. As mentioned above, we defined *encoding success activity* (ESA) as study-phase activity for subsequently remembered vs. forgotten pairs (subsequent memory effect, for a review see Paller & Wagner, 2002), and *retrieval success activity* (RSA) as test-phase activity for hits vs. misses.

It is worth noting that we used misses as a control rather than using correct rejections. An advantage of using misses instead of correct rejections is that the latter tends to elicit MTL activity related to novelty/encoding, which may mask MTL activity related to successful retrieval (Stark & Okado, 2003). Another advantage of using misses is that they allow ESA and RSA analyses to be based on exactly the same set of items (subsequently remembered pairs = hits; subsequently forgotten pairs= misses). More generally, the advantage of using ESA and RSA to compare encoding and retrieval activity is that differences between encoding and retrieval tasks that are not directly associated with successful memory processes (e.g., task difficulty) tend to be subtracted out in the contrast between successful and unsuccessful trials. Thus, the present study allowed a more direct contrast between encoding and retrieval activity than has been possible in previous functional neuroimaging studies.

Subjects

Sixteen participants (5 females), all students at Duke University, with an average age of 19.8 (SD = 1.7) years were scanned and paid for their participation. Data from two participants were excluded due to scanner malfunction and inadequate behavioral performance. Written informed consent was obtained for each participant and the study met all criteria for approval of the Duke University Institutional Review Board.

Stimulus materials

The stimuli consisted of 368 word pairs and 184 unique fonts. The word pairs were constructed from a pool of abstract nouns selected from the MRC Psycholinguistic database (http://www.psy.uwa.edu.au/MRCDataBase/mrc2.html). The words were 4-11 letters in length (mean=7.8, s.d.=1.9) and of moderate frequency (KF written frequency mean=45). All word pairs were balanced for number of letters (± 2 letters) so that perceptual cues such as word length would not influence memory performance. The fonts were selected from a popular website (http://www.1001fonts.com/index.html) based on legibility, as rated by the first author. Each font was scaled to match a template size (Times New Roman, 36 point). Recombined pairings for retrieval were created pseudorandomly to meet the constraints of number of letters.

Procedures

The fMRI study consisted of four semantic runs and four perceptual runs, with the order alternating and counterbalanced across subjects. Each fMRI run contained one encoding block and one retrieval block separated by a 30-sec delay. Each block consisted of 46 trials, each consisting of a word-pair displayed for 3.4 sec. Participants were encouraged to respond within this period, and late responses were not included in the analyses. The number of study trials remaining identical per block was 29, yielding a potential total of 116 encoding trials and 116 retrieval trials per condition. The intertrial

interval (a fixation cross) varied between 0 and 5.4 sec, and was used as baseline in the fMRI analysis (see below).

Encoding and retrieval trials in the semantic and perceptual conditions are illustrated in Figure 1. In each semantic encoding trial, a pair of words in plain font was displayed and subjects rated semantic relatedness (1 = high; 4 = low) while learning the pair (intentional encoding). In each semantic retrieval trial, a pair of words in plain font was displayed, which was either identical to a studied pair or a recombined pair made by pairing words studied in different pairs. Participants made an identical/recombined decision and indicated their confidence (1 = definitely identical, 2 = probably identical, 3 = probably recombined, 4 = definitely recombined). During perceptual encoding trials, the font in which both were presented varied across trials. A different font was used for each pair, thereby avoiding interference effects. Subjects rated how well the font fitted the words (1 = high; 4 = low) while learning the words-font association. In perceptual retrieval trials, identical pairs were as in the semantic condition and recombined pairs were made of studied pairs presented in the font previously seen in a different pair (see Figure 1).

fMRI scanning

Images were collected using a 4T GE scanner. Scanner noise was reduced with ear plugs and head motion was reduced with foam pads and headbands. Stimuli were presented with LCD goggles (Resonance Technology, Inc.), and behavioral responses

were recorded with a 4-key fiber-optic response box (Resonance Technology, Inc.). Anatomical scanning started with a T1-weighted sagittal localizer series. The anterior (AC) and posterior commissures (PC) were identified in the mid-sagittal slice, and 34 contiguous oblique slices were prescribed parallel to the AC-PC plane. High-resolution T1-weighted structural images were acquired with a 450-ms repetition time (TR), a 9-ms echo time (TE), a 24-cm field of view (FOV), a 256^2 matrix, and a slice thickness of 1.9-mm. Functional scanning employed an inverse spiral sequence with a 1700-ms TR, a 31-ms TE, a 24-cm FOV, a 64^2 image matrix, and a 60° flip angle. Thirty-four contiguous slices were acquired with the same slice prescription as the anatomical images. Slice thickness was 3.75-mm, resulting in cubic 3.75-mm^3 isotropic voxels.

fMRI analyses

Data were analyzed using SPM99 (Statistical Parametric Mapping; Wellcome Department of Cognitive Neurology, http://www.fil.ion.ucl.ac.uk/spm). After discarding the first four volumes, time-series were corrected for differences in slice acquisition times, and realigned. Anatomical images were coregistered with the functional images. Next, both anatomical and functional images were spatially normalized to a standard stereotactic space, using the Montreal Neurological Institute (MNI) templates implemented in SPM99 and resliced to a resolution of 3x3x3 mm. The coordinates were later converted to Talairach and Tournoux's space (Talairach & Tournoux, 1988). Finally,

the volumes were spatially smoothed using an 8-mm isotropic Gaussian kernel and proportionally scaled to the whole-brain signal.

For each subject, trial-related activity was assessed by convolving a vector of the onset times of the stimuli with a synthetic hemodynamic response function. The general linear model, as implemented in SPM99, was used to model the effects of interest and other confounding effects (e.g., head movement and magnetic field drift). Statistical Parametric Maps were identified for each participant by applying linear contrasts to the parameter estimates (beta weights) for the events of interest, resulting in a t-statistic for every voxel. The parameter estimates for the different events will be subsequently referred to as effect sizes (see also Pastor, Day, Macaluso, Friston, & Frackowiak, 2004). In both semantic and perceptual conditions, we coded six trial types: encoding fixation baseline, subsequently remembered, subsequently forgotten, retrieval fixation baseline, retrieval hits, and retrieval misses. The mean number of trials contributing to each trial type in the design was 39 (SD: 15). An analysis excluding the 3 subjects with sparse trials (<15) yielded a similar pattern of results as the analysis including all subjects. Subsequently remembered trials were determined by matching the high-confidence retrieval hit responses at test to the relevant trials at study. Similar to other subsequent memory studies (e.g. Sperling et al., 2003), only the high-confidence retrieval hits were considered for analysis (low-confidence retrieval hits were modeled as a separate trial type, not included in any of the relevant analyses) since we were

interested in recollection rather than familiarity or guessing (to maximize the comparison between successful and failed retrieval). Low discriminability (d') scores (.06 in the semantic task and .12 in the perceptual task) provided further justification for excluding low-confidence retrieval hits.

Three analyses were performed to address the three questions described in the Introduction. First, to identify areas showing differences as a function of phase, we isolated regions showing successful activity (hit > miss: $p < 0.001$) in either the encoding or the retrieval phase. Within these regions-of-interest (ROI), masks were used to include areas showing a reliable memory x phase interaction ($p < 0.05$) and to exclude areas showing a memory x content interaction ($p< 0.05$). Second, to identify areas showing differences as a function of content, we isolated regions showing successful memory activity (hit > miss: $p < 0.001$) in either the semantic or the perceptual condition. Within these ROIs, masks were used to include areas showing a reliable memory x content interaction ($p < 0.05$) and to exclude areas showing a memory x phase interaction ($p < 0.05$). For purpose of illustration, regions identified in these comparisons are shown in figures 2 and 3 at thresholds between $p < 0.05$ and 0.005. Finally, to identify regions generally involved in successful RM regardless of memory phase and stimulus content, we performed a *quadruple conjunction* isolating regions showing significant effects in each and all four conditions (semantic ESA, perceptual ESA, semantic RSA, and perceptual RSA). Since the different conditions were presented independently in

separate functional runs, and each showed a hit-miss difference at $p < 0.05$, the significance threshold for the quadruple conduction can be estimated at $p < 0.00001$ (i.e., 0.05^4). This estimate assumes that a region may be activated in one condition without being activated in other conditions, which is a reasonable assumption given the numerous activation differences across conditions reported below. Furthermore, to ensure that regions found were truly general, we excluded regions showing interactions ($p < 0.05$) with memory phase or stimulus content.

Results

Behavioral data

Table 1 lists the proportion of correct and incorrect responses as a function of confidence and task. The proportion of hits was similar for semantic and perceptual conditions overall ($p > 0.20$), but was greater for high confidence responses in the semantic condition ($p < .0001$). T-tests comparing the proportion of hits (correctly identifying identical pairs) to the proportion of false alarms (incorrectly endorsing recombined pairs as identical) revealed significant differences ($p < 0.001$) for both the semantic and perceptual tasks. The proportion of hits was also significantly greater than chance for both the semantic ($p < 0.001$) and perceptual ($p < 0.005$) tasks. Finally, the proportion of high confidence hits was significantly greater than the proportion of high confidence false alarms for both tasks ($p < 0.001$). To control for the difference in

confidence proportions and to reduce the role of guessing overall, only high-confidence hits were included in fMRI analyses. To investigate the possible contribution of item memory to differences between hits and misses, we conducted a behavioral follow-up study to test the level of item memory under encoding conditions equivalent to the ones used in the scanner. A group of nine participants studied the same number of pairs with the same instructions and presentation rate as in the fMRI study, but then, instead of the associative recognition used in the scanner, they performed a forced-choice old/new recognition test. The results of this test show that item recognition performance for the short blocks we employed was high (words: mean=93%, s.d.=6%; fonts: mean=79%, s.d.=7%). Thus, differences in activation between hits and misses in our study mainly reflected differences in relational memory, with differences in item memory playing a relatively small role. Moreover, given that when item memory fails relational memory also fails, the common process separating hits from misses was primarily relational memory.

Table 1: Behavioral Results

Table 1. Behavioral results: mean proportion of responses (SD)

	HC	LC	Total
Intact pairs			
Hits			
Semantic	0.49 (0.16)	0.18 (0.13)	0.67 (0.10)
Perceptual	0.34 (0.19)	0.30 (0.21)	0.64 (0.16)
Misses			
Semantic	0.09 (0.08)	0.23 (0.10)	0.33 (0.10)
Perceptual	0.10 (0.10)	0.27 (0.12)	0.36 (0.16)
Recombined pairs			
Correct rejections			
Semantic	0.32 (0.16)	0.39 (0.11)	0.71 (0.12)
Perceptual	0.23 (0.17)	0.36 (0.14)	0.59 (0.19)
False alarms			
Semantic	0.12 (0.11)	0.17 (0.13)	0.29 (0.12)
Perceptual	0.15 (0.11)	0.26 (0.18)	0.41 (0.19)

HC, High confidence; LC, low confidence.

Reaction times (RTs) during retrieval and during encoding were analyzed with separate 2 (performance: remembered, forgotten) x 2 (content: semantic, perceptual) ANOVAs. The retrieval ANOVA yielded a significant main effect of performance ($p<0.01$), which reflected faster RTs for hits (1736ms, 195 s.d.) than for misses (1983ms, 289 s.d.). This is a typical finding in recognition memory tasks, presumably due to greater monitoring demands (an extended search process). The encoding ANOVA yielded a significant effect of content ($p<0.05$), which reflected faster RTs in the perceptual (1883ms, 359 s.d.) than in the semantic condition (2116ms, 279 s.d.). Separate analyses were done with the RT differences entered as nuisance covariates and the results of these are reported in the tables. Finally, to test whether differences in encoding duration (due to the differential intertrial interval) influenced memory performance, an ANOVA was performed which revealed no significant effect ($p>0.2$) on the proportion of hits across the different intertrial intervals.

fMRI data

Brain regions showing differences between encoding success activity (ESA) and retrieval success activity (RSA) are listed in Table 2 and displayed in Figure 2. In PFC, ESA and RSA were not associated with differences in lateralization but with differences between left PFC subregions: whereas ventrolateral regions (Brodmann Area–BA 47 and BA 44) showed greater ESA than RSA (see Figure 2-A), anterior (BA 10) and dorsolateral (BA 46, see Figure 2-B) regions showed greater RSA than ESA. In MTL, an anterior region (left hippocampus head) showed greater ESA than RSA (see Figure 2-C), whereas a posterior MTL region (left posterior parahippocampal/hippocampal) showed the converse pattern (see Figure 2-D). ESA > RSA differences were also found in anterior cingulate and cerebellar regions, and RSA > ESA differences, in posterior parietal and precuneus regions.

Table 2: Encoding-Retrieval Differences

Table 2. Brain regions showing significant differences between ESA and RSA

		H	BA	Coordinates (T&T)			T	T	T	T
				x	y	z		A	B	C
ESA > RSA										
PFC	ventrolateral	L	47	-49	33	-8	5.73	5.90	5.83	7.19
	opercular	L	44	-56	15	7	3.37	3.06	3.06	3.06
MTL	anterior hippocampus	L		-34	-11	-12	2.36	2.19	2.18	2.02
Anterior cingulate		M	32/8	-4	28	37	2.74	2.74	2.79	2.08
Parietal ctx.		L	7	-23	-64	48	2.43	2.29	2.31	1.52
Putamen		L		-19	10	-7	2.04	1.96	1.96	1.12
Cerebellum		L		-38	-61	-29	2.54	2.54	2.75	2.46
RSA > ESA										
PFC	anterior	L	10/11	-30	51	-9	2.28	2.26	2.24	1.69
	dorsolateral	L	46	-46	28	26	2.30	2.24	2.24	1.58
MTL	post. parahipp. g.	L	30	-19	-41	6	5.19	5.58	5.64	5.21
Parietal ctx.		L	19/39	-34	-72	35	2.59	2.74	2.96	3.16
		L	40	-49	-42	51	2.18	2.26	2.10	1.48
		L	39	-42	-68	31	2.89	3.06	3.52	4.10
		L	7	-34	-72	42	3.04	2.95	3.41	3.87
		R	7/39	27	-62	34	2.10	2.39	2.40	2.12
Parieto-occipital ctx.		L	39/18	-42	-73	14	2.81	2.84	2.74	2.61
Occipital ctx.		L	18	-27	-70	-6	2.30	2.68	2.46	2.48

Notes: H = hemisphere, BA = Brodmann Area, T&T = Talairach & Tournoux (1988), T = statistical value, A=values from analysis with RT nuisance covariate for semantic-perceptual at encoding, B=values from analysis with RT nuisance covariate for miss-hit at retrieval, C=values from analysis with three subjects removed based on sparse numbers of trials

General Notes: The tables show the results from additional analyses that entered reaction time differences into the statistical models (A and B) or removed subjects from the analysis (C) based on having fewer than 15 trials for a given trial type. Additionally, the quadruple conjunction was calculated with these factors entered, resulting in the same area (-27, -26, -5) or a neighboring peak (-27, -30, -5) being found.

Brain regions showing overlaps between ESA and RSA that differed for semantic vs. perceptual conditions are listed in Table 3 and displayed in Figure 3. ESA-RSA overlaps specific to semantic RM were found in a left lateralized cortical and subcortical network, including ventrolateral PFC (see Figure 3-A), insular, striatal, and cerebellar regions. As illustrated by Figure 3-A, the left ventrolateral PFC region associated with semantic RM during both encoding and retrieval (yellow/red area) was more posterior

than the left ventrolateral PFC region associated with encoding of both semantic and perceptual RM (blue area). Whereas the semantic-specific activation occurred primarily in BA 45, the encoding-specific activation occurred primarily in BA 47. There was also another semantic-specific activation in left ventromedial PFC (BA 11). ESA-RSA overlaps specific to perceptual RM were found in posterior brain regions, including left occipitotemporal cortex (BA37/19, see Figure 3-B), bilateral posterior parietal cortex (BA 7/40, see Figure 3-C), and right parahippocampal cortex (see Figure 3-D).

Table 3: Semantic-Perceptual Differences

Table 3. Brain regions showing significant differences between semantic and perceptual ESA/RSA

		H	BA	Coordinates (T&T)			T	T	T	T
				x	y	z		A	B	C
Semantic ESA/RSA > Perceptual ESA/RSA										
PFC	ventrolateral	L	45	-46	26	2	3.84	3.86	3.83	3.34
	ventromedial	L	11	-23	28	-17	2.36	2.31	2.45	2.23
Auditory cortex		L	41	-34	-22	5	3.48	3.07	2.98	2.68
Caudate		L		-15	26	-1	4.24	4.01	4.18	3.41
Putamen		L		-23	1	10	2.41	2.48	2.37	1.95
Subcallosal gyrus		R	25	23	10	-13	2.08	2.17	2.00	1.82
Amygdala		L		-19	-1	-13	1.81	1.86	1.84	1.04
Cerebellum		L		-19	-56	-22	1.93	2.17	2.14	2.12
Perceptual ESA/RSA > Semantic ESA/RSA										
Occipitotemporal ctx.		L	19/37	-42	-71	-16	1.97	2.41	2.25	1.91
Parietal ctx.		R	40	30	-52	59	3.24	3.11	3.34	2.75
		L	7	-23	-72	42	2.96	2.97	2.99	3.44
MTL	parahipp. gyrus	R	35	15	-26	-4	3.22*	3.12	3.08	2.54
Anterior cingulate		M		0	45	5	3.14	2.85	2.79	2.07

Notes: See Table 2, * = p<.05
General Notes: The tables show the results from additional analyses that entered reaction time differences into the statistical models (A and B) or removed subjects from the analysis (C) based on having fewer than 15 trials for a given trial type. Additionally, the quadruple conjunction was calculated with these factors entered, resulting in the same area (-27, -26, -5) or a neighboring peak (-27, -30, -5) being found.

The quadruple conjunction of semantic ESA, semantic RSA, perceptual ESA, and perceptual RSA yielded only one region in the whole brain: the left hippocampus (xyz: -27, -26, -5). As indicated by the bar graph in Figure 4, this region showed successful

memory activity both during encoding (remembered – forgotten) and during retrieval (hits – misses) and for both semantic and perceptual associations. This finding confirms our prediction that the hippocampus plays a general role in successful RM. The MTL region associated with successful RM in general (green MTL area in Figure 2) was located between the anterior MTL region specialized in successful RM encoding (red area) and the posterior MTL region specialized in successful RM retrieval (blue area). Thus, the existence of a common encoding/retrieval region in MTL is compatible with the existence of MTL regions differentially involved in ESA vs. RSA.

Discussion

In summary, the study yielded three main sets of findings. First, ESA-RSA differences were found both within MTL and PFC. Second, several regions activated during encoding were reactivated during retrieval in a content-specific manner. Finally, only one region in the whole brain was associated with successful RM regardless of phase (encoding vs. retrieval) and content (semantic vs. perceptual): the left hippocampus. These three sets of findings are discussed in separate sections below.

Encoding and Retrieval

Within MTL, a more anterior region (left hippocampus head) showed greater ESA than RSA (Figure 2-C) whereas a more posterior region (left parahippocampal/hippocampal region) showed greater RSA than ESA (Figure 2-D). This

double dissociation is consistent with a metaanalysis of functional neuroimaging studies (Lepage, Habib, & Tulving, 1998) which concluded that encoding tends to activate the anterior, and retrieval, the posterior MTL (HIPER model). However, Schacter and Wagner (1999) noted that encoding activations in anterior MTL were sometimes found by RM studies, whereas encoding activations in posterior MTL were sometimes observed in non-RM studies. Thus, they suggested that, rather than encoding-retrieval differences, the anterior-posterior MTL gradient might reflect relational-nonrelational differences. In the present study, RM demands were high during both phases, and hence, this alternative hypothesis cannot easily account for the present dissociation. As for the left parahippocampal/hippocampal activation, it is consistent with the notion that the hippocampus is involved in RM (Eichenbaum, Otto, & Cohen, 1994) and additionally suggests a role of the parahippocampal cortex in RM (Davachi et al. 2003, Duzel et al., 2003; Ranganath et al., 2004).

Although consistent with the HIPER model, three caveats should be noted about the anterior MTL activation (Figure 2-C). First, this activation could reflect novelty rather than encoding per se. Encoding and novelty interpretations are difficult to distinguish because novelty promotes encoding (Ranganath & Rainer, 2003; Tulving & Kroll, 1995) and both tend to engage similar brain regions (Kirchhoff et al., , 2000; Yamaguchi, Hale, D'Esposito, & Knight, 2004). Second, although the anterior MTL activation did not show a significant phase x content interaction, it tended to be larger

for perceptual than for semantic RM. Greater hippocampal activity in the perceptual condition may reflect the use of unusual (novel) fonts, or cross-domain binding between words-fonts (e.g., Mayes et al., 2001). Third, several fMRI studies of episodic encoding have found activations in posterior parahippocampal regions (but see Daselaar, Veltman, & Witter, 2004; e.g. Gabrieli, Brewer, Desmond, & Glover, 1997; Stern et al., 1996). The present results are not inconsistent with these studies, as we are not claiming that only anterior MTL regions are involved in encoding processes. What we found is that, in a direct within-subject comparison, anterior MTL regions showed greater ESA than RSA.

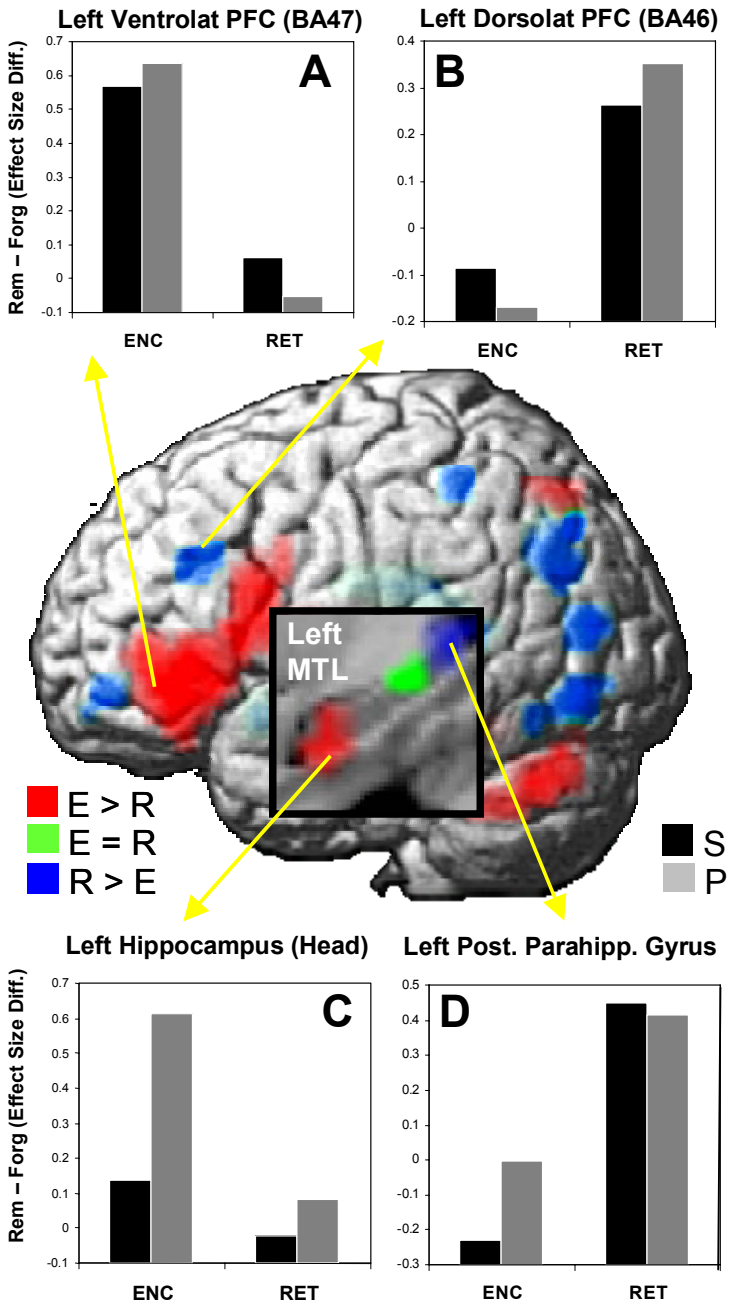

Figure 2. Encoding-Retrieval Differences

Brain regions showing differences between successful relational memory (RM) activity during encoding (ESA) and during retrieval (RSA). The bar graphs display the effect size of activations for remembered vs. forgotten items during encoding (i.e., subsequently remembered vs. forgotten) and during retrieval (i.e., hits vs. misses) for both semantic and perceptual conditions.

Within PFC, the ESA-RSA contrast yielded a double dissociation within left PFC: whereas left ventrolateral regions showed greater ESA (Figure 2-A), left dorsolateral and anterior regions showed greater RSA (Figure 2-B). The finding of ESA in left ventrolateral PFC is consistent with fMRI studies using the subsequent memory paradigm (for a review see Paller & Wagner, 2002). The finding of RSA in left PFC is generally consistent with functional neuroimaging evidence linking left PFC to source memory (e.g. Nolde, Johnson, & D'Esposito, 1998; e.g. Ranganath, Johnson, & D'Esposito, 2000), but not with studies that did not find a difference in this region between successful and unsuccessful source memory trials (Dobbins et al., , 2002; e.g. Kahn, Davachi, & Wagner, 2004). The present study provides the first clear evidence that different left PFC subregions are differentially involved in successful encoding vs. successful retrieval.

A speculative explanation for the dissociation between ventrolateral PFC (ESA>RSA) and dorsolateral PFC (RSA>ESA) is that these two areas are differentially involved in working memory maintenance vs. manipulation (D'Esposito, Postle, Ballard, & Lease, 1999; Owen, 1997; Petrides, 1994b). Successful RM encoding may be more dependent on continuous maintenance of incoming information whereas successful RM retrieval may be more dependent on the reorganization of the retrieved output within working memory. The involvement of anterior PFC in RSA is consistent with evidence that this region is typically activated during retrieval (Cabeza & Nyberg, 2000). The role

of anterior PFC during retrieval has been attributed to retrieval mode (Cabeza et al., , 2002; e.g. Lepage et al., , 2000), manipulation of self-generated information (Christoff et al., 2001), and subgoaling/branching operations (Braver & Bongiolatti, 2002; Koechlin, Ody, & Kouneiher, 2003). All these ideas could account for greater RSA than ESA.

Semantic and Perceptual

As noted earlier, the transfer-appropriate processing (TAP) principle predicts that successful memory performance should involve the reactivation during retrieval of brain regions originally involved in encoding a particular kind of information (e.g., semantic vs. perceptual). The present study confirmed this prediction: several regions showed ESA-RSA overlaps that differed between semantic and perceptual RM conditions (see Figure 3). These encoding-retrieval overlaps cannot be attributed to the overall similarity of encoding and retrieval tasks in the semantic vs. perceptual conditions because activity related to overall similarity was subtracted out by remember minus forgotten subtractions.

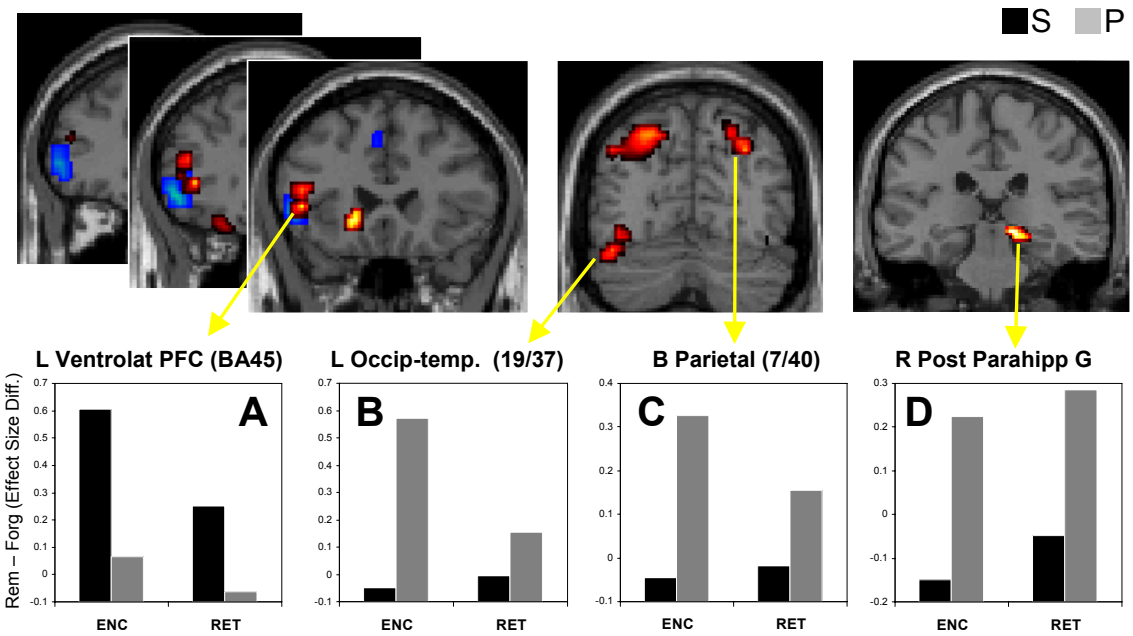

Figure 3. Semantic-Perceptual Differences

Brain regions that showed ESA/RSA overlaps that differed between semantic and perceptual RM conditions. The left ventrolateral PFC region (BA 45, xyz = -46, 26, 2) was slightly more posterior/dorsal than the left ventrolateral PFC region that showed greater ESA than RSA for both semantic and perceptual RM (blue area: BA 47, xyz: -49, 33, -8).

Successful semantic RM was associated with encoding and retrieval activity in left ventrolateral PFC (see Figure 3-A). This finding is consistent with functional neuroimaging evidence linking this area to semantic RM encoding (Kapur et al., 1996; Lepage, Habib, Cormier, Houle, & McIntosh, 2000) and retrieval (Badgaiyan, Schacter, & Alpert, 2002), and to semantic processing in general (for a review, see Thompson-Schill, 2003). As illustrated by Figure 3-A, the left ventrolateral PFC region showing an ESA-RSA overlap for semantic RM (yellow/red area: BA 45, xyz = -46, 26, 2) was more

posterior/dorsal than the left ventrolateral PFC region showing greater ESA than RSA for both semantic and perceptual RM (blue area: BA 47, xyz: -49, 33, -8). Although semantic processing and episodic encoding have been both strongly associated with ventrolateral PFC (Cabeza & Nyberg, 2000), the present study suggests they may involve different subregions within this general area.

Turning to perceptual RM, ESA-RSA overlaps were found in left occipito-temporal (Figure 3-B), bilateral parietal (Figure 3-C), and right parahippocampal (Figure 3-D) regions. Activations in occipitotemporal and posterior parietal regions are frequently found during visual memory and imagery tasks (Cabeza & Nyberg, 2000). The left occipito-temporal activation occurred in a region known as *visual word form area,* which includes patches specialized in letter processing (for a review, see McCandliss, Cohen, & Dehaene, 2003). Parietal regions have been strongly associated with attentional processes (Cabeza & Nyberg, 2000), and may reflect visual attention to fonts' features. Finally, the right parahippocampal activation is consistent with evidence that right MTL is involved in encoding and retrieval of nonverbal stimuli (e.g., Kelley et al., 1998; Simons, Graham, Owen, Patterson, & Hodges, 2001).

General RM processes

In the whole brain, only one brain region was associated with successful RM regardless of memory phase (encoding vs. retrieval) and stimulus content (e.g., semantic vs. perceptual): the left hippocampus. This region was located between the anterior MTL

region that was differentially involved in encoding and the posterior MTL region differentially involved in retrieval. Thus, the distinction between anterior and posterior MTL regions can be seen as an encoding/retrieval gradient with a middle convergence region shared by both stages (e.g. Small et al., 2001). This finding is consistent with evidence from separate functional neuroimaging studies that the left hippocampus is activated during both RM encoding (Henke, Buck, Weber, & Wieser, 1997; Henke, Weber, Kneifel, Wieser, & Buck, 1999; Lepage, Habib, Cormier, Houle, & McIntosh, 2000) and retrieval (e.g., Giovanello, Schnyer, & Verfaellie, 2004; Preston, Shrager, Dudukovic, & Gabrieli, 2004), and during both semantic (Davachi & Wagner, 2002; Henke, Weber, Kneifel, Wieser, & Buck, 1999; Jackson & Schacter, 2004; Lepage, Habib, Cormier, Houle, & McIntosh, 2000) and perceptual RM (Gonzalo, Shallice, & Dolan, 2000; Henke, Buck, Weber, & Wieser, 1997; Killgore et al., , 2000; Montaldi et al., 1998; Preston et al., , 2004). However, results from separate studies cannot prove that a common hippocampal region is activated across all these different conditions. The present study is the first to do so.

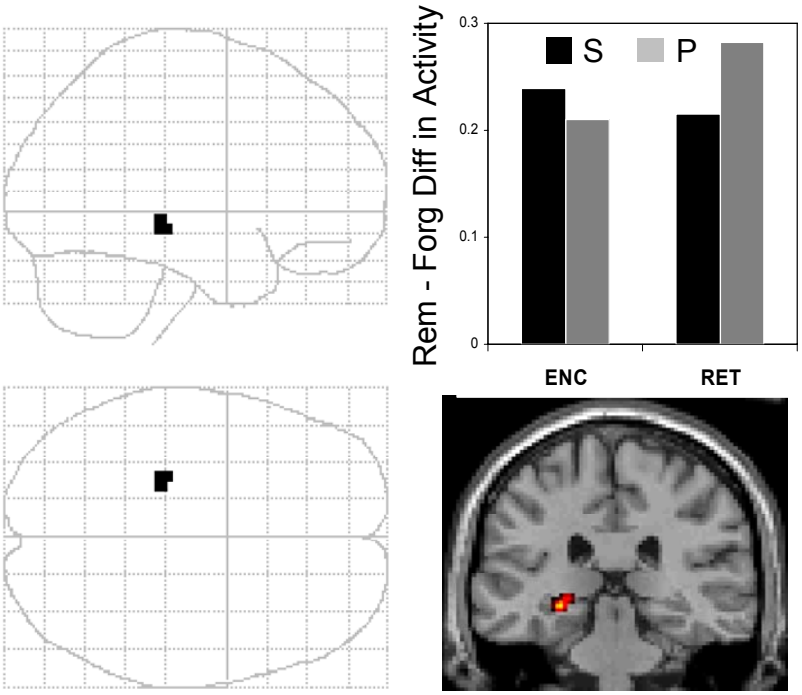

Figure 4. Quadruple Conjunction

Results of a quadruple conjunction analysis that identified regions showing successful relational memory activity (remembered – forgotten) during semantic encoding, semantic retrieval, perceptual encoding, and perceptual retrieval. Only one region was identified: the left hippocampus (xyz: -27, -26, -5).

This finding fits very well with dominant theories about hippocampal function. First, it is consistent with the hypothesis that the hippocampus holds indexes of stored memory traces (Squire, 1992; Teyler & DiScenna, 1985). This hypothesis predicts that the hippocampus should be activated both when a new index is formed (encoding) and when the index is accessed (retrieval). This idea is not incompatible with the notion of hippocampal regions differentially involved in encoding vs. retrieval, and the two ideas can be harmonized by the hypothesis of an encoding-retrieval gradient with a middle

region shared by both processes. Second, the present finding is consistent with the view that the hippocampus plays a general and fundamental role in RM (Eichenbaum, Otto, & Cohen, 1992). The finding of a hippocampal region associated with successful RM both during encoding and retrieval and both for semantic and perceptual associations provides strong support to this view.

Conclusions

The study yielded three main sets of findings. First, encoding-retrieval (ESA-RSA) differences were found both within MTL and PFC. Within MTL, successful encoding engaged a more anterior region, and successful retrieval, a more posterior region. Within PFC, successful encoding recruited a left ventrolateral area, and successful retrieval, left dorsolateral and anterior areas. Second, several regions activated during encoding were reactivated during retrieval in a content-specific manner. For semantic RM, encoding-retrieval overlaps were found in left ventrolateral PFC, and for perceptual RM, in occipital, parietal, and right parahippocampal areas. Finally, only one region in the whole brain was associated with successful RM regardless of phase (encoding vs. retrieval) and content (semantic vs. perceptual): the left hippocampus. These results shed new light on the neural correlates of RM and how they change as a function of memory phase and stimuli.

Although this study represents a comprehensive investigation of RM encoding and retrieval, there are aspects warranting further investigation. First, content-specific

effects were found by comparing semantic to perceptual aspects of word-pairs. However, presentation of semantic stimuli typically yields semantic processing. Thus, testing content domains with well-established dissociable neural correlates, such as memory for objects versus spatial locations, would extend the present findings and may yield stronger effects. Second, RM was studied using memory success subtractions for two different RM content-types. However, direct comparison to an item memory baseline condition would strengthen the present findings.

3. Content-based Memory Success

Introduction

A central issue in cognitive neuroscience is whether certain brain regions act as modules that respond rapidly and automatically to specific stimuli. According to Fodor (1983), fundamental properties of modules include obligatory responses and informational encapsulation (operate without regard to other ongoing brain processes) for a particular stimulus class (but cf. Coltheart, 1999). Modules are typically described as performing sensory processing for a particular stimulus class to the exclusion of others. Functional imaging studies have identified brain regions exhibiting stimulus-sensitive processing for place stimuli in the posterior parahippocampal gyrus (Epstein & Kanwisher, 1998), frequently referred to as the *parahippocampal place area* (PPA), and for face stimuli in the fusiform gyrus (Kanwisher, McDermott, & Chun, 1997) and occipital cortex (Rossion, Schiltz, & Crommelinck, 2003), frequently referred to as the *fusiform face area* (FFA) and *occipital face area* (OFA), respectively. These place and face specialized regions are frequently characterized as modular in that they rapidly and automatically support the perception of those stimuli, but not other stimuli like objects, birds, cars, or bodies (but cf. Gauthier, Skudlarski, Gore, & Anderson, 2000; Grill-Spector, Sayres, & Ress, 2006; but cf. Haxby et al., 2001). However, other evidence suggests that stimulus-sensitive regions might not simply respond to the presence of specific content, but also additionally be modulated by focused attention (Wojciulik, Kanwisher, & Driver, 1998), repetition (Henson, Shallice, Gorno-Tempini, & Dolan, 2002), and novelty or mnemonic

status (Epstein et al., 1999; Kuskowski & Pardo, 1999; Rossion, Schiltz, & Crommelinck, 2003; Turk-Browne, Yi, & Chun, 2006). Previous functional neuroimaging studies have used techniques such as repetition suppression or blocked comparisons to examine processing in these stimulus-sensitive regions.

Using event-related fMRI, we scanned the encoding and retrieval memory stages for face and place stimuli. The behavioral paradigm is illustrated in Figure 1. Participants were scanned while encoding and then retrieving individual places or individual places. For encoding trials, participants rated either the pleasantness of a place or the friendliness of a face, while learning the information (intentional encoding). For retrieval trials, participants made a combined old/new distinction and confidence level response (definitely old, probably old, probably new, or definitely new). Successful memory was defined as the highest confidence old responses versus all other trials, with encoding trials sorted based on later outcome.

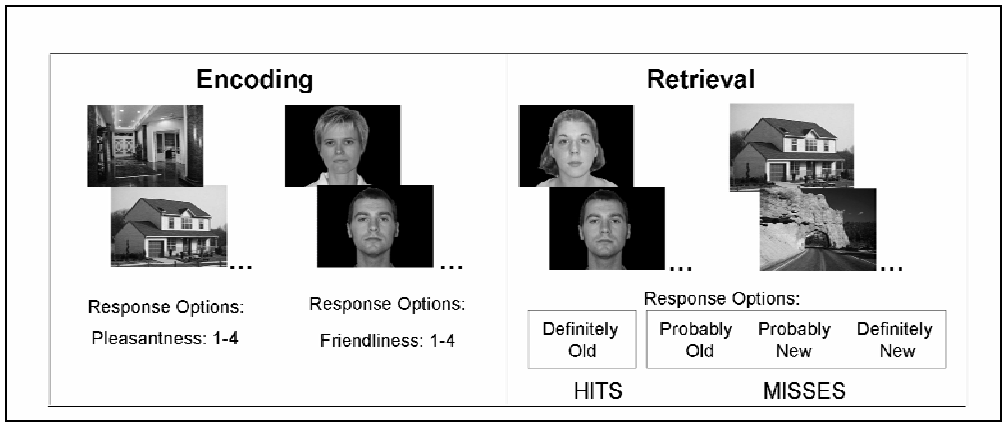

Figure 1. Behavioral Paradigm

Examples of stimuli shown during place and face encoding and retrieval trials. Response options were not shown during the experiment and retrieval responses are grouped to illustrate trials that were used for hit (Definitely Old) versus miss (all other responses) comparisons.

To investigate the role of content and process in memory, we compared subsequently remembered vs. forgotten trials at encoding and hits vs. misses at retrieval. We had four central goals which involved identifying 1) stimulus sensitive memory success effects at encoding and 2) stimulus sensitive memory success effects at retrieval, 3) stimulus sensitive memory success, regardless of memory stage, and 4) stimulus independent (general) memory success effects.

Although studies have reported a role for stimulus-sensitive regions in successful encoding (e.g. Brewer et al., 1998, Turk-Browne et al., 2006), it is not clear whether regions such as the PPA and FFA are also involved in successful retrieval. One possibility is that reactivation, in the exact areas that support better encoding, would benefit retrieval. Another possibility is that enhanced activity in stimulus-sensitive regions only occurs for encoding success. Furthermore, regions outside of those typically reported as stimulus-sensitive (in the ventral visual stream) may support content-based memory success. In opposition to specialization for stimulus content, regions involved in memory success as a general phenomenon, regardless of content or memory stage represent the most fundamental cognitive operations. Based on studies of subsequent memory (Kirchhoff et al., 2000) retrieval success (Eldridge et al., 2000), and encoding-retrieval-content conjunctions (Prince et al., 2005), the hippocampus was predicted to play such a role in general memory success.

Methods

Subjects

Nineteen right-handed participants (10 females), all students at Duke University, with an average age of 22.7 years (SD = 4.1) were scanned and paid for their participation. Data from three participants were excluded, one due to equipment malfunction and two due to inadequate behavioral performance (overall response rate less than two-thirds). Written informed consent was obtained for each participant and the study met all criteria for approval of the Duke University Institutional Review Board.

Stimulus materials

The stimuli consisted of 144 photographs of places and 144 photographs of faces. Photos of places consisted of common indoor (50%) and outdoor (50%) scenes, which were obtained from an online database (http://www.corbis.com) and set to a standard size of 576 x 432. Face photos were obtained, with permission, from an online database (http://agingmind.cns.uiuc.edu/facedb) and represent the age spectrum from young adults to older adults as well as different racial groups (Minear & Park, 2004). The database contains some faces with various emotional expressions, however only faces with neutral expressions (as determined by Minear and Park) were used in the current experiment. As shown in Figure 1, faces were set on a solid black background. White fixation crosses were shown between successive stimuli.

Procedures

The fMRI study was completed in a single session and consisted of two place and three face runs for encoding and the same number of runs for retrieval. There were also six total runs in which faces were paired with places (data from these runs reported elsewhere). Overall run order was fixed based on pilot testing designed to elicit equivalent performance across tasks. Trial timing and jitter durations during encoding were also determined by pilot testing in order to attain similar performance. Place encoding trials were 1475 milliseconds (ms) and face encoding trials were 2475ms in duration, both followed by a variable jitter ranging from 1275 to 1775ms (mean jitter length was 1525ms). Retrieval trials in all conditions were 3000ms in duration, followed by a variable jitter ranging from 1500ms to 2500ms (mean jitter length was 2000ms). Participants were encouraged to respond within the allotted period. The total number of old study trials was 108, yielding a potential total of 108 encoding trials and 108 retrieval trials per condition. Additionally, 36 new trials, per condition, were included during retrieval. Finger order for button press responses was counterbalanced across participants at both encoding and retrieval

In each stimulus condition, the measures of interest were activity associated with subsequent hit versus subsequent miss subtractions during encoding (Dm effect, Wagner et al., 1998; Brewer et al., 1998), referred to here as *Encoding Success Activity* (ESA), and hit versus miss subtractions during retrieval, referred to here as *Retrieval Success Activity* (RSA). Additionally, *General Success Activity* (GSA) was defined as regions that showed both ESA and RSA, without a greater effect for one versus the

other. For a description of the masking procedures which were used to isolate specific stimulus and stage effects and general memory success effects, see table 1.

Scanning & Image Processing

Images were collected from a 4T GE scanner. Scanner noise was reduced with ear plugs and head motion was reduced with foam pads and headbands. Stimuli were presented with LCD goggles (Resonance Technology, Inc.), and behavioral responses were recorded with a 4-key fiber-optic response box (Resonance Technology, Inc.). Anatomical scanning started with a T1-weighted sagittal localizer series. The anterior (AC) and posterior commissures (PC) were identified in the mid-sagittal slice, and 34 contiguous oblique slices were prescribed parallel to the AC-PC plane. High-resolution T1-weighted structural images were acquired with a 450-ms repetition time (TR), a 9-ms echo time (TE), a 24-cm field of view (FOV), a 256^2 matrix, and a slice thickness of 1.9-mm. Functional scanning employed an inverse spiral sequence with a 1500-ms TR, a 31-ms TE, a 24-cm FOV, a 64^2 image matrix, and a 60° flip angle. Thirty-four contiguous slices were acquired with the same slice prescription as the anatomical images. Slice thickness was 3.75-mm, resulting in cubic 3.75-mm^3 isotropic voxels.

Data were processed using SPM2 (Statistical Parametric Mapping; Wellcome Department of Cognitive Neurology, http://www.fil.ion.ucl.ac.uk/spm). The first six volumes were discarded to allow for scanner equilibration. Time-series were then corrected for differences in slice acquisition times, and realigned. Functional images were spatially normalized to a standard stereotactic space, using the Montreal Neurological Institute (MNI) templates implemented in SPM2 and resliced to a

resolution of 3.75 mm^3. The coordinates were later converted to Talairach and Tournoux's space (Talairach & Tournoux, 1988) for reporting in Tables. Finally, the volumes were spatially smoothed using an 8-mm isotropic Gaussian kernel and proportionally scaled to the whole-brain signal.

fMRI analyses

For each subject, trial-related activity was assessed by convolving a vector of the onset times of the stimuli with a synthetic hemodynamic response function. The general linear model, as implemented in SPM2, was used to model the effects of interest and other confounding effects (e.g., head movement and magnetic field drift). Statistical Parametric Maps were identified for each participant by applying linear contrasts to the parameter estimates (beta weights) for the events of interest, resulting in a t-statistic for every voxel. In both stimulus conditions, we coded four trial types: subsequent hits, subsequent misses, retrieval hits, and retrieval misses. The mean number of trials contributing to each trial type in the design was 52 (standard deviation = 14.5). Subsequent hit trials were determined by matching the high-confidence retrieval hit responses at test to the relevant trials at study. Similar to other subsequent memory studies, only high-confidence retrieval hits were considered subsequent hits and all other trials were modeled as subsequent misses (Otten, Quayle, Akram, Ditewig, & Rugg, 2006; Schon, Hasselmo, Lopresti, Tricarico, & Stern, 2004).

The analyses were conducted according to the previously stated goals. For each of the goals, we identified areas showing a primary effect, in which the memory success

based contrast of interest (encoding, retrieval, or both) was set at a threshold of $p < 0.005$. Direct comparison secondary contrasts were then used as inclusive or exclusive masks (dependent on the particular effect investigated) and these double subtraction contrasts were set at a threshold of $p < 0.07$. For example, Place Enc is comprised of Place ESA (subsequent hit > subsequent miss at $p < 0.005$), inclusively masked with both stimulus (Place ESA > Face ESA at $p < 0.07$) and stage (Place ESA> Place RSA at $p < 0.07$). The complete description of the masking procedure for all reported effects is listed in Table 1. Because each effect requires the spatial overlap of at least three separate contrasts, the precise statistical threshold is difficult to estimate. However, every overlap that involves an independent stimulus or stage can be assumed to represent the multiplied value of the individual thresholds. The p-value for the inclusive masks is therefore estimated at between 0.005 and 0.00002. To further reduce the chance for false clusters, an extent threshold of five voxels was used in all of the analyses. Thus, the significance thresholds employed were very conservative, varying according to one calculation (Forman et al., 1995) between 0.0005 and 0.000004.

Table 1: Masking Procedure

Table 1. Procedure of inclusive and exclusive masking for isolating stimulus-sensitive and general effects

CONTRAST	MAIN	AND (INCLUSIVE)	NOT (EXCLUSIVE)
Place Enc	Place ESA (subs hit > subs miss)	Place ESA > Face ESA } STIM Place ESA > Place RSA } STAGE	
Face Enc	Face ESA (subs hit > subs miss)	Face ESA > Place ESA } STIM Face ESA > Face RSA } STAGE	
Place Ret	Place RSA (hit > miss)	Place RSA > Face RSA } STIM Place RSA > Place ESA } STAGE	
Face Ret	Face RSA (hit > miss)	Face RSA > Place RSA } STIM Face RSA > Face ESA } STAGE	
Place Mem	Place GSA	Place ESA, Place RSA Place ESA > Face ESA Place ESA > Place RSA } STIM	Place ESA > Place RSA Place RSA > Place ESA } STAGE
Face Mem	Face GSA	Face ESA, Face RSA Face ESA > Place ESA Face RSA > Place RSA } STIM	Face ESA > Face RSA Face RSA > Face ESA } STAGE
General Mem	GSA	Place ESA, Face ESA, Place RSA, Face RSA	Place ESA > Face ESA, Face ESA > Place ESA Place RSA > Face RSA, Face RSA > Place RSA } STIM Place ESA > Place RSA, Face ESA > Face RSA Place RSA > Place ESA, Face RSA > Face ESA } STAGE

Results

Behavioral data

Table 2 lists the proportion of high and low confidence responses for correct (hit, correct rejection) and incorrect (miss, false alarm) place and face trials. There was no significant difference ($p = 0.16$) between the proportion of high confidence hit responses for places versus faces. Confidence had a strong effect on accuracy for old items, with 90.2% accuracy for high confidence responses, but only 59.7% accuracy for low confidence responses. This pattern justifies including only high-confidence responses in the hit category in fMRI analyses. T-tests comparing places versus face reaction times for high confidence hits revealed no significant differences at encoding ($p > 0.44$) or retrieval ($p > 0.97$).

Table 2: Behavioral Results

Table 2. Behavioral results: mean proportion of responses and RTs in milliseconds

		Hi Conf.	Lo Conf.	Total	Hi Conf.	Lo Conf.	Total
Old Trials		**Hits**			**Misses**		
Place		0.58	0.20	0.78	0.06	0.16	0.22
	Encoding RTs	1582	1488		1533	1539	
	Retrieval RTs	1530	2258		1980	2406	
Face		0.53	0.26	0.79	0.06	0.15	0.21
	Encoding RTs	1653	1721		1750	1721	
	Retrieval RTs	1528	2155		1990	2224	
New Trials		**Correct Rejections**			**False Alarms**		
Place		0.45	0.39	0.84	0.06	0.10	0.16
Face		0.43	0.39	0.82	0.04	0.14	0.18

fMRI data

Tables 3 to 5 list the regions according to the effects of interest. Since all analyses involved conjunctions of general effects with multiple direct comparison effects, the resulting clusters have neither a single peak, nor a single t-value that encompasses all of them. As such, the center of mass and the averaged t-value of all voxels within each cluster are reported. In each table, average cluster t-values are reported for individual encoding effects and the direct contrast between them, individual retrieval effects and the direct contrast between them, and finally the encoding versus retrieval t-values for one or both stimulus types. Columns in bold are intended to highlight the t-values of individual effects within the conjunction.

Stimulus-sensitive encoding effects

Place Enc activations (Table 3) were located in the occipital, parietal and temporal lobes. The parahippocampal gyrus regions closely match previously reported coordinates for PPA, with a larger cluster in the right hemisphere (see Figure 2A). The graph in the figure (and later figures) shows the significance value of ANOVAs and t-

tests conducted on the parameter estimates (beta weights) extracted from individual subjects from the cluster shown.

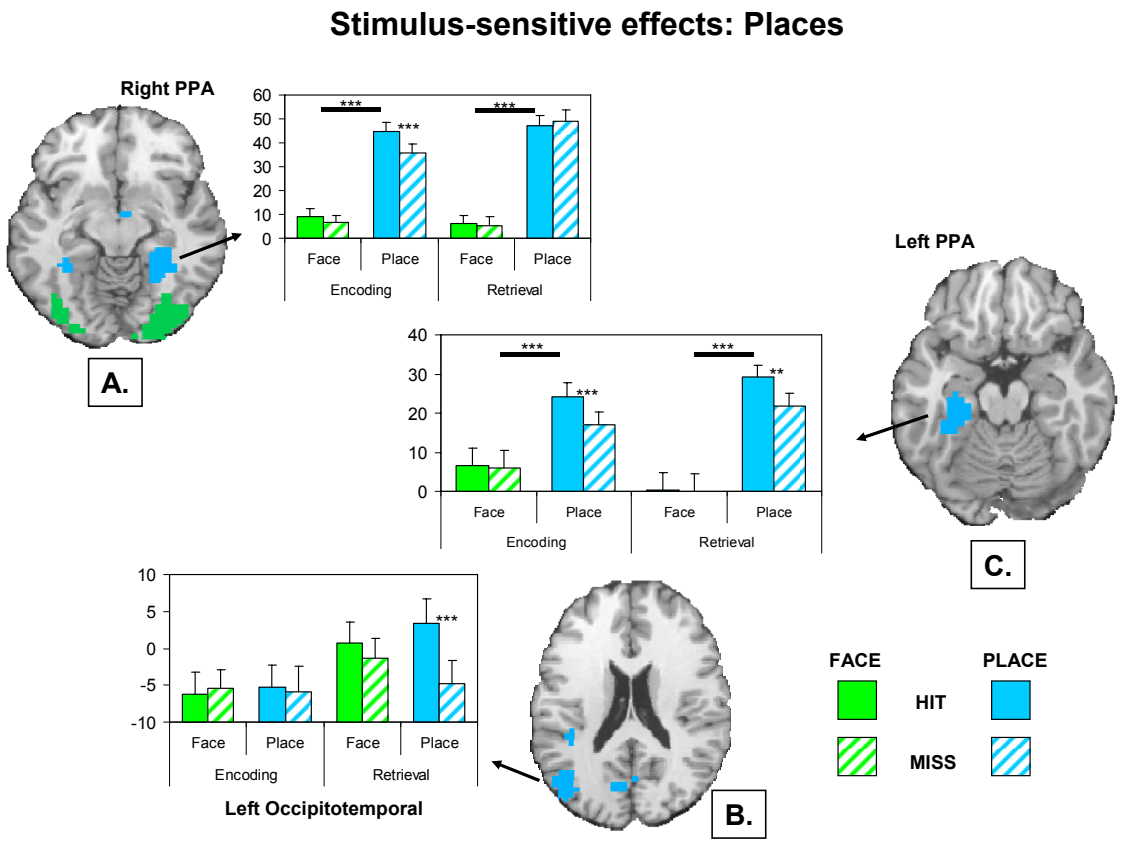

Figure 2. Place vs. Face

Brain regions showing effects of stimulus (place vs. face). A. Right Parahippocampal Place Area (PPA), B. Left occipitotemporal cortex, and C. Left Parahippocampal Place Area (PPA). Y-axis unit for all graphs is the fMRI effect size (parameter estimate or beta weight with standard error bars). ** = $p < 0.01$, *** = $p < 0.001$. Dark horizontal bars represent ANOVA results for main effect of stimulus.

The right PPA had a significant content x memory interaction at encoding, but only a main effect of content at retrieval. Face Enc activations (Table 3) were located in the posterior occipital lobes, fusiform gyrus, and prefrontal cortex (PFC). The occipital and fusiform regions closely match previously reported coordinates for OFA and FFA, with larger clusters in the right hemisphere (see Figure 3A, 3B, 3C, 3D).

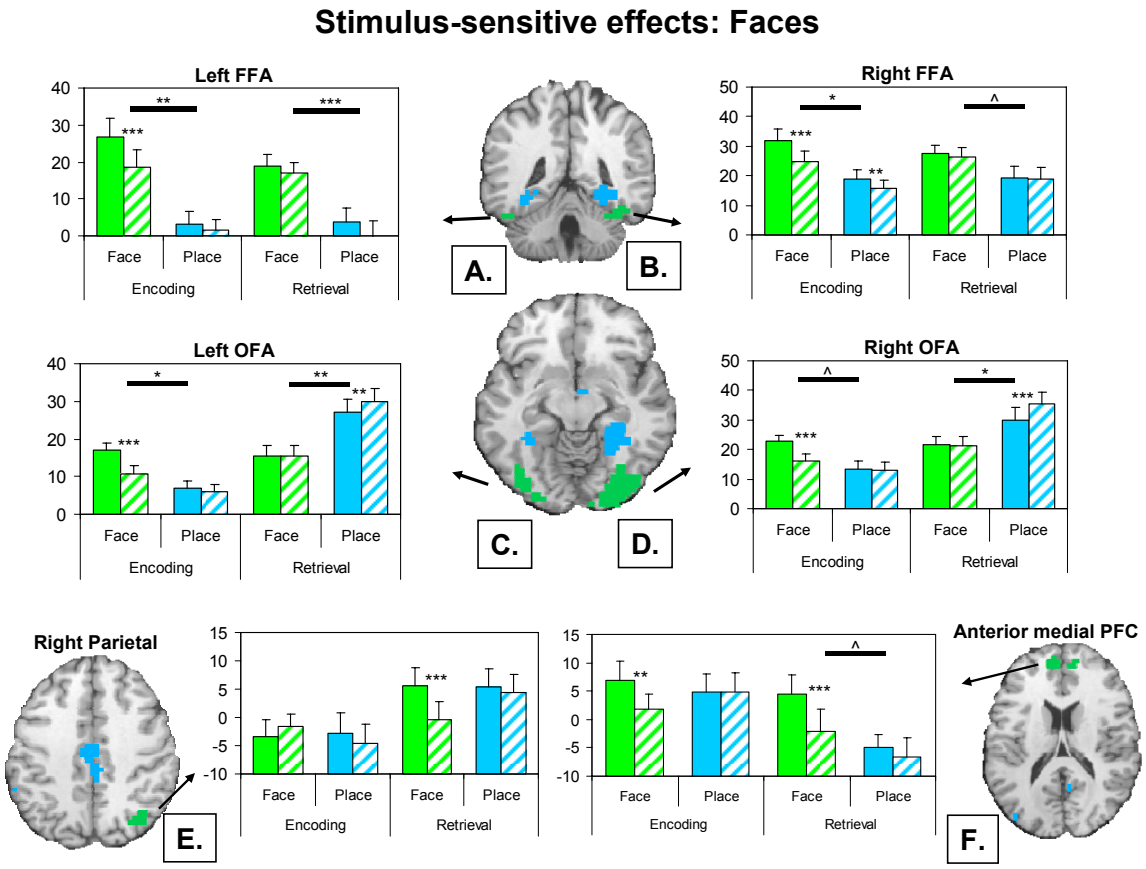

Figure 3. Face vs. Place

Brain regions showing effects of stimulus (face vs. place). A. Left Fusiform Face Area (FFA) and B. Right FFA,.C. Left Occipital Face Area (OFA) and D. Right OFA, E. Right parietal cortex, and F. Anterior medial prefrontal cortex. Y-axis unit for all graphs is the fMRI effect size (parameter estimate or beta weight with standard error bars). ^ = $p < 0.10$, * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$. Dark horizontal bars represent ANOVA results for main effect of stimulus.

Stimulus-sensitive retrieval effects

Place Ret activations (Table 3) were located in occipital, temporal, parietal, prefrontal, and posterior midline cortices. Face Ret activations (Table 3) were located in the right parietal, posterior cingulate and left anterior prefrontal cortices. Thus, occipital, temporal, lateral and midline parietal, and PFC subregions differentially contributed to

successful retrieval based on whether the stimulus was a place or a face (Figures 2B and 3E).

Table 3: Stimulus and Stage Effects

Table 3. Brain Regions showing effects of stimulus and stage

							Memory Success Based Stimulus Effects						
PLACE Enc					TAL			**ESA**			RSA		**ESA>RSA**
Region	BA	voxels	H	x	y	z	Face	**Place**	**PvsF**	Face	Place	PvsF	**Place**
parahippocampus (PPA)	37\36	86	R	29	-41	-8	1.32	**4.67**	**2.95**	0.80	-1.11	-1.52	**3.78**
inferior parietal	40\19	41	R	28	-60	41	0.03	**4.06**	**2.52**	1.08	-1.56	-2.07	**3.60**
superior occipital	19	16	R	35	-77	30	1.86	**4.63**	**2.17**	-0.68	1.10	1.29	**2.63**
parahippocampus (PPA)	37\36	14	L	-32	-45	-7	0.90	**3.96**	**2.62**	0.74	0.09	-0.52	**2.16**
somatosensory cortex	4	11	R	12	-28	59	-1.27	**3.52**	**2.85**	-0.58	0.07	0.47	**1.89**
posterior cingulate	30	10	R	17	-57	15	-1.54	**3.26**	**4.27**	0.10	-0.48	-0.49	**2.41**
brainstem\mammillary		7	M	3	-7	-11	1.39	**4.05**	**1.90**	1.43	0.20	-0.91	**2.00**
FACE Enc					TAL			**ESA**			RSA		**ESA>RSA**
Region	BA	voxels	H	x	y	z	**Face**	Place	**FvsP**	Face	Place	FvsP	**Face**
inferior occipital (OFA)	18\19	192	R	31	-83	-3	**4.38**	0.48	**3.24**	0.18	-2.74	**2.44**	**2.62**
		88	L	-35	-84	-3	**4.32**	1.02	**2.54**	0.16	-1.88	**1.57**	**2.47**
anterior medial PFC	10	45	M	3	60	16	**4.26**	-0.31	**3.45**	0.93	0.82	0.03	**2.09**
fusiform (FFA)	37	32	R	40	-47	-18	**4.50**	2.70	**2.17**	0.61	0.21	0.23	**2.77**
	37\36	21	L	-45	-52	-21	**3.98**	1.42	**2.18**	0.94	1.35	-0.80	**2.62**
right inferior PFC	44	15	R	50	12	22	**3.31**	1.24	**2.06**	-0.60	0.48	-0.77	**2.73**
superior PFC	8	5	M	-3	42	48	**4.01**	1.17	**1.62**	0.12	1.51	-1.02	**2.10**
PLACE Ret					TAL			ESA			**RSA**		**RSA>ESA**
Region	BA	voxels	H	x	y	z	Face	Place	PvsF	Face	**Place**	**PvsF**	**Place**
occipitotemporal	19\39	103	L	-44	-70	23	-0.46	0.33	0.62	1.01	**4.24**	**2.58**	**2.91**
posterior cingulate	24\31	51	M	0	-21	41	-2.79	-3.24	0.59	0.73	**4.27**	**2.32**	**5.26**
precuneus	31	39	M	-6	-68	20	-2.15	-2.14	0.50	0.42	**3.80**	**2.32**	**4.02**
lateral temporal	22	24	L	-48	-36	17	-1.65	-0.29	1.15	0.10	**3.57**	**2.54**	**2.43**
parahippocampus	30	18	L	-14	-32	3	0.25	0.26	-0.16	1.07	**3.47**	**2.24**	**2.58**
retrosplenial	29	13	M	-8	-50	11	-1.39	0.81	**1.88**	1.76	**3.30**	**1.82**	**2.74**
lateral temporal	39\22	12	R	55	-56	15	-2.07	-2.18	0.24	-0.45	**3.55**	**2.27**	**3.75**
amygdala\claustrum		11	L	-33	-5	-9	-0.46	0.41	0.56	2.02	**3.68**	**1.99**	**2.29**
dorsolateral PFC	9	9	L	-23	36	30	-0.82	-1.97	-0.68	0.98	**3.85**	**1.89**	**4.26**
lateral parietal	40	6	L	-58	-40	35	-2.83	-2.12	-0.29	0.03	**3.61**	**1.86**	**3.95**
insula	13	5	R	46	-14	-3	-1.42	-1.57	-0.07	-0.65	**3.18**	**2.61**	**3.50**
FACE Ret					TAL			ESA			**RSA**		**RSA>ESA**
Region	BA	voxels	H	x	y	z	Face	Place	FvsP	**Face**	Place	**FvsP**	**Face**
inferior parietal	39\40	25	R	37	-64	40	-0.88	1.36	-1.89	**3.71**	0.61	**2.37**	**2.81**
posterior cingulate	31	12	R	11	-43	33	-2.13	-1.05	-0.83	**3.90**	1.20	**2.28**	**3.94**
anterior lateral PFC	47\10	6	L	-46	42	-4	1.63	0.94	0.38	**4.07**	1.78	**2.06**	**2.20**

Place Enc, Face Enc, Place Ret and Face Ret defined in text, BA, Brodmann's Area, H, Hemisphere, TAL, Talairach & Tournoux, ESA, Encoding Success Activity, RSA, Retrieval Success Activity, P, Place, F, Face, PPA, Parahippocampal place area, OFA, Occipital face area, FFA, Fusiform face area, PFC, Prefrontal cortex. Table lists the center-of-mass and cluster average t-values. t(16): 1.34 = p < 0.10, 1.56 = p < 0.07, 1.75 = p < 0.05, 2.60 = p < 0.01, 2.95 = p < 0.005, 3.73 = p < 0.001, 4.88 = p < 0.0001.

Stimulus-sensitive effects regardless of memory stage

Table 4 and Figures 2C and 3F show effects of stimulus (Face > Place or Place > Face), regardless of memory stage (both ESA and RSA = GSA). The only Face Mem region was in anterior medial PFC (BA 10) (see Figure 3F). Place Mem regions included left PPA (see Figure 2C), left occipital, and right occipitoparietal cortex. Whereas the right PPA showed both stimulus and stage effects (ESA > RSA, see above) the left PPA showed stimulus effects but no stage effects (ESA ≈ RSA). The difference between the two activation patterns is evident when comparing the bar graphs in Figures 2A and 2C. To confirm that this difference was statistically significant, we conducted a 2 (left PPA vs. right PPA) x 2 (face vs. place) x 2 (enc vs. ret) ANOVA on average memory success effects extracted from the left and right PPA clusters. Confirming the dissociation between left and right PPA, this ANOVA yielded a significant 3-way interaction ($p < 0.0001$). Moreover, separate 2 (face vs. place) x 2 (enc vs. ret) ANOVAs showed a significant 2-way interaction in right PPA ($p < 0.001$) but not in left PPA ($p = 0.97$). In sum, whereas right PPA was associated with place encoding but not with place retrieval, left PPA was associated both with place encoding and retrieval.

General Memory Success Regardless of Content or Memory Stage

Table 5 and Figure 4 show effects of memory success, regardless of content (both place and face = General) or memory stage (both ESA and RSA = GSA). The largest General Mem clusters were located in bilateral anterior medial temporal lobes (MTL). The MTL activations in the left hippocampus (see Figure 4A) and right hippocampus (see Figure 4B) included voxels in the amygdala and rhinal cortex. Additional

activations were located in temporal cortex along the ventral visual stream and in PFC. Consistent with previous findings, an MTL region, here including the anterior hippocampus, bilaterally) was associated with successful memory, regardless of content or memory stage.

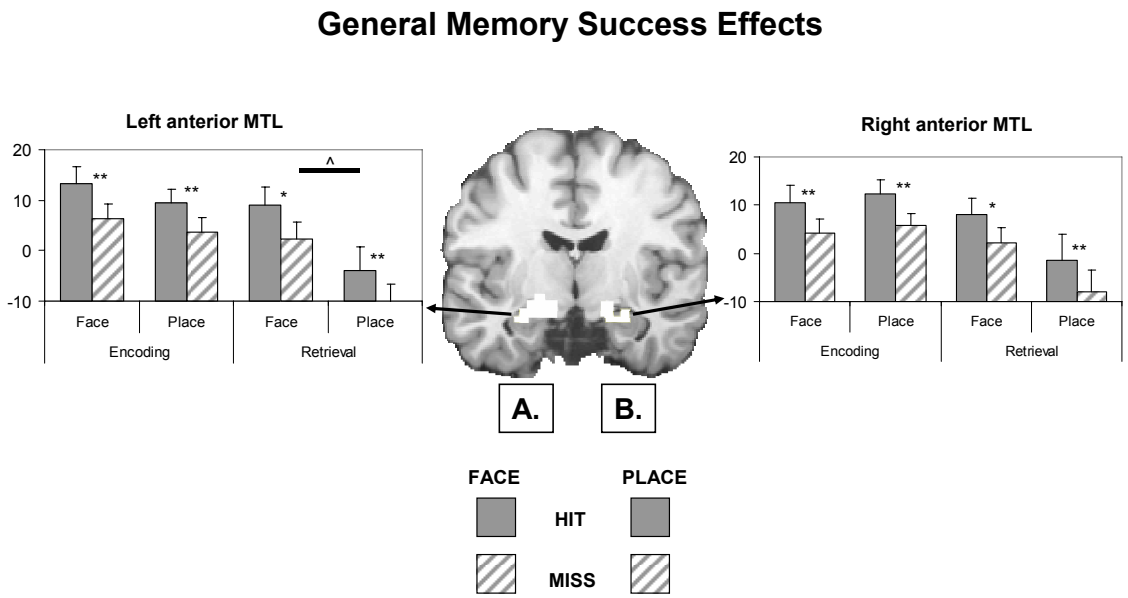

Figure 4. General Memory Success

Brain regions involved in general memory success. A. Left hippocampus, and B. Right hippocampus. Y-axis unit for all graphs is the fMRI effect size (parameter estimate or beta weight with standard error bars). ^ = $p < 0.10$, * = $p < 0.05$, ** = $p < 0.01$. Dark horizontal bars represent ANOVA results for main effect of stimulus.

Table 4: Stimulus Effects Regardless of Stage

Table 4. Brain Regions showing effects of stimulus, regardless of stage

							Memory Success Based Stimulus Effects						
PLACE Mem				TAL			**ESA**			**RSA**			ESA>RSA
Region	BA	voxels	H	x	y	z	Face	**Place**	**PvsF**	Face	**Place**	**PvsF**	Place
parahippocampus (PPA)	36	45	L	-30	-33	-14	0.51	**3.51**	**2.80**	0.40	**2.97**	**2.55**	0.08
mid-occipital	19	9	L	-38	-82	23	-1.07	**2.20**	**2.84**	0.06	**2.65**	**2.98**	-0.68
angular gyrus	19\39	8	R	36	-78	34	-0.66	**3.88**	**3.07**	-1.30	**2.19**	**2.43**	0.97
somatosensory cortex	4	8	L	-20	-28	60	-1.35	**2.24**	**2.16**	0.27	**2.18**	**1.83**	-0.20
precuneus/post. cingulate	23	5	M	8	-57	15	-1.32	**2.31**	**3.37**	0.37	**2.32**	**1.92**	-0.57
FACE Mem				TAL			**ESA**			**RSA**			ESA>RSA
Region	BA	voxels	H	x	y	z	**Face**	Place	**FvsP**	**Face**	Place	**FvsP**	Face
anterior medial PFC	10	18	M	-8	54	13	**2.88**	0.12	**2.34**	**3.30**	0.69	**2.15**	-0.56
anterior medial PFC	10	9	R	12	55	9	**2.73**	-1.52	**3.03**	**2.44**	-0.77	**2.05**	0.41

Place Mem, defined in text, Face Mem, defined in text, BA, Brodmann's Area, H, Hemisphere, TAL, Talairach & Tournoux, ESA, Encoding Success Activity, RSA, Retrieval Success Activity, P, Place, F, Face, L, Left, M, Mid, R, Right, post., posterior, PPA, Parahippocampal place area, PFC, Prefrontal cortex. Table lists the center-of-mass and cluster average t-values.
t(16): 1.34 = $p < 0.10$, 1.56 = $p < 0.07$, 1.75 = $p < 0.05$, 2.60 = $p < 0.01$, 2.95 = $p < 0.005$, 3.73 = $p < 0.001$.

Table 5: General Memory Success

Table 5. Brain Regions showing effects of general memory success, regardless of stimulus or stage

General Mem				TAL			**ESA**			**RSA**			ESA>RSA	ESA>RSA
Region	BA	voxels	H	x	y	z	**Face**	**Place**	FvsP	**Face**	**Place**	FvsP	Face	Place
anterior MTL		20	L	-19	-10	-12	**2.50**	**2.43**	0.24	**2.07**	**2.78**	-0.07	0.06	-0.32
		20	R	19	-11	-12	**2.43**	**2.44**	-0.01	**2.14**	**2.32**	-0.18	0.10	0.04
fusiform	37	11	L	-27	-47	-14	**3.67**	**2.44**	0.26	**2.02**	**2.22**	-0.93	0.59	-0.39
		9	L	-52	-54	-14	**2.79**	**3.08**	0.37	**1.93**	**2.31**	-0.82	0.75	-0.38
medial dorsal frontal	8	8	M	-8	44	41	**3.33**	**2.30**	0.79	**1.96**	**2.04**	0.33	0.05	-0.22
posterior temporal	37	5	R	44	-56	-3	**1.95**	**3.47**	-0.98	**2.15**	**1.94**	-0.03	-0.04	0.90
anterior lateral PFC	47\10	5	L	-48	35	0	**3.37**	**2.07**	0.45	**2.11**	**2.59**	0.01	-0.18	-0.61

General Mem, defined in text, BA, Brodmann's Area, H, Hemisphere, TAL, Talairach & Tournoux, ESA, Encoding Success Activity, RSA, Retrieval Success Activity, P, Place, F, Face, L, Left, M, Mid, R, Right, PFC, Prefrontal cortex, MTL, Medial temporal lobe.
Table lists the center-of-mass and cluster average t-values.
t(16): 1.34 = $p < 0.10$, 1.56 = $p < 0.07$, 1.75 = $p < 0.05$, 2.60 = $p < 0.01$, 2.95 = $p < 0.005$, 3.73 = $p < 0.001$.

Discussion

The overall goals of this study were to tease apart the brain regions contributing to memory success for 1) stimulus-sensitive encoding, 2) stimulus-sensitive retrieval, 3) stimulus-sensitive memory, regardless of memory stage, and 4) general purposes, regardless of content or memory stage. There were four main findings. First, we found regions that are well known for their preference to places versus faces (PPA) and faces versus places (FFA, OFA) to be differentially associated with the successful encoding, but not retrieval, of their relevant stimulus class. Second, other regions in occipital, temporal and parietal cortices were differentially associated with stimulus-sensitive retrieval success, but not encoding. Third, the anterior medial PFC was associated with stimulus-sensitive face memory and the left PPA with stimulus-sensitive place memory, equivalently for encoding and retrieval. Finally, general memory success, regardless of the content or memory stage, was associated with bilateral areas in the anterior MTL, including the hippocampus. These four findings are discussed in separate sections below.

Stimulus-sensitive effects at encoding

Within known stimulus-sensitive cortices, several interesting patterns were observed. In the parahippocampal gyrus, we found evidence for a strong role for the right PPA in place encoding success, confirmed by a 2 x 2 ANOVA of beta values

displaying a highly significant stimulus x stage interaction. The differential involvement of right PPA in encoding may reflect a primary role of this region in enhancing novelty effects associated with perceptual processing of places. It is important to note that this region did not simply "shut down" or lose all association with place processing during retrieval. In fact, the right PPA showed a highly significant place versus face effect in the retrieval ANOVA, but no longer displayed enhanced activation for successful memory trials (retrieval hits versus misses). This suggests that a region can help individuate a particular instance from an ongoing set, at encoding (above and beyond stimulus-sensitivity), and later respond in a stimulus-sensitive manner at retrieval with no mnemonic benefit. In this regard, the right PPA behaved as a module with additional encoding enhancing properties.

Face Enc yielded activations in fusiform and occipital regions, previously referred to as FFA and OFA. This finding again implicates stimulus sensitive cortical regions, not just in perception, but in the successful encoding, of faces. Both the right and left FFA behave as modules, with additional encoding enhancing properties. These regions therefore may help individuate particular faces from the ongoing set during encoding. Like the right PPA, bilateral FFA areas do not "shut down" at retrieval, instead only showing stimulus-sensitivity while not contributing to retrieval success.

Taken together, the results in bilateral FFA and right PPA suggest that stimulus-sensitive brain regions display both automatic (encoding and retrieval stimulus main

effects) and strategic (memory enhancement at encoding) recruitment. Although this idea does not fit with a strict interpretation of the idea that a module should display informational encapsulation (operate without regard to other ongoing brain processes), it merely suggests a modification be made to the most rigid definition of a module, along the lines of what Coltheart (1999) suggests. Studies of working memory that have employed face and place stimuli as distractors during the delay period have shown that active suppression of modular cortices can occur, and can benefit performance when a stimulus from a different class is shown during the delay (Gazzaley, Cooney, McEvoy, Knight, & D'Esposito, 2005). Additional support for the idea of strategic control over modules comes from a recent functional connectivity study (Summerfield et al., 2006) in which the authors found left dorsolateral PFC to potentially mediate top-down control of posterior stimulus-sensitive regions in association with successful encoding.

A large number of Face Enc voxels were found in the so-called OFA, a region some have suggested as being critical for normal face perception. Although it displays strong stimulus-sensitive memory success interactions, in contrast to the FFA, the main effect of stimulus is significant in the reverse direction at retrieval (see figure 3C, 3D). This finding suggests that the OFA is involved in face processing, but perhaps not in an automatic (or modular) manner, solely due to the stimulus. Other researchers have hypothesized that this region plays a role in face feature analysis by way of a feedback mechanism from the fusiform gyrus (Rossion et al., 2003; Steeves et al., 2006). These

ideas suggest that the OFA itself is not a module, but may receive information from specialized regions further along in the visual stream.

The implication of the reversal of content-based memory effects in the OFA is that activity in this region is beneficial to encoding of faces, but detrimental to retrieval of places. Although it is unclear why a region would behave in such a way, a speculative account is that this region actually subserves analysis of fine details within a visual image, which can individuate faces at encoding, but may detract from place retrieval if the focal point within a place is a generic object such as a tree or a door. Additional research is needed to investigate the contribution of this region to both the perception and memory of visual information and the nature of its interactions with other specialized cortical regions. Regardless of the underlying role of the so-called OFA, it does not meet the criteria of a module, because while exhibiting a preference for face content at encoding, this region does not appear to process faces to the exclusion of other content.

Stimulus-sensitive effects at retrieval

Place Ret regions included left occipitotemporal (BA 19/39) and posterior midline cortices. These regions are often implicated in retrieval success and here we find evidence for preferential effects for place stimuli. Face Ret regions included right parietal, posterior midline cortex, and left anterior PFC. Together, these results suggest that commonly reported retrieval success regions can additionally display stimulus-

sensitivity. It is possible that activity in these regions reflects the recruitment of different retrieval strategies for different stimuli. Alternatively, the inherent spatial differences in the stimuli may elicit activity in specific regions in a more automatic manner. However, these regions do not behave in a modular manner based on automatic and consistent stimulus-sensitivity. More research is needed to understand how these regions interact within broader memory networks.

Stimulus-sensitive effects regardless of memory stage

Facilitation of retrieval performance for a particular stimulus may occur by reactivation of regions involved in successful encoding. One prediction would be that sensory regions involved in the initial (and preferential) perception of a stimulus at encoding should also contribute to memory success at encoding as well as retrieval, via reactivation. However, we found that only a subset of regions contributed to both ESA and RSA in a stimulus-sensitive manner. Furthermore, for place memory, a dissociation was found such that the left PPA was associated with Place Mem while the right PPA was associated only with Place Enc. The hemispheric difference is supported by the previously described results of a 2 x 2 x 2 ANOVA performed on individual subject parameter estimates. This lateralization difference fits with ideas from both the object identification/priming literature (Koutstaal et al., 2001; Marsolek, Kosslyn, & Squire, 1992; Marsolek, Schacter, & Nicholas, 1996; Simons, Koutstaal, Prince, Wagner, & Schacter, 2003) and the episodic memory literature (Burgess, Maguire, & O'Keefe, 2002;

Garoff, Slotnick, & Schacter, 2005; Maguire et al., 1998) regarding the contribution of the right hemisphere to form-specific visual details as compared to the left hemisphere contribution to more abstract (gist-based) or episodic details. The current results suggest that while successful encoding of places may rely on both specific and general information, stage-independent successful memory for places may rely on abstract or episodic information to a greater extent. The left lateralized PPA effects may also indicate the use of a semantic label that would serve to benefit both encoding and retrieval success.

Face Mem was associated with anterior medial PFC (BA 10). This region has previously been shown to respond more strongly to upright versus inverted faces (Epstein, Higgins, Parker, Aguirre, & Cooperman, 2006), suggesting a role in processing configural information. It has also been found to respond more strongly to famous versus novel faces(Leveroni et al., 2000). A parsimonious supposition is that this region may respond to the *gestalt* of a face, rather than particular features within the face, thereby providing a holistic representation, greater than the sum of the parts. Such a representation should be more available in upright versus inverted and famous versus novel faces, as well as benefit encoding and retrieval by establishing a gist-based trace. Adjacent to this region is another cluster that only enhanced encoding success (Table 3). This suggests that only a subset of a larger area that contributes to encoding is involved (or reactivated) at retrieval. The proximity of this region of BA 10 to the skull may make

it a suitable candidate for more direct testing of these ideas in future studies using transcranial magnetic stimulation.

Conclusions

This study investigated the contribution of different brain regions to memory success that further displayed: 1) stimulus-sensitive effects at encoding, 2) stimulus-sensitive effects at retrieval, 3) stimulus-sensitive effects regardless of memory stage, and 4) general memory success effects, regardless of content or memory stage. The main findings were as follows: 1) many place and face preferential regions played a greater role in the successful encoding of those stimuli, 2) stimulus-sensitive retrieval effects were found in regions typically associated with retrieval success, 3) stimulus-sensitive success effects of a general nature were found in anterior medial PFC and left PPA for faces and places, respectively, and 4) general success effects, independent of content or memory stage were found in bilateral anterior MTL, including the hippocampus.

Taken together, these results implicate modular regions in the successful encoding (FFA and right PPA) or successful encoding and retrieval (left PPA) of their specific content-preference and further suggest that the OFA does not meet the criteria for a module. Parietal cortex and occipitotemporal regions were associated with stimulus-sensitive retrieval success but not enhanced encoding, suggesting unique influences of content by memory stage. However, another mechanism whereby retrieval may be enhanced is by reactivation of areas that initially process particular sensory

representations (L. Nyberg, R. Habib, A. R. McIntosh, & E. Tulving, 2000; Wheeler, Petersen , & Buckner, 2000). In this study, regions including the left PPA and anterior medial PFC displayed activity patterns consistent with the notion of reactivation. Finally, basic and fundamental memory processes, such as those subserved by the hippocampus and other MTL regions, may dictate situational demands or set the 'neural context'. Future research into consolidation effects on memory and the timing and requirements of retrieval tests should help to clarify the interactions between content-independent and stimulus-sensitive regions.

In summary, this experiment showed place and face sensitive cortical regions to be associated not only with the perception, but also successful memory of these content classes. These regions help to individuate visual information in a stimulus-sensitive manner. We found evidence for regions contributing to detail-level (right PPA, bilateral FFA) as well as gist-based (left PPA, anterior medial PFC) processing of place and face content. We argue that many modular regions display additional activity above and beyond perceptual identification, and therefore are engaged in more than simply automatic responses to particular content classes. To our knowledge, this is the first study to directly compare, within subjects, encoding and retrieval success for place and face content. By directly comparing content classes and memory stages, this study further clarifies how and when specific brain regions contribute to memory success.

4. Item and Relational Memory Success

Introduction

Item memory (IM) is typically described as recognition of a single stimulus whereas relational memory (RM) refers to a bound representation of an item to some type of contextual information (for review, see Davachi, 2006). Although a topic of debate, studies of animal and human patient lesion groups suggest that subregions within the medial temporal lobes (MTL, rhinal cortex versus hippocampus) may play differential roles in IM and RM, respectively (Aggleton & Brown, 1999; Brown & Aggleton, 2001; Mayes et al., 2001). According to Aggleton and Brown (1999), there are two different and potentially separable systems underlying memory impairment seen in amnesia; a perirhinal-medial dorsal thalamic system that mediates familiarity-based item recognition and a hippocampal-anterior thalamic system that mediates recollection. In patient populations and animal lesion studies, it is difficult to assess whether these systems are required for successful encoding or retrieval, or both.

Event-related functional neuroimaging affords an opportunity to test, within subjects, which regions are associated with mnemonic success at a particular memory stage. Brain activity associated with the encoding and retrieval of IM and RM has been investigated using a variety of tasks involving objects, words, spatial arrangements, colors, face-name pairs, etc. (Achim & Lepage, 2005; Davachi, Mitchell, & Wagner, 2003;

Davachi & Wagner, 2002; Kirwan & Stark, 2004; Kohler, Danckert, Gati, & Menon, 2005; S. E. Prince, Daselaar, & Cabeza, 2005; Staresina & Davachi, 2006; Stark & Squire, 2000, , 2001; Uncapher, Otten, & Rugg, 2006). For the most part, functional neuroimaging studies of IM and RM have focused on one particular memory stage (but see Achim and Lepage, 2005). Additionally, most studies investigating RM use the same two to four sources (spatial locations, colors, encoding tasks) for all stimuli shown. These designs facilitate showing only the item at retrieval and having the subject respond, for example, with the choices old-source A, old-source B, or new. However, in addition to potentially not capturing the full complexity of RM, these procedures rely on the use of recall tests for RM and recognition tests for IM. Furthermore, at retrieval, experiments that do use recognition tests (and unique sources) for RM have either compared hits to correct rejections in characterizing retrieval success (Stark & Squire, 2000, , 2001), or considered intact trials classified as intact to be RM and intact trials classified as recombined to be IM (Kirwan & Stark, 2004; S. E. Prince, Daselaar, & Cabeza, 2005). Both approaches may have problems based on findings of MTL involvement in processing novel stimuli (for a review, see Ranganath & Rainer, 2003) or novel relations (Kohler, Danckert, Gati, & Menon, 2005) and questions about whether associative recognition paradigms can verify that IM is fully intact when RM fails.

Regarding the role of rhinal cortex and hippocampus in IM versus RM, the evidence is equivocal. Some studies find different MTL regions to contribute to IM and

RM (Davachi, Mitchell, & Wagner, 2003; Davachi & Wagner, 2002; Staresina & Davachi, 2006; Uncapher, Otten, & Rugg, 2006) whereas others found equivalent roles in IM and RM (Stark & Squire, 2000, , 2001) or RM to be associated with broad regions across the entire MTL (Kirwan & Stark, 2004). We previously reported a fundamental role for the hippocampus in RM, based on a quadruple conjunction performed on encoding and retrieval success for semantic and perceptual associations (Prince et al., 2005). One goal of the present study was to investigate RM with direct contrasts to IM, to more rigorously test relational (e.g. Cohen et al., 1999; e.g. Eichenbaum, Otto, & Cohen, 1994) compared to unitary (e.g. Squire, Stark, & Clark, 2004) theories of the MTL. While MTL subregions may drive successful RM versus IM at both encoding and retrieval, it is also possible that that such specialization occurs only at a specific memory phase, or that overall MTL involvement is equivalent for IM and RM.

The current study, using an event-related design, investigates memory success for an IM condition, an RM condition, and across both conditions, at encoding and retrieval. Based on findings in the literature, we expected that MTL subregions might differentially be involved in IM versus RM conditions. However, regions outside of the MTL (including parietal and prefrontal cortex and the thalamus) might also differentiate IM from RM. General encoding was predicted to recruit regions previously found in studies of the subsequent memory effect (e.g. Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998; Wagner et al., 1998) including PFC and fusiform/parahippocampus, while

retrieval was predicted to recruit regions previously found in studies of retrieval success (e.g. Eldridge, Knowlton, Furmanski, Bookheimer, & Engel, 2000; Shannon & Buckner, 2004) including the hippocampus and parietal cortex.

Methods

Subjects

Nineteen right-handed participants (10 females), all students at Duke University, with an average age of 22.7 years (SD = 4.1) were scanned and paid for their participation. Data from three participants were excluded, one due to equipment malfunction and two due to inadequate behavioral performance (overall response rate less than two-thirds). Written informed consent was obtained for each participant and the study met all criteria for approval of the Duke University Institutional Review Board.

Condition materials

The stimuli consisted of 144 photographs of scenes, 144 photographs of faces, and 144 photographs of face-scene pairs. The scene photos consisted of common indoor (50%) and outdoor (50%) environments, which were obtained from an online database (http://www.corbis.com) and set to a standard size of 576 x 432. Face photos with neutral emotional expressions were obtained, with permission, from an online database (http://agingmind.cns.uiuc.edu/facedb) and represent the age spectrum from young

adults to older adults as well as different racial groups (Minear & Park, 2004). Face-scene pairs were pseudorandomly created and assembled using Matlab (Mathworks, Natick, MA) software.

Procedures

Using event-related fMRI, we scanned the encoding and retrieval memory stages for various condition types. The study was completed in one session and consisted of two scene, three face, and three face-scene pair (relational) runs for encoding and the same number of runs for retrieval. Overall run order was fixed based on pilot testing designed to elicit equivalent performance across tasks. Trial timing during encoding and retrieval was also determined by pilot testing to equate performance. Scene encoding trials were 1475 milliseconds (ms) and face encoding trials were 2475ms in duration, both followed by a variable jitter ranging from 1275 to 1775ms (mean jitter length was 1525ms). Relational encoding trials as well as retrieval trials in all conditions were 3000ms in duration, followed by a variable jitter ranging from 1500ms to 2500ms (mean jitter length was 2000ms). Participants were encouraged to respond within the allotted period. The total number of old study trials was 108, yielding a potential total of 108 encoding trials and 108 retrieval trials per condition. Additionally, 36 new trials (or recombinations for the relational task), per condition, were included during retrieval.

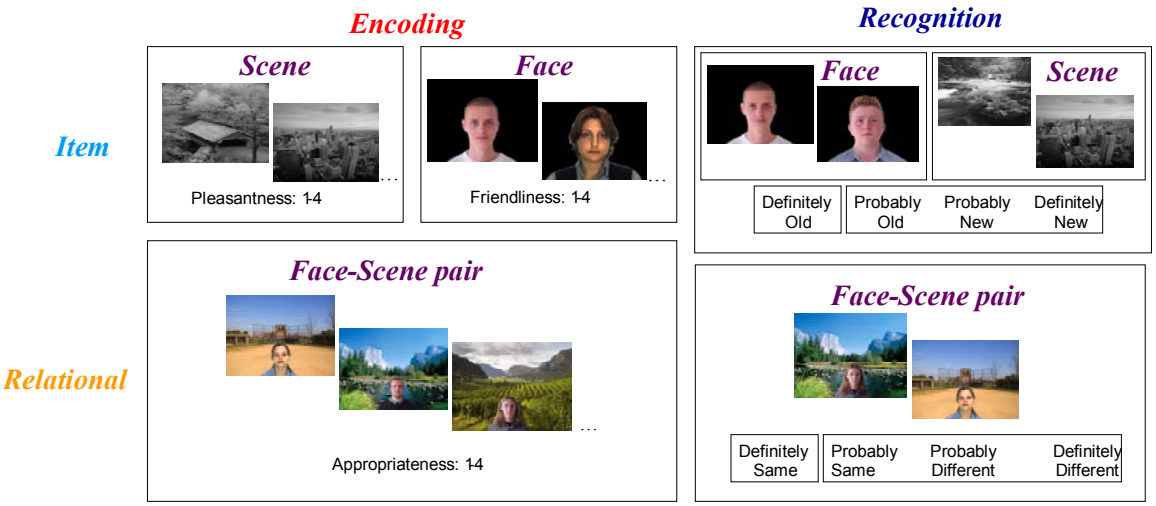

Figure 1. Behavioral Paradigm

Examples of stimuli shown during item (scene and face) and relational (face-scene pair) encoding and retrieval trials. Response options were not shown during the experiment and retrieval responses are grouped to illustrate trials that were used for hit (Definitely Old/Same) versus miss (all other responses) comparisons. All trials were separated in time with a fixation cross (not shown) of varying duration.

The behavioral paradigm is illustrated in Figure 1. Participants were scanned while encoding and then retrieving individual scenes (item), individual faces (item), and face-scene pairs (relational). Of note, IM trials included the separately presented (but unique) components of RM trials, thereby providing good control. Additionally, assignment of faces and scenes to IM and RM conditions was counterbalanced across subjects. For encoding trials, participants rated either the pleasantness of a place, the friendliness of a face, or the appropriateness (fit) of a face-scene pair, on a 1-4 scale (finger order was counterbalanced across participants) while learning the information (intentional encoding). For item retrieval trials, participants made a combined old/new

distinction and confidence level response (definitely old, probably old, probably new, or definitely new) and for relational retrieval trials, participants made a combined associative recognition distinction and confidence level response (definitely same, probably same, probably different, or definitely different). Button responses for retrieval trials were also counterbalanced across subjects.

In both the item and relational conditions, we calculated subsequently remembered versus subsequently forgotten subtractions during encoding (Dm effect, Wagner et al., 1998; Brewer et al., 1998), referred to here as Encoding Success Activity (ESA), and hit versus miss subtractions during retrieval, referred to here as Retrieval Success Activity (RSA). Additionally, ESA and RSA were calculated across all trials to use in identifying encoding and retrieval effects regardless of condition.

Scanning & Image Processing

Images were collected from a 4T GE scanner. Scanner noise was reduced with ear plugs and head motion was reduced with foam pads and headbands. Stimuli were presented with LCD goggles (Resonance Technology, Inc.), and behavioral responses were recorded with a 4-key fiber-optic response box (Resonance Technology, Inc.). Anatomical scanning started with a T1-weighted sagittal localizer series. The anterior (AC) and posterior commissures (PC) were identified in the mid-sagittal slice, and 34 contiguous oblique slices were prescribed parallel to the AC-PC plane. High-resolution T1-weighted structural images were acquired with a 450-ms repetition time (TR), a 9-ms

echo time (TE), a 24-cm field of view (FOV), a 256^2 matrix, and a slice thickness of 1.9-mm. Functional scanning employed an inverse spiral sequence with a 1500-ms TR, a 31-ms TE, a 24-cm FOV, a 64^2 image matrix, and a 60° flip angle. Thirty-four contiguous slices were acquired with the same slice prescription as the anatomical images. Slice thickness was 3.75-mm, resulting in cubic 3.75-mm^3 isotropic voxels.

Data were processed using SPM2 (Statistical Parametric Mapping; Wellcome Department of Cognitive Neurology, http://www.fil.ion.ucl.ac.uk/spm). The first six volumes were discarded to allow for scanner equilibration. Time-series were then corrected for differences in slice acquisition times, and realigned. Functional images were spatially normalized to a standard stereotactic space, using the Montreal Neurological Institute (MNI) templates implemented in SPM2 and resliced to a resolution of 3.75 mm^3. The coordinates were later converted to Talairach and Tournoux's space (Talairach & Tournoux, 1988) for reporting in tables. Finally, the volumes were spatially smoothed using an 8-mm isotropic Gaussian kernel and proportionally scaled to the whole-brain signal.

fMRI analyses

For each subject, trial-related activity was assessed by convolving a vector of the onset times of the stimuli with a synthetic hemodynamic response function. The general linear model, as implemented in SPM2, was used to model the effects of interest and other confounding effects (e.g., head movement and magnetic field drift). Statistical

Parametric Maps were identified for each participant by applying linear contrasts to the parameter estimates (beta weights) for the events of interest, resulting in a t-statistic for every voxel. In both conditions, we coded four trial types: subsequent hits, subsequent misses, retrieval hits, and retrieval misses. The mean number of trials contributing to each trial type in the design was 51.7 (standard deviation = 18.1). Subsequent hit trials were determined by matching the high-confidence retrieval hit responses at test to the corresponding trials at study. Similar to other subsequent memory studies, only high-confidence retrieval hits were considered subsequent hits and all other trials were modeled as subsequent misses (Otten, Quayle, Akram, Ditewig, & Rugg, 2006; Schon, Hasselmo, Lopresti, Tricarico, & Stern, 2004).

Analyses were first conducted based on comparisons of IM and RM at encoding and retrieval. To isolate each condition effect, we identified areas showing the primary effect, in which the memory success based contrast of interest (Item ESA, Relational ESA, Item RSA, or Relational RSA) was set at a threshold of $p < 0.001$ and extent threshold of two voxels. Direct comparison secondary contrasts were then used as inclusive masks and these double subtraction contrasts were set at a threshold of $p < 0.05$. For example, Item Enc is comprised of Item ESA (subsequent hit > subsequent miss, $p < 0.001$), inclusively masked with the condition comparison (Item ESA > Relational ESA, $p < 0.05$). The same logic applies for all reported condition effects.

In order to identify stimulus independent memory phase success, regardless of condition, the contrast of interest (ESA or RSA) was set at a threshold of $p < 0.001$. To verify that the effect was significant in each condition, inclusive masks were applied at $p < 0.05$. To verify that the effect was not greater in one condition versus another, exclusive masks were applied at $p < 0.05$. For example encoding success was calculated in an overall contrast of subsequent hit > subsequent miss at $p < 0.001$. This contrast map was then inclusively masked with Item ESA and Relational ESA (each at $p < 0.05$) and exclusively masked with Item ESA > Relational ESA and Relational ESA > Item ESA (each at $p < 0.05$). The same logic applies for calculating the overall retrieval success effect.

Results

Behavioral data

Table 1 lists the proportion of high and low confidence responses for correct (hit, correct rejection) and incorrect (miss, false alarm) item and relational trials. There was no significant difference ($p = 0.91$) between the proportion of high confidence hit responses for items versus relations. Confidence had a strong effect on accuracy for old items, with 91.7 percent accuracy for high confidence responses, but only 62.0 percent accuracy for low confidence responses. T-tests performed on reaction time data for item versus relational high confidence hits revealed significant differences at both encoding

($p < 0.001$) and retrieval ($p < 0.001$). Given that relational trials combined the same information present in two separate item trials, this difference is not surprising.

Table 1: Behavioral Performance

Table 1. Behavioral results: mean proportion of responses and RTs in milliseconds

		Hi Confidence	Lo Confidence	Total	Hi Confidence	Lo Confidence	Total
Old Trials		Hits			Misses		
Item		0.55	0.23	0.78	0.06	0.16	0.22
	Encoding RTs	1617	1604		1642	1587	
	Retrieval RTs	1529	2206		1981	2315	
Relational		0.56	0.26	0.82	0.04	0.14	0.18
	Encoding RTs	2284	2242		2269	2382	
	Retrieval RTs	1646	2366		2415	2537	
New Trials		Correct Rejections			False Alarms		
Item		0.44	0.39	0.83	0.05	0.12	0.17
Relational		0.53	0.29	0.82	0.07	0.10	0.17

fMRI data

Table 2 lists regions according to condition effects of interest (Item encoding, Relational encoding, Item retrieval, and Relational retrieval). t-values are reported for the direct contrast between conditions and the individual item and relational effects. Columns displayed in bold text highlight the t-values of the individual effect of interest within the conjunction. Table 3 lists regions according to memory phase effects (encoding success and retrieval success). The t-value is reported for the encoding effect, the retrieval effect, and the direct contrast between encoding success and retrieval success.

Table 2: Condition Effects at Encoding and Retrieval

Table 2. Brain regions showing condition effects at encoding and retrieval

Item Enc			TAL					
Region	BA	Hemi	x	y	z	**Item vs Rel**	**Item**	Rel
rhinal cortex	35\36	L	-26	-5	-28	**3.17**	**4.58**	-0.99
occipitotemporal	19\37	L	-45	-58	-4	**2.65**	**8.11**	0.79
mid-occipital	18\19	R	38	-91	1	**2.23**	**7.58**	0.46
occipitotemporal	37\20	R	49	-55	-7	**2.15**	**6.79**	0.69
parahippocampal cortex	36	R	38	-30	-14	**1.97**	**5.38**	0.21
mid-occipital	18\19	L	-38	-88	-2	**1.92**	**6.56**	1.37
amygdala		L	-19	-8	-12	**1.78**	**4.81**	-0.28
brainstem		M	4	-8	-9	**1.78**	**6.32**	-0.33

Relational Enc			TAL					
Region	BA	Hemi	x	y	z	**Rel vs Item**	Item	**Rel**
superior frontal	8	R	34	28	47	**5.78**	-2.07	**4.90**
thalamus (ventral anterior)		L	-11	0	7	**3.16**	-0.17	**4.07**
occipito-temporal parietal	19\39	R	38	-68	25	**2.29**	1.40	**4.05**
cerebellum		R	19	-85	-31	**2.24**	1.25	**3.87**
inferior PFC	45	L	-38	19	17	**2.12**	1.31	**4.19**
cerebellum		R	41	-52	-20	**2.07**	4.95	**5.06**
fusiform	37	L	-45	-38	-17	**1.91**	2.54	**5.96**
medial superior PFC	9	M	-8	49	36	**1.78**	2.21	**5.48**

Item Ret			TAL					
Region	BA	Hemi	x	y	z	**Item vs Rel**	**Item**	Rel
occipitotemporal	37\20	R	48	-55	-7	**4.13**	**4.68**	-0.47
anterior lateral PFC	10	L	-45	40	1	**3.72**	**5.76**	0.30
precuneus	31	M	-4	-64	24	**2.83**	**4.76**	-0.18
dorsolateral PFC	9	L	-26	27	37	**2.71**	**4.47**	0.24
inferior parietal	19\39	L	-41	-71	35	**2.26**	**4.67**	0.54
posterior cingulate	24	M	-4	-35	33	**1.91**	**4.03**	1.37
posterior cingulate	31	M	7	-46	34	**1.79**	**3.93**	0.47

Relational Ret			TAL					
Region	BA	Hemi	x	y	z	**Rel vs Item**	Item	**Rel**
medial PFC	24\32\10	M	0	47	-6	**4.49**	2.20	**5.72**
anterior dorsal PFC	9	L	-22	53	32	**3.60**	1.75	**5.98**
medial PFC	10	M	0	58	4	**3.14**	2.37	**6.21**
superior parietal	7	R	7	-48	65	**2.77**	0.07	**4.26**
hippocampus		L	-30	-26	-8	**2.70**	3.14	**4.39**
claustrum		L	-33	0	7	**2.57**	1.20	**5.78**
insula		L	-37	-15	-6	**2.23**	3.72	**7.51**
lateral temporal	39	L	-52	-65	14	**1.98**	4.72	**5.73**
lateral temporal	37\21	R	52	-58	3	**1.83**	2.61	**3.98**

BA, Brodmann's Area, Hemi, Hemisphere, TAL, Talairach & Tournoux (1988) coordinates, PFC, Prefrontal cortex. t(16): 1.75 = $p < 0.05$, 2.60 = $p < 0.01$, 2.95 = $p < 0.005$, 3.73 = $p < 0.001$, 4.88 = $p < 0.0001$, 6.11 = $p < 0.00001$, 7.46 = $p < 0.000001$.

Memory Type Effects at Encoding

Item encoding versus Relational encoding activations were located in rhinal, occipitotemporal and occipital cortices. Relational encoding versus Item encoding activations were located in frontal and thalamic (ventral anterior nucleus) regions and at the border of occipital, temporal and parietal cortex.

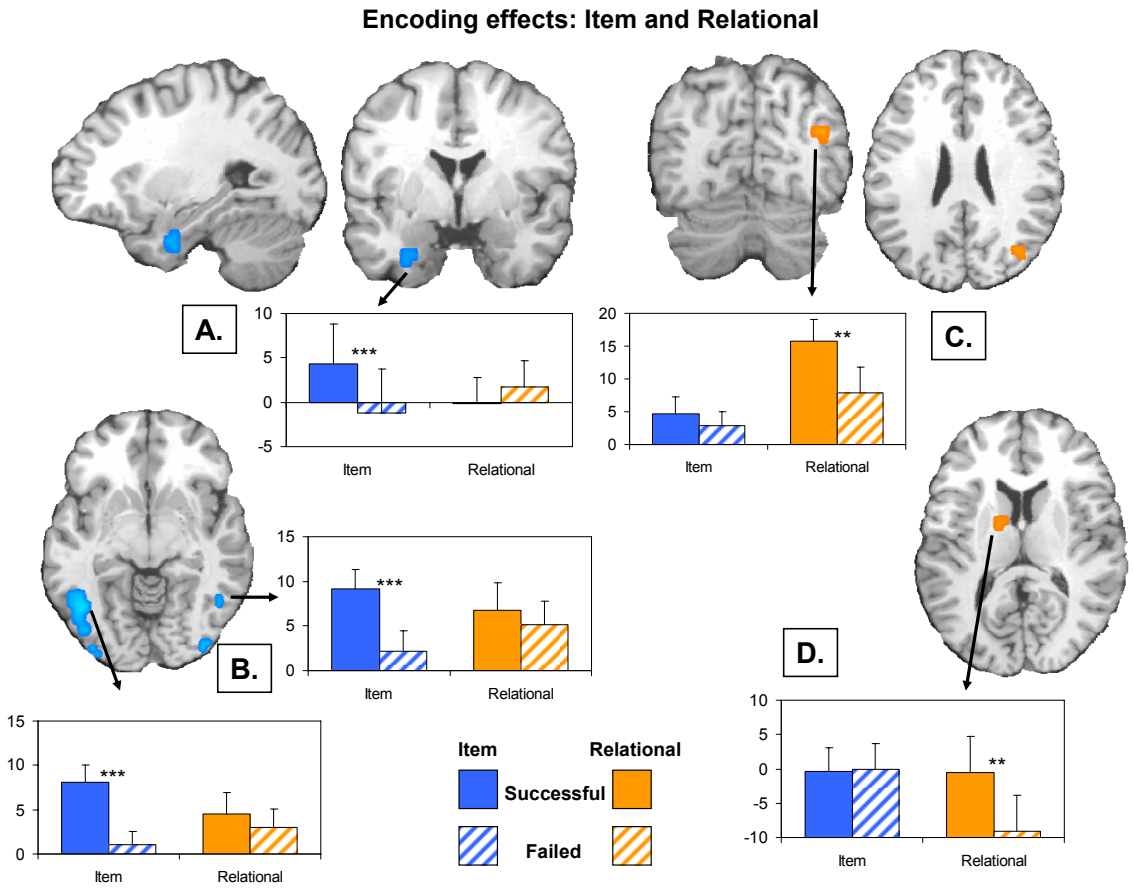

Figure 2. Item and Relational Encoding

Brain regions involved specifically in encoding of item or relational information. A. Left rhinal cortex, B. Bilateral occipitotemporal cortex, C. Right occipitotemporal-parietal junction and D. Anterior thalamus. Y-axis unit for all graphs is the fMRI effect size (arbitrary units) for trials versus baseline. Significance of paired t-test of effect sizes is shown between bars, ** = $p < 0.01$, *** = $p < 0.001$. Rem, Subsequently remembered, Forg, Subsequently forgotten, Rel, Relational.

Memory Type Effects at Retrieval

Item retrieval versus Relational retrieval activations were located in occipitotemporal, left prefrontal and parietal cortices. Relational retrieval versus Item retrieval activations were located in medial and dorsal prefrontal , subcortical regions in the left hemisphere, bilateral lateral temporal regions and the left hippocampus.

Phase Effects Independent of Memory Type

Encoding success activations included bilateral fusiform gyrus (extending into the parahippocampal gyrus), bilateral inferior prefrontal cortex (PFC), right lateral temporal and occipital cortices, and bilateral substantia nigra. In all but four of the listed regions, the direct comparison to retrieval success was significant at $p < 0.05$. These included the bilateral substantia nigra (which had subthreshold retrieval success effects) and two midline superior frontal regions (which had significant retrieval success effects at $p < 0.05$).

Retrieval success activations included bilateral posterior temporal cortices, bilateral hippocampus, anterior and left dorsolateral PFC, right amygdala, posterior cingulate and insular cortex. In all but two of the listed regions, the direct comparison to encoding success was significant at $p < 0.05$. These regions were the left fusiform (which had a significant encoding success effect at $p < 0.001$) and right amygdala (which had a

subthreshold encoding success effect). Furthermore, four regions displayed significantly negative encoding success effects (subsequent miss > subsequent hit). These included insular cortices and the posterior cingulate.

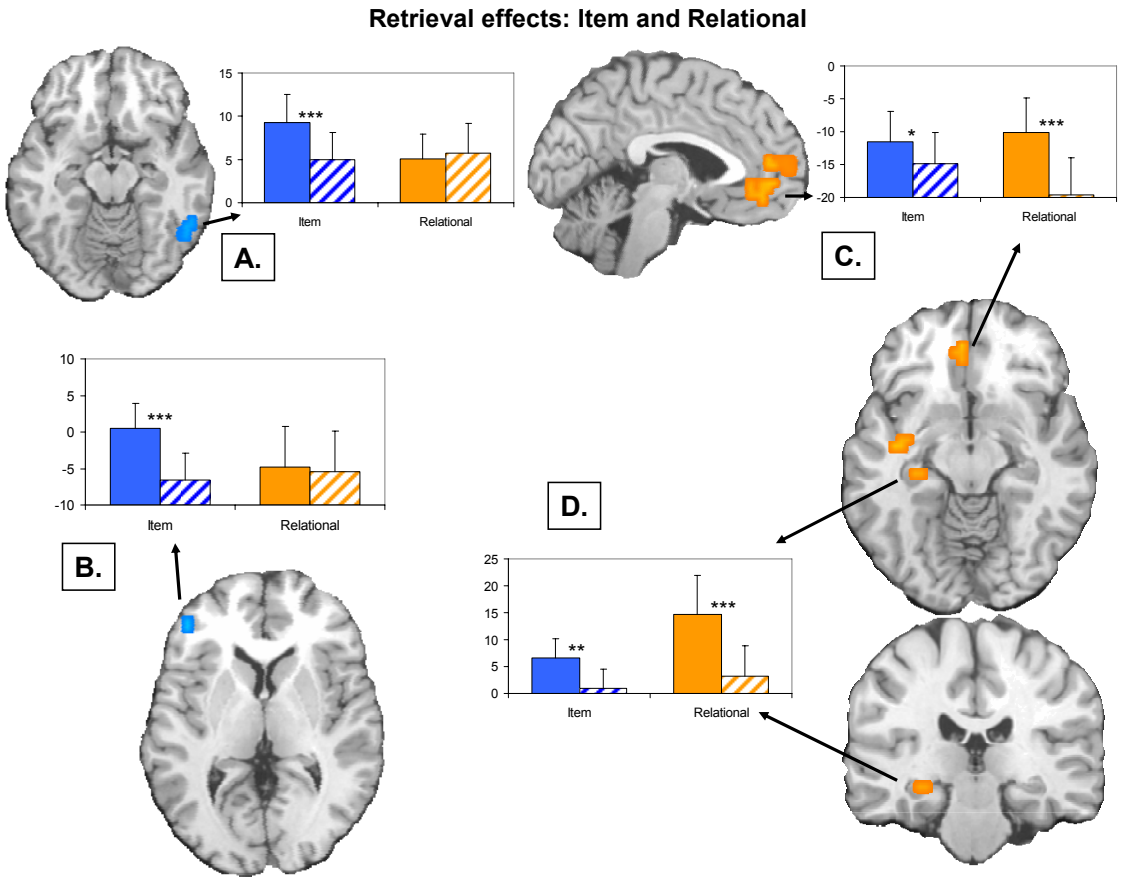

Figure 3. Item and Relational Retrieval

Brain regions involved specifically in retrieval of item or relational information. A. Right occipitotemporal cortex, B. Left anterior lateral PFC, C. Medial prefrontal cortex (PFC), and D. Left hippocampus. Y-axis unit for all graphs is the fMRI effect size (arbitrary units) for trials versus baseline. Significance of paired t-test of effect sizes is shown between bars, * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$. Rem, Subsequently remembered, Forg, Subsequently forgotten, Rel, Relational.

Table 3: General Encoding and Retrieval Success

Table 3. Brain regions showing encoding or retrieval effects, excluding condition

Encoding Success (ESA)			TAL					
Region	BA	Hemi	x	y	z	**ESA**	RSA	**ESA vs RSA**
fusiform	37	R	41	-48	-20	**8.37**	0.95	**2.24**
fusiform	37	L	-45	-48	-17	**7.85**	0.99	**2.50**
inferior PFC	45	R	56	26	16	**6.53**	0.17	**3.67**
lateral occipital	19	R	48	-73	-6	**5.64**	1.17	**2.48**
inferior PFC	44\45	L	-37	8	21	**5.61**	-0.99	**3.73**
occipital	19	R	33	-83	22	**5.59**	-0.72	**4.00**
occipital	18	R	33	-91	-2	**5.55**	-3.03	**4.47**
superior frontal	9	M	-7	56	25	**5.14**	**1.90**	1.29
inferior PFC	45	L	-48	29	6	**5.11**	0.59	**3.18**
lateral temporal	21	R	56	-52	-13	**4.31**	2.31	**1.89**
superior frontal	8	M	-7	49	40	**3.98**	**1.81**	0.24
substantia nigra		R	11	-15	-9	**3.94**	1.37	1.16
substantia nigra		L	-11	-15	-9	**3.79**	1.41	1.14
occipital	19	L	-33	-86	18	**3.74**	-0.23	**3.44**

Retreival Success (RSA)			TAL					
Region	BA	Hemi	x	y	z	ESA	**RSA**	**RSA vs ESA**
posterior temporal	39	L	-48	-65	14	-0.24	**6.44**	**3.11**
insula		L	-33	-15	-6	-0.68	**5.63**	**2.74**
hippocampus/amygdala		L	-26	-22	-12	0.86	**5.62**	**3.30**
anterior PFC	10	M	-4	58	4	**2.25**	**5.40**	**2.53**
orbitofrontal	11	M	0	43	-12	-0.92	**5.29**	**4.89**
fusiform	37	L	-52	-52	-17	**3.86**	**5.15**	-0.50
hippocampus		R	26	-22	-8	0.71	**5.04**	**2.48**
insula	13	L	-48	-28	19	**-3.87**	**4.46**	**5.21**
posterior temporal	39	R	52	-65	10	1.00	**4.39**	**1.96**
posterior cingulate	31	M	-7	-35	37	**-3.75**	**4.20**	**5.10**
occipitotemporal	37	L	-48	-73	0	0.35	**4.14**	**3.03**
dorsolateral PFC	9	L	-22	49	36	0.66	**4.10**	**2.03**
amygdala		R	19	-8	-9	1.02	**3.94**	0.97
insula/claustrum		L	-41	-8	-9	**-4.21**	**3.94**	**5.11**
insula		L	-37	0	3	**-2.79**	**3.75**	**4.57**

BA, Brodmann's Area, Hemi, Hemisphere, TAL, Talairach & Tournoux (1988) coordinates, PFC, Prefrontal cortex. t(16): 1.75 = $p < 0.05$, 2.60 = $p < 0.01$, 2.95 = $p < 0.005$, 3.73 = $p < 0.001$, 4.88 = $p < 0.0001$, 6.11 = $p < 0.00001$, 7.46 = $p < 0.000001$.

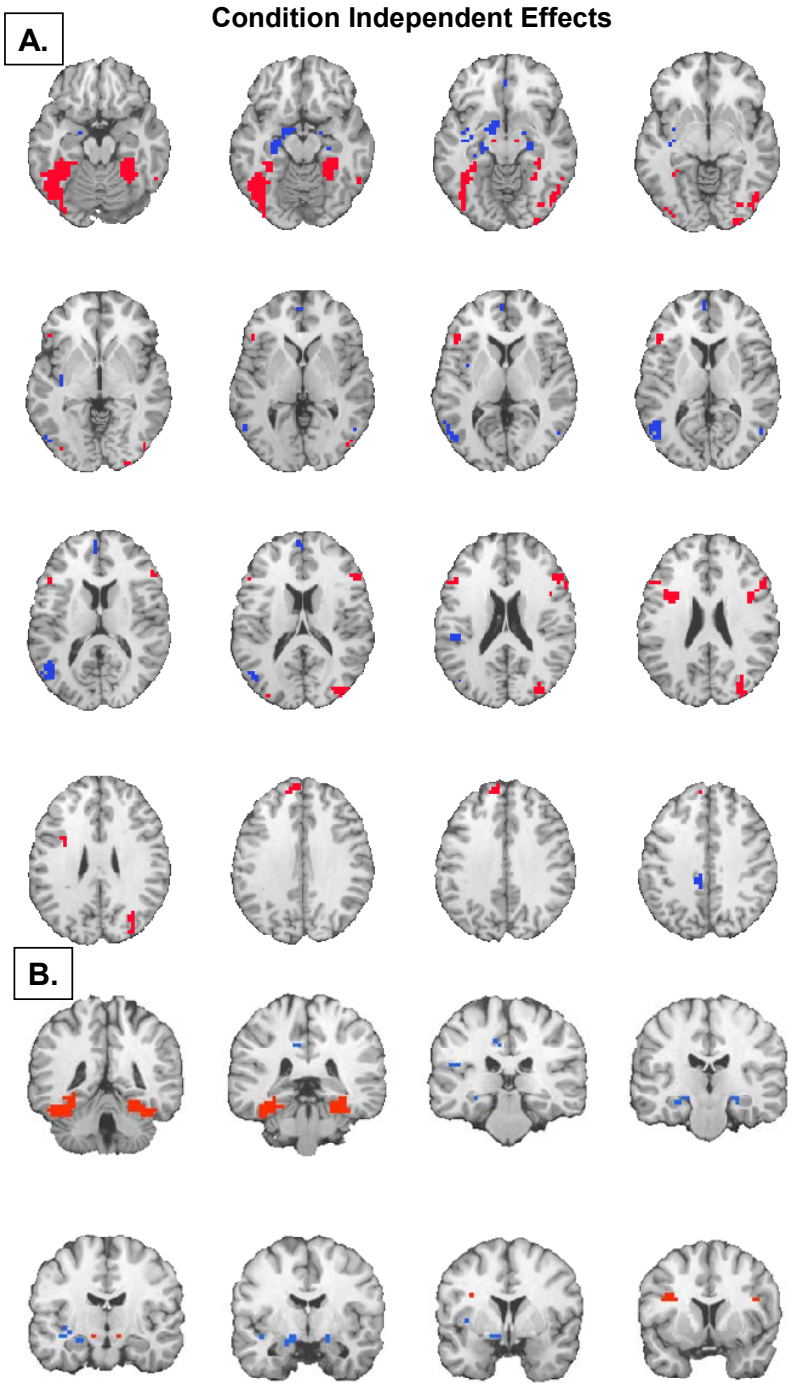

Figure 4. Encoding and Retrieval Success Effects

Brain regions involved in encoding (red) or retrieval (blue), regardless of item or relational condition. A. Axial slice view B. Coronal slice view.

Discussion

The overall goal of this study was to tease apart regions contributing to memory success for IM from those contributing to RM and vice versa at both encoding and retrieval. Theoretical as well as empirical accounts suggest that subregions within the MTL differentially contribute to IM and RM (Aggleton & Brown, 1999; Cohen et al., 1999; Eichenbaum, Otto, & Cohen, 1994), although these are not without dispute (e.g. Squire, Stark, & Clark, 2004). Aggleton & Brown (1999) suggest that two separable systems mediate IM and RM. According to their model, the perirhinal-medial dorsal thalamic system mediates familiarity-based item recognition and a hippocampal-anterior thalamic system mediates recollection. Functional neuroimaging support for this view comes from studies finding differential contribution of perirhinal cortex to IM encoding and of the hippocampus to RM encoding (for a review, see Davachi, 2006). However, in the majority of these studies, encoding trials contain both IM and RM components. This requires subjects to generate the RM information at retrieval as opposed to merely recognizing the item as old for IM. Furthermore, the subsequent memory paradigm has been the most commonly employed technique and therefore studies have focused mainly on the encoding processes supporting IM and RM (but see Eldridge, Knowlton, Furmanski, Bookheimer, & Engel, 2000; Preston, Shrager, Dudukovic, & Gabrieli, 2004). In the current study, we tested memory success at both encoding and retrieval and used a technique where IM and RM were based on unique

stimuli, with forgotten trials serving as a baseline for all comparisons. At retrieval, subjects did not have to generate the correct source or context information, but rather simply verified whether the stimulus pairing was identical to that at encoding or had been recombined. By directly comparing memory success in this RM condition to the IM condition, we created a rigorous test for relational versus non-dichotomous (Unitarian or declarative) accounts of MTL function.

Memory Type Effects at Encoding

While RM encoding did not show differential MTL effects, regions with differential activation, including the right occipitotemporal-parietal junction (see figure 2C) and the ventral anterior thalamus (see figure 2D) are consistent with the general notion of binding operations. Patients with Balint's syndrome display symptoms of impaired visual processing of multiple objects at a time within the same visual field and this is most prominently associated with damage to the right occipito-temporal junction (Rizzo & Vecera, 2002; Robertson, 2003). Furthermore, regions in the parietal cortex have been shown to both bind feature information (Shafritz, Gore, & Marois, 2002) and differentially predict memory for bound features (Uncapher, Otten, & Rugg, 2006). A greater difference for RM encoding success in the anterior thalamus is potentially consistent with the proposal of Aggleton & Brown (1999) regarding the anterior thalamus playing a role in RM. This difference may reflect the attentional components of binding. IM encoding success was differentially associated with left rhinal cortex (see

figure 2A) and bilateral occipitotemporal regions (see figure 2B). Thus, within the ventral visual stream and MTL, subregions display specialization for memory success for individual items.

Memory Type Effects at Retrieval

RM retrieval success was differentially associated with regions in medial PFC (see figure 3C) and left hippocampus (see figure 3D). The bar graphs and table values indicate that IM retrieval success is significant in these regions, but RM retrieval success effects are greater. Medial PFC has been associated with self-referential processing (Cabeza et al., 2004; Gusnard, Akbudak, Shulman, & Raichle, 2001) and is a region typically found to be tonically active during rest and to decrease activity during attention demanding tasks (Raichle et al., 2001). A speculative account for the pattern observed is that subjects may be more apt to forget the details of a previous encounter (RM) when they are further deactivated from the default or self-referential state. The greater hippocampal retrieval success effect is consistent with the idea that subregions within the MTL show specialized processing. However, the fact that IM retrieval is significant suggests that such specialization may be a matter of degree rather than of type.

IM retrieval success effects included left anterior lateral PFC (see figure 3B) and right occipitotemporal cortex (see figure 3A). Activity in lateral PFC has been shown to relate to the ability to organize items and thereby facilitate memory (Bor, Cumming,

Scott, & Owen, 2004). This may be reflected here in a strategic difference between successful IM and RM (which shows a greater reliance on medial PFC) retrieval. The right occipitotemporal region is essentially identical to the IM encoding region (see table 2 and figure 2C), suggesting that reactivation of a specialized IM encoding region can benefit IM retrieval.

General Encoding and Retrieval

Successful encoding, regardless of IM or RM, was associated with large portions of the ventral visual stream, bilateral inferior PFC, and bilateral substantia nigra (see table 3 and figure 4). The substantia nigra, although not commonly highlighted in encoding studies, has recently been found to support episodic encoding in a variety of tasks (Schott et al., 2006; Schott et al., 2004; Wittmann et al., 2005), perhaps by dopaminergic enhancement of consolidation in the MTL. The ventral visual stream (including the fusiform gyrus and parahippocampal gyrus) and inferior PFC regions are similar to those most consistently reported in studies of subsequent memory (Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998; Gutchess et al., 2005; Kirchhoff, Wagner, Maril, & Stern, 2000; Otten, Henson, & Rugg, 2002; S. E. Prince, Daselaar, & Cabeza, 2005; Reber et al., 2002; Wagner et al., 1998; Weis, Klaver, Reul, Elger, & Fernandez, 2004; Wittmann et al., 2005). Enhanced activation in these regions during study predicts better memory performance on a later test, and based on our results, the predictive value at encoding is significantly greater than any memory effect during retrieval. Activity in

these regions may therefore reflect an automatic response to novel information (Kirchhoff, Wagner, Maril, & Stern, 2000; Ranganath & Rainer, 2003), strategic processes associated with encoding (Reber et al., 2002), or some combination of novelty, attention and strategy.

Successful retrieval, regardless of IM or RM, was associated with temporal, parietal, prefrontal, and subcortical regions (see table 3 and figure 4). All but two of the regions had significantly greater retrieval success compared to encoding success effects. The two regions not associated with greater retrieval success were the left fusiform and right amygdala. Together with the results from encoding, this suggests that temporal, frontal, midbrain and MTL regions can contribute to both encoding and retrieval success, which is consistent with previous imaging findings (Daselaar, Veltman, & Witter, 2004; Kahn, Davachi, & Wagner, 2004; Meltzer & Constable, 2005; S. E. Prince, Daselaar, & Cabeza, 2005; Small et al., 2001; Weis, Klaver, Reul, Elger, & Fernandez, 2004). Of note however, was the fact that bilateral hippocampus had a significantly greater retrieval success compared to encoding success effect. Retrieval success effects in the hippocampus are consistent with previous imaging findings (Eldridge, Engel, Zeineh, Bookheimer, & Knowlton, 2005; Eldridge, Knowlton, Furmanski, Bookheimer, & Engel, 2000; S. E. Prince, Daselaar, & Cabeza, 2005; Ranganath, Cohen, Dam, & D'Esposito, 2004) and here we found a relatively anterior region to differentially contribute to retrieval. Although this represents a different pattern from what we

observed in a previous study (S. E. Prince, Daselaar, & Cabeza, 2005), it is possible that the visual (as opposed to verbal) stimuli employed here as memoranda resulted in a shift in the MTL regions supporting memory success (Lepage, Habib, & Tulving, 1998; Schacter & Wagner, 1999). However, the significant negative encoding success effect in the insula and posterior cingulate is consistent with our previous data (Daselaar, Prince, & Cabeza, 2004), and here is extended to encompass retrieval activation patterns. The strong flip in memory success behavior in these regions suggests fundamentally opposite processes. We speculate that this is related to encoding and retrieval relying on external versus internal attentional focus, respectively.

In summary, we investigated brain regions associated with memory success for IM, RM, or regardless of the condition, at both encoding and retrieval. There were four main findings: 1) IM encoding was associated with rhinal cortex and bilateral occipitotemporal cortices, whereas RM encoding was associated with anterior thalamus and the right occipitotemporal-parietal junction, 2) IM was associated with the same right occipitotemporal region and a left anterior lateral PFC region, while RM was associated with medial PFC and left hippocampus, 3) General encoding effects were found, bilaterally, in the ventral visual stream, inferior PFC, and substantia nigra, and 4) General retrieval effects were found, bilaterally, in the hippocampus and amygdala, dorsolateral and anterior PFC, the left insula and posterior cingulate cortex.

The first two findings provide support for the idea that MTL subregions and thalamic nuclei support the specialized processing of distinct memory types. However, because the left hippocampal region that was differentially associated with RM retrieval was also significant for IM retrieval success, it suggests that specialization may be reflected in graded, rather than all-or-none responses. Visual processing regions may also be differentially recruited based on item versus relational task demands. For example, the right occipitotemporal-parietal junction, which was associated with RM encoding, is commonly damaged in patients with Balint's syndrome, suggesting it may play a role in both the perception and memory of spatially overlapping information. A right occipitotemporal region displayed IM effects at both encoding and retrieval, which fits the notion of 'reactivation' of an encoding success region benefiting retrieval. PFC differences for memory type may reflect the importance of self-referential processing and strategic components of retrieval.

General encoding success effects in the present study replicate a consistent pattern of subsequent memory effects in the fusiform gyrus, parahippocampal gyrus, and inferior frontal PFC that has been established across many studies. While the substantia nigra is not a typically reported subsequent memory region, its role in episodic memory has been reported in other studies and may represent a connection between neurotransmitter systems and consolidation processes in memory. Finally,

general retrieval success effects in the present study support a role for distinct MTL, PFC insular and parietal cortices in retrieval, specifically.

Taken together, the findings implicate regions typically associated with sensory processing in the higher cognitive process of successful memory encoding. General encoding success regions, such as inferior PFC, may facilitate these memory benefits by top-down modulation, but further study is warranted to support this claim. Reactivation of encoding success regions benefits retrieval in some situations, but in others, a complete reversal of encoding activation benefits retrieval. Finally, evidence for differential processing for item and relational memory in subregions of the MTL, thalamus and PFC may ultimately support a strict dichotomy of brain function, but it may also suggest a graded specialization.

5. Conclusion

Experiments in the cognitive neuroscience of human memory have examined brain regions associated with a particular cognitive process or with specific stimulus content, typically employing blocked designs. For example, neural correlates have been described for processes such as encoding versus retrieval (e.g. Nyberg, Cabeza, & Tulving, 1996; L. Nyberg, R. Habib, A. R. McIntosh, & E. Tulving, 2000) as well as for content-based memory for verbal versus pictorial and/or nonverbal information such as words, patterns, faces, and scenes (e.g. Golby et al., 2001; Kohler, Moscovitch, Winocur, & McIntosh, 2000). These studies address global differences across the variables tested, which may or may not relate to successful memory.

Advances in fMRI techniques have allowed for event-related analyses in which trials can be sorted based on memory outcome and directly compared to each other (e.g. Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998; Wagner et al., 1998), providing a more clear association with memory success, in effect predicting which episodes will be remembered. However, an episode consists of not only individual item memory (IM), but also relational memory (RM), or the relations between multiple items (or the context in which the items were experienced). These distinctions have also been investigated, typically at encoding, and using the same trials for both IM and RM success (e.g. Davachi, Mitchell, & Wagner, 2003; Davachi & Wagner, 2002). Although much was known about the MTL and PFC regions associated with memory success, the details of

how content and process influence the particular brain regions recruited in memory success, at both phases, had been largely unexplored.

The experiments described in this thesis were designed to address questions of process, content, interactions of process and content, and general memory success, regardless of process or content. In each experiment, event-related analyses were used to compare encoding success. Experiment 1 used semantic and perceptual word pairs to investigate effects of process, content, and general RM success. Experiment 2 used faces and scenes to investigate the interaction of process and content, purely content-based memory success, and general IM success. Experiment 3 used items (faces and scenes) and relational pairings (face-scene) to investigate IM, RM, and general memory success. Following are brief descriptions of each experiment followed by a comprehensive review and analysis of the findings, across experiments.

Summary of the experiments and their findings

In all three experiments, event-related fMRI was used to reveal the neural correlates underlying encoding success and retrieval success. Encoding success was identified by comparing study-phase activity for items subsequently remembered (hits) versus forgotten (misses), and retrieval success, by comparing test-phase activity for hits versus misses. The use of inclusive masks allowed for the identification of higher level effects, such as encoding success versus retrieval success or IM encoding success versus RM encoding success. The use of exclusive masks allowed for the identification of more

general memory phenomena, by excluding higher level effects. Unfortunately, eye-tracking was not available (either during or following performance of the tasks), which has the potential to inform and clarify fMRI results (e.g. LaBar, Gitelman, Parrish, & Mesulam, 1999). Furthermore, although behavioral performance across subjects was variable, the data were modeled to investigate common and consistent regions of activation, across subjects.

Experiment 1 investigated successful relational memory (RM) during encoding and retrieval, for semantic and perceptual associations, or in general, independent of phase and content. Participants were scanned while encoding and later retrieving associations between pairs of words (semantic RM) or associations between words and fonts (perceptual RM). The study yielded three main sets of findings. First, encoding-retrieval differences were found within the medial temporal lobes (MTL) and within the prefrontal cortex (PFC). Within left MTL, encoding was greater in anterior hippocampus, and retrieval, in posterior parahippocampal cortex/hippocampus. This finding is consistent with the notion of an encoding-retrieval gradient along the longitudinal MTL axis. Within left PFC, encoding was greater in ventrolateral PFC, and retrieval, in dorsolateral and anterior PFC. This is the first evidence of a dissociation in successful encoding and retrieval activity within left PFC. Second, consistent with the transfer-appropriate processing principle, some encoding regions were re-activated during retrieval in a content-specific manner. For semantic RM, these regions included

left ventrolateral PFC, whereas for perceptual RM, they included occipito-parietal and right parahippocampal regions. Finally, only one region in the whole brain was associated with RM in general (i.e., for both semantic and perceptual encoding and retrieval): the left hippocampus. This finding highlights the fundamental role of the hippocampus in RM.

Experiment 1 raised two issues. First, content-specific effects were found by comparing semantic to perceptual aspects of word-pairs underscoring the need for further investigation of the role of content on brain regions underlying memory success. Among the most fundamental issues in cognitive neuroscience is how the brain may be organized in process-based and content-based regions. In the memory domain, most functional neuroimaging studies have focused on the former dimension, typically investigating the neural correlates of various memory processes. Although Experiment 1 investigated the role of content, the interaction of content and process was not described. Additionally, both the semantic and perceptual conditions involved semantic processes, which may be more variable in neuroanatomical substrates than well established content-based distinctions in the literature, such as faces and scenes. Thus, there is little information about what role stimulus-sensitive brain regions play in memory encoding versus retrieval.

The second issue raised by Experiment 1 was that of a fundamental role for the hippocampus in RM. This finding was based on comparisons across two types of RM.

While successful RM requires a binding operation at encoding and the recovery of bound information at retrieval, successful IM requires formation and recovery of only a single element. Direct comparisons of IM versus RM potentially provide a stronger control for establishing the specificity of RM effects. Although studies have focused on IM versus RM success at a particular memory stage, there is little information about the nature of IM versus RM success at both encoding and retrieval.

To investigate content effects using a stronger manipulation, Experiment 2 focused on the role of stimulus-sensitive brain regions, such as the parahippocampal place area (PPA), the fusiform face area (FFA), and the occipital face area (OFA), in successful memory encoding and retrieval processes. In addition to comparing stimulus-sensitive memory success at encoding versus retrieval, we identified stimulus-sensitive memory success regions, regardless of memory stage. Finally, we isolated memory success regions, regardless of content or memory stage. There were four main findings. First, PPA, FFA, and OFA regions played a differential role in the successful encoding of their corresponding stimuli, indicating that these regions are specialized not only in the perceptual but also in the memory domain. Second, regions in occipital, temporal, and parietal cortices played a differential role in stimulus-sensitive retrieval success. Third, regions including the left PPA and anterior medial prefrontal cortex were involved in successful memory (regardless of memory stage) for places and faces, respectively. Finally, anterior medial temporal regions were associated with memory success,

regardless of memory stage or stimulus content. Taken together, these results clarify the contribution of different brain regions to content-based and content-independent memory processes.

As noted above, Experiment 1 found a fundamental role for the hippocampus in RM. However, both conditions involved RM and therefore this result may not represent a differential role in RM. To directly compare RM to IM, we created an item condition that comprised the individual components of our relational task and performed subtractions, with stimulus complexity held approximately constant. Experiment 3 focused on IM and RM regions that were differentially, as well as commonly, recruited for successful encoding or retrieval.

Within the MTL, subregions including the perirhinal cortex and hippocampus have been suggested to differentially contribute to item and relational memory, respectively (for a review see Davachi, 2006).In Experiment 3, we scanned subjects during encoding and retrieval in two different conditions; individual scenes or faces (Item) and face-scene pairs (Relational). Memory success based comparisons were performed for item versus relational conditions, as well as regardless of condition, at encoding and retrieval. Item encoding was associated with greater activation in rhinal and bilateral occipitotemporal cortices whereas relational encoding was associated with greater activation in the anterior thalamus and at the right occipitotemporal-parietal junction. At retrieval, item memory was differentially associated with parietal and

lateral prefrontal cortex (PFC), whereas relational memory was differentially associated with left hippocampus and medial PFC. Encoding success, regardless of condition, was associated with bilateral inferior PFC and large areas of the ventral visual stream. Retrieval success, regardless of condition, was associated with bilateral hippocampus, anterior and dorsolateral PFC, parietal, temporal, and subcortical regions. The results suggest that sensory buffers contribute to encoding success based on task demands. At retrieval, strategic task demands differentially recruit regions associated with memory success.

In summary, three event-related fMRI experiments were conducted to address fundamental but largely unexplored issues in the cognitive neuroscience of human memory. These include the influence of process, content, the interaction between process and content, and general memory success, regardless of process and/or content.

Experiment 1 investigated successful RM and reported regions underlying process-based (encoding versus retrieval), content-based (semantic versus perceptual), and general memory success. Dissociations were found in the MTL and PFC for encoding versus retrieval. Semantic and perceptual success differentially reactivated specific regions of PFC, MTL, and the ventral visual stream, and general RM success was associated with the left hippocampus.

Experiment 2 investigated successful IM and reported regions underlying content-based (faces versus scenes) memory, content-process interactions (content

effects for specific memory stages) in memory, and general memory success. Content-based dissociations were found in well-known stimulus sensitive regions including the FFA and PPA, and other regions including the OFA and anterior medial PFC. General IM was associated with bilateral anterior MTL, including the hippocampus.

Experiment 3 investigated successful IM and RM and reported regions differentially versus commonly supporting their encoding and retrieval. The differences between IM and RM are considered to reflect the interaction of content and process. At encoding, IM was associated with rhinal cortex whereas RM was associated with anterior thalamus and occipito-temporal parietal junction. At retrieval, IM was associated with lateral ventral visual stream and lateral left PFC whereas RM was associated with left hippocampus and medial PFC. General encoding success was associated with bilateral inferior PFC and ventral visual stream regions, whereas general retrieval success was associated with parietal and bilateral MTL regions.

Together, the three experiments add to cognitive neuroscience by exploring the unique versus common neural correlates underlying memory success for process, content, and their interactions. A major advantage of the designs employed is the fact that the remembered and forgotten trials are the same at encoding and retrieval and these measures were obtained within subjects. A disadvantage of the RM experiments (1 and 3) is that, although defined in many ways, only word-word associations, word-font associations, and face-scene associations (where the information was overlapping) were

presently tested. Other manipulations such as transitive inference, multisensory associations (e.g. auditory-visual), and separated versus integrated contexts, will further inform and clarify the nature of IM and RM success. However, collectively, the experiments represent a rather extensive investigation of how memory success occurs and the factors that do and do not influence it.

Influence of Process

The results of our experiments indicated that the neural correlates of successful encoding and successful retrieval are dissociable. Experiments 1 and 3 investigated the brain regions associated specifically with encoding success or retrieval success. Previous studies of encoding versus retrieval either compared them at the block level (e.g. Nyberg, Cabeza, & Tulving, 1996) or did not use a success-based subtraction (e.g. Heun et al., 1999; Jessen et al., 2001). The present results strongly suggest that the successful formation versus recovery (or recognition) of a memory relies on distinct regions of the PFC and MTL. Although the PFC regions are not identical across studies, a ventral versus dorsal/anterior distinction best characterizes encoding versus retrieval success, respectively. Within the MTL, the precise regions vary across studies, but the hippocampus and posterior parahippocampus are implicated in encoding success and retrieval success in experiment 1 and vice versa in experiment 3. This variation may be a result of verbal versus visual stimuli. Future studies employing high resolution scanning of the MTL will enable 'unfolding' of the subregions of the MTL and perhaps more

power to tease apart differences as well as identify commonalities in function, across stimulus classes.

In general, PFC and MTL subregions distinguished encoding success from retrieval success. In experiment 1, encoding success was differentially associated with left inferior PFC and left anterior MTL and in experiment 3, with bilateral inferior PFC and bilateral ventral visual stream (encompassing the fusiform and parahippocampal gyri). Together, these results implicate left inferior PFC in successful encoding of a general nature with the right inferior PFC likely contributing when stimuli are pictorial (Kelley et al., 1998). The MTL also differentially contributes to encoding success, but the precise location seems to vary based on verbal versus visual information. The visual materials encoded in experiment 3 have a three-dimensionsality not present in the word-pairs from experiment 1 and thus may rely on the ventral visual stream to a greater extent. Another possibility is that RM encoding demands for verbal stimuli in particular, rely on the anterior hippocampus (e.g. Jackson & Schacter, 2004), whereas encoding single words or pictures may recruit posterior MTL regions in the fusiform and parahippocampal gyri (e.g. Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998; Wagner et al., 1998). Additional experiments directly comparing encoding success to retrieval success for verbal versus pictorial information (and RM versus IM) will help to clarify the present results.

PFC and MTL subregions were differentially recruited not only during encoding, but also during retrieval, for successful memory. Retrieval success was differentially associated with anterior and dorsolateral PFC and left posterior hippocampus/parahippocampal gyrus in experiment 1 and anterior and dorsolateral PFC and bilateral mid-anterior hippocampus/amygdala in experiment 3. Together, these results implicate PFC and MTL regions specifically in retrieval success. The left MTL is implicated in retrieval success of a general nature with the right MTL likely contributing when stimuli are pictorial (Kelley et al., 1998). Although experiment 1 found evidence consistent with an anterior-posterior gradient in memory for encoding and retrieval, this gradient may be dependent on the content of memoranda (Lepage, Habib, & Tulving, 1998; Schacter & Wagner, 1999).

Encoding and retrieval most likely rely on different strategic, perceptual, attentional, reflective, and cognitive components. Isolating the neural correlates of the processes themselves and the components supporting them is an important goal for cognitive neuroscience research, with these experiments representing a step towards that goal. The broader significance of these findings is that distinct PFC and MTL regions are differentially implicated in encoding success or retrieval success. These regions may reflect attentional components at encoding versus reflective components at retrieval. Greater attention to external information should benefit encoding, but may be detrimental to retrieval. Testing these ideas with divided attention paradigms or

incidental encoding of information during retrieval processes would help to clarify how phase selectivity operates to support memory success.

Influence of Content

The results of our experiments indicated that content has a strong influence on the neural correlates underlying memory success. In the perceptual domain, content has been shown to preferentially recruit specific cortical regions (e.g. Epstein & Kanwisher, 1998; Kanwisher, McDermott, & Chun, 1997). The role of content in the memory domain, across memory phases, has also been investigated (L. Nyberg, R. Habib, A. R. McIntosh, & E. Tulving, 2000; Wheeler, Petersen , & Buckner, 2000) and the results support the general notion that reactivation of sensory regions supporting encoding (or perception) can benefit retrieval. However, memory success was not addressed in most of these comparisons. Successful retrieval has been shown to benefit from reactivation or recapitulation of encoding activity (Kahn, Davachi, & Wagner, 2004) and here we directly compare content classes to test the specificity of such effects. Experiment 1 investigated content-related memory success based dissociations in the verbal domain, while Experiment 2 investigated content-related memory success based dissociations in the pictorial domain.

In the verbal domain, regions that specialize in different levels of analysis for word stimuli differentially contributed to semantic versus perceptual memory success. Whereas memory success specific to semantic aspects of verbal stimuli was associated

with the left inferior PFC, memory success specific to perceptual aspects of verbal stimuli was associated with regions in the left ventral visual stream (referred to as the 'visual word form area' - for a review, see McCandliss, Cohen, & Dehaene, 2003), bilateral parietal cortex, and right parahippocampal gyrus. These results were interpreted within the context of the transfer-appropriate processing principle (Morris, Bransford, & Franks, 1977), whereby the overlap between encoding and retrieval processes results in better performance. Overlap in brain activity can also be framed in terms of reactivation (also referred to as recapitulation or redintegration). Replication of these effects in future experiments that use free or cued recall would provide an even stronger argument for the role of such specialized regions in memory success.

In the visual domain, we also found content-based effects that implicate the reactivation of a level of analysis, or possibly the holistic representation of a stimulus. Memory success specific to scenes was supported by the left PPA whereas memory success specific to faces was supported by anterior medial PFC. These regions were discussed as differentially processing the gist and/or holistic representations of their preferred visual information. Reactivation of this representation level at retrieval was found to benefit memory performance. Again, replication of these effects with different forms of retrieval tests would provide the strongest arguments for specialized roles in memory success.

Together these findings implicate distinct cortical regions in successful mnemonic operations, regardless of the memory stage, and preferentially for particular content types. The broader significance of these findings is that certain brain regions are highly specialized for particular situations one may encounter in the world. The benefit of such fractionation of cognitive function is that damage to any one of these regions would still leave other content-based memory intact, which is an idea described by Fodor (1983). Furthermore, reactivation of highly focused regions might be sufficient to cue memory for specific content. Using divided attention or transcranial magnetic stimulation to disrupt ongoing processes, future experiments exploring the role of such regions in encoding and retrieval, will help to further clarify how and when they support content-based cognitive processes.

Interaction of Process and Content

In addition to content- and process-related differences, our studies yielded interactions between these factors. Experiments 2 and 3 investigated the brain regions associated with successful memory, in particular situations. Such specialization highlights the interaction of attention, perception, cognition, task goals, and task demands and their influence on the neural correlates underlying memory success. Although these interactions are likely to occur in unique ways for each subject, the analyses were designed to obtain regions commonly recruited across subjects. The results implicate sensory processing regions in the ventral visual stream, PFC and MTL

subregions, and parietal and subcortical regions in contributing to memory success when the process and content uniquely require them.

In the ventral visual stream, previously described sensory-specialized regions generally supported the successful encoding, but not retrieval of their preferred content, whereas in parietal regions previously associated with retrieval success, content-based memory was also evident. In experiment 2, the right PPA was associated with successful scene memory, at encoding but not retrieval, whereas bilateral FFA and OFA were associated with successful face memory, at encoding but not retrieval. At retrieval, but not encoding, left parietal and right parietal cortices were associated with scene and face memory, respectively. Additional evidence for content and process interactions comes from a follow-up analysis of the semantic encoding condition of experiment 1 (S.E. Prince, Tsukiura, & Cabeza, 2007), in which a subregion of the left inferior PFC was implicated in successful encoding, specifically when semantic retrieval was successful. Together, these results suggest that content-based memory effects sometimes arise only when other necessary preconditions are met.

Both within and outside the MTL, evidence was found for IM and RM to rely on unique neural substrates. In experiment 3, MTL subregions differentiated IM from RM. The left rhinal cortex was associated with IM, but not RM encoding, whereas the left hippocampus was associated with RM, but not IM retrieval. Although previous studies suggest that the hippocampus should play a differential role in RM encoding, regions

including the anterior thalamus and occipital-temporal parietal junction were found. These regions are associated with RM and visuospatial binding and may be sufficient to bind the information presented. Another possibility for further exploration is that encoding separated, but not integrated context information differentially relies on the hippocampus. Outside of the MTL, regions in occipitotemporal cortices and PFC were differentially associated with IM more than RM, further supporting the idea of specialization of function. The process of binding information at encoding and recovering bound information at retrieval relies on a specific set of regions that is different from those recruited for IM processes.

Taken together, these findings suggest an important role for sensory/perceptual regions in encoding success, as well as functional specialization by task type and/or content, in areas inside and beyond the MTL and PFC. This specialization may allow for greater flexibility, such that perception and cognition adjust based on the situation (e.g. Bussey & Saksida, 2005). Furthermore, while reactivation of regions associated with encoding success is one mechanism found to benefit retrieval success (Kahn, Davachi, & Wagner, 2004 ; L. Nyberg, R. Habib, A. R. McIntosh, & E. Tulving, 2000; Wheeler, Petersen , & Buckner, 2000 and data previously described here), it is not the only mechanism by which successful retrieval occurs.

General Memory Success

In addition to the previously discussed evidence for functional specialization, we also found evidence for MTL regions to be fundamentally involved in memory success, regardless of all other factors. Although some theories of hippocampal function focus on spatial or navigational aspects of memory (O'Keefe & Nadel, 1978), our data implicate the hippocampus in memory success for multiple content types (including verbal and pictorial) and in both memory phases. Our memory testing was performed within the same scanning session but other studies suggest that, at encoding, memory success effects in the hippocampus are delay invariant (Uncapher & Rugg, 2005) and at retrieval, memory success effects in the hippocampus and amygdala are still evident when tested after one year delay (Dolcos, LaBar, & Cabeza, 2005). This fundamental role in memory has been theorized to reflect the physiological mechanism of long-term potentiation, which may store an index of the neocortical regions activated by an experience (Teyler & DiScenna, 1985). Future research investigating the connectivity and timing of interactions of specific neocortical regions with the hippocampus will help to test the validity of this theorized mechanism.

The hippocampus is an "all-purpose" memory region, underlying memory success at encoding and retrieval for various types of information. Experiments 1 and 2 investigated memory success, regardless of the phase or content of memoranda. In both experiments, MTL regions were associated with this all-purpose memory success.

Although different subregions were found (left mid-posterior hippocampus in experiment 1 and bilateral anterior MTL including hippocampus and amygdala in experiment 2), the MTL as a structure is implicated in fundamental memory success. Reliance on separate MTL subregions may reflect a neural defense mechanism such that damage to a particular subregion may not be as universally devastating. Alternatively, the localization of general memory success regions in the MTL may, somewhat paradoxically, depend on the verbal/visual nature of the to-be remembered information. However, these results add to the previous findings of content and process specialization in the MTL, by showing that the MTL potentially supports both specific and general memory success.

Summary

Together, the experiments described in this thesis provide a detailed investigation of successful memory at encoding and retrieval. The influence of content and process, and the interaction of or insensitivity to content and process, were explored. On the whole, there is considerable evidence for the role of sensory, perceptual, and cognitive processes that support successful encoding, retrieval, or both. Evidence from multiple experiments supports a fundamental role for the hippocampus in memory success and future experiments should explore whether this is facilitated by indexing other neocortical regions. Although the MTL has regions that support memory in the most general way, the data summarized herein strongly support the idea of

functional specialization, achieved by highly specific regions and/or networks. Examples of such specialization include the PPA, anterior medial PFC, visual word form area, and left inferior PFC, for scenes, faces, word form, and word meaning, respectively. Memory success for varying content also shares common brain regions at encoding (inferior PFC and MTL) and retrieval (MTL and dorsolateral and anterior PFC). Future experiments will add to the understanding of the timing and interactions between these regions and whether the contributions they make to memory success are automatic or strategic, as well as necessary or sufficient.

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Biography

Steven Eric Prince was born in Brooklyn, New York on August 8th 1975. He attended Stuyvesant High School in Manhattan, graduating in 1993. In May of 1997, he obtained a Bachelor of Science degree in Human Development, with a concentration in Cognitive Science, from Cornell University in Ithaca, New York. He is married to Deborah Goldstein and they have a son, Avery.

Representative Publications:

Prince, S. E., Tsukiura, T. & Cabeza, R. (2007). Distinguishing the neural correlates of episodic memory encoding and semantic memory retrieval. Psychological Science,18(2), 144-151.

Daselaar, S. M., Fleck, M. S., **Prince**, S. E., & Cabeza, R. (2006). The medial temporal lobe distinguishes old from new independently of consciousness. J Neurosci, 26(21), 5835-5839.

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