Title
The roles of the hippocampus in recognition memory

Author
Wais, Peter Edward

Publication Date
2008

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA, SAN DIEGO

The Roles of the Hippocampus in Recognition Memory

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

in

Psychology

by

Peter Edward Wais

Committee in charge:

Professor John Wixted, Chair
Professor Larry Squire, Co-Chair
Professor Stephan Anagnostaras
Professor James Brewer
Professor Jaime Pineda

2008

This Dissertation of Peter Edward Wais is approved, and it is acceptable in quality and form for publication on microfilm:

Co-Chair

Chair

University of California, San Diego

2008

TABLE OF CONTENTS

TABLE OF CONTENTS (continued)

ACKNOWLEDGEMENTS

I would like to acknowledge the immense contributions from John Wixted in all of the work discussed here and in mentoring the development of my analytical skill.

I would also like to acknowledge the valuable and indelible contributions from Larry Squire, which include an inner voice that causes me to weigh the suitability and accuracy of each word I write.

I would also like to acknowledge the assistance of my collaborators: Christine Smith for elucidating the mysteries of fMRI analysis; Rayshawn Tabaldo, Emily Johnson and Kristen Wisner for diligence and excellence as experimenters; and, most notably, Laura Mickes for making me smile when I did not want to.

I would also like to acknowledge the inspiration and support I enjoy from Paul Wais and Alison Bedard, which carry a value for me that I cannot really express, let alone explain in words.

Experiment 1, in full, is a reprint of the material as it appears in The Hippocampus Supports both the Recollection and the Familiarity Components of Recognition Memory in *Neuron, 49*. Wais, P. E., Wixted, J. T., Hopkins, R. O. and Squire, L. R. (2006). 459-466. The dissertation author was the primary investigator and author of this paper.

Experiment 2, in full, is a reprint of the material as it appears in Remember/Know Judgments Probe Degrees of Recollection in *Journal of Cognitive Neuroscience, 20.* Wais, P. E., Mickes, L. and Wixted, J. T. (2008). The dissertation author was the primary investigator and author of this paper.

Experiment 3, in full, has been submitted for publication of the material as it may appear in Recognition Memory Processes in the Medial Temporal Lobe: A Quantitative Meta-Analysis of fMRI Results in *Neuropsychologia.* Wais, P. E. (2008). The dissertation

ACKNOWLEDGEMENTS (continued)

author was the investigator and author of this paper.

Experiment 4, in full, has been submitted for publication of the material as it may appear in fMRI Evidence for Recollection and Familiarity Signals in the Hippocampus in *Journal of Cognitive Neuroscience.* Wais, P. E., Squire, L. R. and Wixted, J. T. (2008). The dissertation author was the primary investigator and author of this paper.

VITA

1976	Bachelor of Arts in Journalism, University of California, Berkeley
2002—2004	Research Assistant at the Gabrieli Cognitive Neuroscience Laboratory, Stanford University. Advisor: John Gabrieli, Ph.D.
2004—2008	Graduate student in the Department of Psychology, University of California, San Diego. Advisors: John Wixted, Ph.D. & Larry Squire, Ph.D.
2006	Master of Arts in Psychology, University of California, San Diego
2008	Doctor of Philosophy in Psychology, University of California, San Diego

Area of Study

My research interests pursue a more complete understanding of the cognitive neuroscience of declarative memory, the functional roles of the hippocampus and the medial temporal lobe, and how affect modulates memory.

Awards

Innovative Research Grant awarded by the Kavli Institute for Brain and Mind (2007).

Publications

Wais, P., Squire, L. & Wixted, J. (2008). The hippocampus subserves recollection of word pairs and strong memory associated with item recognition. *in preparation*

Mickes, L., Wais, P. & Wixted, J. (2008). Recollection is a continuous process: implications for dual process theories of recognition memory. *in review*

Wais, P., Squire, L. & Wixted, J. (2008). An fMRI signal for both familiarity and recollection in the hippocampus. *in review*

Wais, P. (2008). Recognition memory processes in the medial temporal lobe: a quantitative meta-analysis of fMRI results. *in review*

Wais, P., Mickes, L., & Wixted, J. (2008). Remember/Know judgments probe degrees of recollection. *The Journal of Cognitive Neuroscience, 20.* 400-405.

Mickes, L., Wixted, J. & Wais, P. (2007). A direct test of the unequal-variance signal-detection model of recognition memory. *Psychonomic Bulletin & Review, 14.* 858-865.

Wais, P., Wixted, J., Hopkins, R. & Squire, L. (2006). The hippocampus supports both the recollection and the familiarity components of recognition memory. *Neuron, 49.* 459-466.

Anderson, A., Wais, P. & Gabrieli, J. (2006). Emotion enhances remembrance of neutral events past. *Proceedings of the National Academy of Sciences, 103.* 1599-1604.

Mather, M., Canli, T., English, T., Whitfield, S., Wais, P., Ochsner, K., Gabrieli, J. & Carstensen, L. (2004). Amygdala responses to emotionally valenced stimuli in older and younger adults. *Psychological Science 15, 4*. 259-263.

ABSTRACT OF THE DISSERTATION

The Roles of the Hippocampus in Recognition Memory

by

Peter Edward Wais

Doctor of Philosophy in Psychology

University of California, San Diego, 2008

Professor John Wixted, Chair
Professor Larry Squire, Co-Chair

Recognition is our awareness of prior experience and is thought to depend upon the recollection and familiarity processes. Recollection refers to remembering an experience with associated contextual details, whereas familiarity refers to a sense of awareness absent recollection. Some psychological models have proposed that when recollection is available, confidence in a recognition decision is categorically high. Other models propose that recollection and familiarity are both continuous processes and, therefore, differences in memory strength *per se* do not separate recollection from familiarity. Functional magnetic resonance imaging (fMRI) has been used extensively to examine the neural correlates of recollection and familiarity, yet interpretation of these data and how recognition is supported by the brain remain open debates. The two dual-process views make different interpretations about whether the fMRI results suggest a division of labor between medial temporal lobe (MTL) structures. The typical conclusion in these fMRI studies is that the hippocampus selectively subserves recollection. In this dissertation, Experiments 1 and 2 tested the hypotheses of both dual-process models (i.e., whether recollection is categorical or continuous). The results from both experiments showed that highly confident memory is not categorically based on recollection. Experiment 3 performed a meta-analysis on the relevant fMRI literature and considered the two model-based interpretations of the results. This analysis showed that although these studies intended to dissociate MTL activity on the basis of recognition processes, their interpretations dissociated activity on the basis of memory strength. Experiment 4, which scanned a source memory test during retrieval, took a new approach to compare correct source judgments (recollection) and incorrect source judgments (familiarity) while equating for old/new memory strength by including only high-confidence hits in the analysis. This approach avoided the complication from previous studies (identified in Experiment 3) that confounded recollection and familiarity with strong and weak memories. After equating for memory strength, activity in the hippocampus in association with high-confidence hits was greater than for forgotten items, regardless whether source judgments were correct (recollection succeeded) or incorrect (recollection failed).

The conclusion in this dissertation, drawn from the results of the four experiments, is that the hippocampus serves a broader role than selectively supporting recollection. Two views are discussed about how this role may work. One view hypothesizes that the summation of MTL input associated with item identification, contextual information and arousal is mediated by the hippocampus. In this framework, the role of the hippocampus is to enhance the retrievability of salient experiences. Another view suggests that the hippocampus abstracts bits of information from prior experience. This role does not map onto specific recognition processes (i.e., recollection and familiarity) or measurements of memory strength. Further work is needed to examine the range of hippocampal sensitivity for memory strength. Taken as a whole, these developments elucidate a critical role for the hippocampus in recognition and not solely in recollection.

The Roles of the Hippocampus in Recognition Memory

Introduction

We recognize something when we can match it with an experience from our past. Bringing facts and events into a conscious state of mind from our past relies upon the processes of declarative memory (Squire, 1992). Although cognitive models for different declarative memory processes are well defined, the interpretation of how recognition is supported by the brain remains an open debate. Neuroscience research has demonstrated that the organization of the central nervous system is specialized by behavioral function, but the details of a functional organization in the brain that subserves recognition memory have yet to be completely worked out.

The development of a functional map of how the brain supports recognition memory began with the study of patient HM, which found the first empirical data showing how the human brain mediates memory processes (Scoville & Milner, 1957). A large literature has subsequently elucidated the model for a cortical-hippocampal system for declarative memory (Squire & Zola-Morgan, 1991; Eichenbaum, 2000; Aggleton & Brown, 2006) and identified the hippocampus and the entorhinal, perirhinal and parahippocampal cortices as the medial temporal lobe (MTL) regions that participate in this system. This research demonstrates how the hippocampal region is critical for recognition (the hippocampal region includes the dentate gyrus, the hippocampus proper and the subicular complex). These studies reach no consensus, however, about how the functional organization of the hippocampal region (hereafter, simply referred to as the hippocampus) and adjacent MTL structures support different processes in recognition.

To examine the roles of the hippocampus in this system further, it is important to consider existing models of recognition processes, how the models have been tested, and how these models have been applied to interpret the correlation between hippocampal activity and behavior in memory tasks. This dissertation considers each of these models and then, in a series of three new experiments, tests how well the models explain relevant results for MTL activity associated with recognition. The findings from the first three experiments suggest a fourth new experiment that sheds further light on how recognition processes are subserved by the hippocampus.

Recollection, Familiarity and Model-Based Interpretations.

Recognition is described in most memory research as relying on two processes, recollection and familiarity (Mandler, 1980; Curran & Hintzman, 1995). Recollection refers to remembering an experience with associated contextual details, whereas familiarity refers to a sense of awareness about a prior experience when such awareness is absent any contextual information. There are two principal distinctions between recollection and familiarity that have been quantified behaviorally: the durability of information retrieved by each process and the latency for the retrieval effort. Mandler, Pearlstone & Koopmans (1969) first developed a dual-process model that accounted for their finding that recognition associated with contextual information was more durable than context-free recognition. According to this model, as the number of details remembered in elaboration of an experience increases, the better that memory will be retrieved over time. Mandler (1980) extended this model to explain how, given other research (Atkinson & Juola, 1973), recognition based on familiarity (context-free recognition) occurs significantly more rapidly than recognition accompanied by the effortful recollection of specific contextual information.

Based on such evidence suggesting that recollection and familiarity are independent processes, Yonelinas (1994) proposed the high-threshold/dual-process model as a way to isolate recognition decisions based on recollection from those based on familiarity. The high-threshold view assumes that such a separation can be made easily because successful recollection always yields highly confident recognition. More specifically, the high-threshold model views the strength of familiarity as being continuous (i.e., ranging from weak confidence based on familiarity to strong confidence based on familiarity), whereas it views recollection as a categorical process that, when it occurs, only gives rise to the strongest confidence. Because recollection reliably yields responses with the highest memory confidence, this model assumes that the occurrence of recollection preempts familiarity and that such responses are based exclusively on recollection. If recollection does not occur, then the response is exclusively based on familiarity instead (Parks & Yonelinas, 2007). Therefore, the high-threshold view holds that recollection and familiarity are independent, rather than redundant, processes leading to a recognition decision. Accordingly, recognition decisions made with the highest confidence can be taken to primarily denote recollection, whereas recognition decisions made with confidence below that threshold can be taken to denote familiarity.

Similar considerations apply to experiments that use the Remember/Know/New procedure (Gardiner & Richardson-Klavehn, 2000; Tulving, 1985). Standard instructions for this procedure ask subjects to respond “Remember” based on recollection whenever it occurs and to otherwise respond “Know” based on a strong sense of familiarity. The

Remember/Know procedure assumes that responses are based exclusively on one process or the other and that the recollection process will preempt the familiarity process, just as the high-threshold view does.

An alternative model holds that recognition decisions are based on a continuous strength variable (Wixted, 2007) that conjoins input from the recollection process and the familiarity process. The aggregated-strength/dual-process model assumes that recollecting the contextual details about an experience is a separable process from recognizing the familiarity of an item. However, this model, which is compatible with standard signal-detection theory, uniquely holds that both processes contribute to an individual recognition decision (Kelley & Wixted, 2001; Wixted, 2007). According to this view, the strength of recollection underlying recognition responses varies from weak to strong, just as the strength of underlying familiarity varies from weak to strong (Slotnick & Dodson, 2005). Such a view of how recognition processes work means that the strength of memory *per se* cannot be interpreted as a sign of underlying recollection or familiarity (Wixted, 2007; Dunn, 2008).

The MTL Supports Recognition Memory

Neuroanatomical studies in humans and nonhuman primates have traced pathways indicating that the perirhinal and parahippocampal cortices, as well as the hippocampal region, contribute directly to declarative memory (Lavenex & Amaral, 2000; Suzuki & Amaral, 1994; and Amaral & Insausti, 1990). Some findings from comparative psychology suggest a dissociation in how different MTL regions subserve different recognition memory processes. Results from studies with rats, whose MTL anatomy is comparable to humans, have been interpreted to show that recollection depends upon the hippocampus (Fortin, Wright & Eichenbaum, 2004) and that item recognition (which is analogous to familiarity in humans) depends on the perirhinal cortex (Brown & Aggleton, 2001). Some research with humans suggests a similar dissociation and has been interpreted to show that specific MTL regions subserve only selective roles in recognition memory processes (Yonelinas, Kroll, Quamme, Lazzara, Sauve, Widaman & Knight, 2002).

Other research, however, shows that although memory is impaired for amnesic patients in comparison to healthy controls, no functional selectivity for the hippocampus was indicated for either familiarity or recollection (Manns, Hopkins, Reed, Kitchener & Squire, 2003; Wais, Wixted, Hopkins & Squire, 2006). Additionally, evidence from cellular recordings measured in humans suggests that some hippocampal cells are active selectively when stimuli are novel while others are active selectively when stimuli are familiar, whether or not task-relevant source information is recollected (Rutishauser, Mamelak & Schuman, 2006; Rutishauser, Schuman & Mamelak, 2008). These data have been interpreted to reflect activity associated with item recognition in the absence of source recollection and to mean that the hippocampus supports familiarity-based decisions, though one cannot exclude the possibility that it instead reflects unmeasured recollection of task-irrelevant information. In any case, such research opportunities with humans are few, and a more common approach relies on event-related functional magnetic resonance imaging (fMRI) to measure neural activity in healthy participants during encoding or retrieval tasks.

fMRI is capable of fine spatial resolution that can locate signals associated with specific memory responses to the hippocampal region and the adjacent structures along the parahippocampal gyrus. A dissociation between the activity associated with recollection and the activity associated with familiarity would suggest that these separable recognition processes are supported by different structures within the MTL. One caveat about fMRI, however, is that it measures activity associated with performance on a task and does not indicate whether the activity in a particular region is causal for the behavior. Moreover, fMRI data alone do not distinguish between recollection and familiarity— it is the application of a particular psychological model that makes such interpretations.

Experiments

Experiments 1, 2 and 3 test (a) model-based interpretations of ROC data produced by patients with hippocampal lesions, (b) the Remember/Know procedure, and (c) model-based interpretations of fMRI data, respectively. Experiment 4 examines the neural correlates of recollection and familiarity with a new procedure that equates recognition memory strength for the observations that denote recollection-based responses with the observations that denote familiarity-based responses.

Experiment 1: The Hippocampus Supports both the Recollection and the Familiarity Components of Recognition Memory

Summary

The receiver operating characteristic (ROC) has been used to investigate the component processes of recognition memory. Some studies using this technique have been taken to indicate that the hippocampus selectively supports the process of recollection, whereas adjacent cortex in the parahippocampal gyrus supports the process of familiarity. We analyzed ROC data from young adults, memory-impaired patients with limited hippocampal lesions, and age-matched controls. The shape of the ROC changed in similar ways from asymmetric to symmetric, as a function of the strength of memory (strong to weak) in both the young adults and the patients. Moreover, once overall memory strength was similar, the shape of the patient ROC was asymmetric and matched the control ROC. These results suggest that the component processes that determine the shape of the ROC are operative in the absence of the hippocampus, and they argue against the idea that the hippocampus selectively supports the recollection process.

Introduction

One of the most widely studied examples of declarative memory is recognition memory, the capacity to judge an item as having been encountered previously. Recognition memory is commonly thought to consist of two component processes, recollection and familiarity (Mandler, 1980). Recollection involves remembering specific details about the episode in which an item was encountered, and familiarity involves simply knowing that an item was presented, even when no information can be retrieved about the episode itself. A fundamental but controversial issue concerns the anatomical basis of this distinction: how are recollection and familiarity supported by the brain structures important for declarative memory? Some studies suggest that the hippocampus is critical for recollection, whereas familiarity is supported by the adjacent cortex in the parahippocampal gyrus (Brown & Aggleton, 2001; Fortin et al., 2004; Yonelinas et al., 2002). Other studies suggest that the hippocampus is important for both recollection and familiarity (Manns et al., 2003; Wixted & Squire, 2004).

Signal detection techniques have recently been used to address these anatomical questions about the component processes of recognition memory (Fortin et al., 2004; Yonelinas et al., 1998; Yonelinas et al., 2002). The receiver operating characteristic (ROC) is a plot of the hit rate vs. the false alarm rate across different decision criteria. For example, multiple pairs of hit and false alarm rates can be obtained by asking subjects to provide confidence ratings for their yes/no recognition decisions. A pair of hit and false alarm rates is then computed for each level of confidence, and the paired values are plotted across the confidence levels to construct an ROC.

The approach has been to compare the shape of the normal ROC to the ROC produced by memory-impaired patients (Yonelinas et al., 1998, 2002) or rats with hippocampal lesions (Fortin et al., 2004). These ROCs were typically curvilinear, but they differed in that the curve produced by controls was asymmetrical (as is usually the case), and the curve produced by the patients (and by the rats with lesions) was symmetrical (**Figure 1.1**). These data have been interpreted in the light of a dual-process/detection model (Yonelinas et al., 1998), which holds that the degree of asymmetry in an ROC directly reflects the degree to which the recollection process is involved in recognition decisions. Accordingly, a symmetrical ROC indicates that recognition decisions were based solely on familiarity, but an asymmetrical ROC indicates that recollection occurred for some of the items as well (Yonelinas et al., 1998). By this view, the finding that memory-impaired patients (and hippocampal rats) yield a symmetrical ROC, instead of the more typical asymmetrical ROC, suggests that the recollection process is selectively impaired.

Although the two ROC curves just described are qualitatively different with respect to symmetry, they are also quantitatively different because memory-impaired patients (and rats with lesions) have weaker memories than controls. Indeed, the standard signal detection model of recognition memory (Macmillan & Creelman, 2005), in contrast to the dual process/detection model, explains the transition from asymmetrical to symmetrical ROCs as a simple loss of memory strength (Glanzer et al., 1999). If symmetry of the ROC is related to memory strength, then the difference in symmetry between impaired and unimpaired subjects may simply reflect the difference between weaker and stronger memories (not qualitative differences in the integrity of underlying recognition memory processes).

We first analyzed the shape of the ROC over a wide range of memory strength conditions by testing young adults after one of 5 retention intervals (1 hr, 1 day, 1 wk, 2 wk and 8 wk). These conditions were included to determine how the ROC changes as memory strength weakens. We next tested 6 memory-impaired patients with bilateral damage thought to be limited to the hippocampal region (CA fields, dentate gyrus, and subiculum), as well as a matched control group. If the hippocampus selectively subserves recollection, and if the asymmetry of an ROC is indicative of recollection, then these patients would be expected to yield a symmetric ROC regardless of memory strength. Alternatively, if the hippocampus does not selectively support recollection (because recollection depends on adjacent medial temporal lobe structures as well), then hippocampal patients should produce asymmetrical ROCs like the matched controls, once differences in memory strength are accounted for.

Results

The recognition performance of the young adults decayed as expected over time (**Figure 1.2**). Performance in the 8-wk condition, while low, was above chance levels ($t_{(18)} = 2.43$, $p < .05$). The ROCs were curvilinear at every retention interval and, as is generally the case, were accurately described by the standard signal-detection model (**Figure 1.3**). In addition, the ROC was, as expected, asymmetric at the short (1-hr) retention interval (slope = 0.63) and became ever more symmetric as performance decreased. Still, the slopes remained less than 1.0 (*p*s <.05) up to the longest retention interval, which yielded a slope of 1.03 (indicating a symmetric ROC). These data establish that as memory strength weakens, the slope of the ROC increases toward 1.0 and that the shape of the ROC remains curvilinear even when memory strength is very weak**.**

One can fit the dual-process/detection model (Yonelinas et al., 1998) to these ROC data to derive estimates of recollection and familiarity, something that is commonly done (e.g., Aggleton et al., 2005; Fortin et al. 2004; Yonelinas et al., 2002), and the results are shown in Table 1.1. The increasing symmetry of the ROC as a function of retention interval is reflected in the fact that the recollection estimate decreases over time to a value close to zero (i.e., a symmetric ROC yields a recollection estimate of 0). The familiarity parameter from this model also decreases over time but is still greater than zero even at the 8-wk retention interval. Thus, according to this model, our results imply that recollection faded faster than familiarity.

The next question of interest is how the shape of the ROC changes as a function of memory strength for the patients with hippocampal lesions and how the performance of the patients compares with the performance of their matched controls. The recognition performance of the hippocampal group in the 50-item condition (H-50, **Figure 4**) was poorer than control performance (C-50) ($p < .05$). When only 10 items were studied instead of 50, patient performance (H-10) substantially improved ($p < .05$) to a level closer to that of the controls ($p > .25$). The ROCs produced by the patients and controls were all curvilinear (**Figure 5**). The slope of the ROC from the H-50 condition (1.14) was greater than the slope of the ROC from the H-10 condition (0.83, $p < .05$) and also greater than the slope of the ROC from the C-50 condition (0.83, $p < .05$). Thus, as was true of the young adults, the hippocampal ROC was more symmetric when memory was weak compared to when memory was relatively strong (H-50 vs. H-10, respectively). Further, when the overall strength of memory was similar for patients and controls, as it was in the H-10 and C-50 conditions, the degree of asymmetry in the ROC was similar as well. These findings accord with earlier work (Glanzer et al., 1999), showing that whatever method is used to alter memory strength (e.g., study time, repetition, word frequency, or list length) the results are always the same: the symmetry of the ROC (and the slope) increases as memory strength decreases.

Although the mean age of the two groups did not differ significantly, the controls were, on average, 4.5 years older than the patients. Accordingly, we performed an additional ROC analysis after excluding the three oldest controls. The mean age of the remaining 5 controls was the same as that of the patients (56 years). The slope of the ROC for these 5 controls was now .80, instead of 0.83, and was still similar to and not significantly different from the slope of 0.83 produced by the patients.

As with the ROC data produced by the young adults in our study, the ROC data produced by the patients and their controls can be fit by the dual-process/detection model (Yonelinas et al., 1998) to derive theoretical estimates of recollection and familiarity. As shown in Table 1, the recollection parameter estimate was equal to zero in the H-50 condition (its lowest possible value) and was greater than zero (.23) for the controls (C-50). Similarly, the familiarity estimate was lower in the H-50 condition than for the controls (0.83 vs. 1.64). In contrast, the estimated probability of recollection in the H-10 condition was virtually identical to that of the controls (.22 and .23, respectively). Thus, according to this model, the recollection process is present in both patients and controls, and the nearly identical recollection estimates offer no evidence of a selective deficit in that process after hippocampal lesions. Finally, the familiarity estimates for the two groups were similar as well (1.21 and 1.64, p=.11).

The traditional signal detection model and the dual-process/detection model are both commonly fit to ROC data, as we have done here, but the signal detection model usually provides the better fit. This was true of our ROC data as well. Specifically, the chi-square goodness-of-fit statistic associated with the fits of the signal detection model was lower (indicating a better fit) than that of the dual-process/detection model for all 5 of the ROCs in Figure 3 and for all 3 of the ROCs in Figure 5. Summed across the 8 ROCs, the chi-square value for the signal-detection fits was 72.2, whereas the corresponding value for the dual-process/detection fits was 107.2. This result agrees with the findings of a recent study (Heathcote, 2003) that manipulated a number of variables in four experiments and found that the signal detection model provided a better fit in every condition of every experiment. Thus, the dual-process/detection model does not adequately account for ROC data, as others have noted (Glanzer et al., 1999; Heathcote, 2003), and studies of familiarity and recollection are likely to be misled to the extent that they depend on this model.

One of the 6 hippocampal patients, AB was ineligible for MRI because he wears a pacemaker, though his history, neurological exam, and computer-assisted tomography (CAT scan) are consistent with a limited hippocampal lesion (Schmolck et al., 2002). The findings were similar when AB's data were excluded. Thus, the slopes of the patient ROCs were now 1.15 and 0.85, respectively, for the H-50 and H-10 conditions (compare Figure 5), and the difference between these values was marginally significant (p = .059).

Discussion

The performance of memory-impaired patients with selective hippocampal lesions differed quantitatively, but not qualitatively, from that of controls. The ROC from the patients exhibited the same relationship between symmetry and memory strength as the ROC from the young adults. Moreover, the patient ROC was identical to that of age-matched controls when the overall strength of memory was similar (H-10 vs. C-50). Accordingly, the component processes of recognition memory that determine the shape of the ROC appear to be operative in patients with hippocampal lesions, and these processes are not differentially impaired.

The specific implications of our findings differ somewhat depending on which of two prominent models is used to interpret the data. According to the traditional signal-detection model (Macmillan & Creelman, 2005), an asymmetrical ROC reflects greater variance in the memory strengths of the targets relative to the lures. The exact manner in which recollection and familiarity combine to determine the variance of the targets is not constrained by this model. One possibility is that items supported by recollection, or by both recollection and familiarity, tend to have greater memory strength than items supported mainly by familiarity (Wixted & Stretch, 2004). In any case, the fact that the ROCs produced by patients and controls exhibited the same characteristics as a function of memory strength suggests that the component processes of recognition, however they might combine to produce memory strength, do so in the same way for patients and controls.

The dual-process/detection model (Yonelinas et al., 1998) explicitly connects the degree of asymmetry in the ROC to the probability of recollection: the more asymmetric the ROC, the greater the contribution of recollection. Yet, if the hippocampus selectively supports recollection, then the absence of that process in the hippocampal patients should have been evident as a more symmetrical ROC, even when overall memory strength was similar for patients and controls. Contrary to that prediction, Table 1 indicates that recollection was normal in the hippocampal group under those conditions (H-10 vs. C-50).

Fortin et al. (2004) studied odor recognition memory in rats and analyzed the shape of the ROC under conditions very similar to the conditions of our study. ROCs in their experiment were generated by varying the reward magnitude and the effort needed to acquire the reward (i.e., a reinforcement biasing manipulation). Control rats produced a typical asymmetrical, curvilinear ROC when recognition was tested following a short (30-min) retention interval. By contrast, rats with hippocampal lesions tested under the same conditions exhibited weaker memory and produced a symmetrical curvilinear ROC. Both these results match what we found with humans. Control rats were also tested following a longer (75-min) retention interval, which yielded a level of recognition memory performance similar to that of the hippocampal rats. Even so, the ROC associated with this long retention-interval condition was not symmetrical (as in the hippocampal rats) but was essentially linear. Fortin et al. (2004) interpreted their data in terms of the dual-process/detection model (Yonelinas et al., 1998) and argued that responding in the long-delay condition was based purely on recollection (presumably because familiarity faded rapidly to zero as the retention interval increased). This finding contrasts sharply with the increasingly symmetric and always curvilinear ROCs that we found in young adults as the retention interval increased. Even at the longest retention interval, where the ROC necessarily becomes more linear as it approaches the diagonal, our data were symmetric and curvilinear rather than linear. Further, according to the parameter estimates of the dual-process/detection model (Yonelinas et al., 1998) that were applied to our data from young adults (Table 1), recollection faded more rapidly than familiarity as retention interval increased, not the other way around.

A linear ROC in an Old/New recognition procedure -- which is what the control rats exhibited following a long retention interval -- is an unprecedented finding despite more than 40 years of ROC data. The only published linear ROCs known to us were obtained using distinctly different recognition memory procedures -- namely, source memory and associative recognition procedures (Yonelinas, 1997, 1999) -- and a substantial body of subsequent research has shown that even those ROCs are virtually always curvilinear, not linear (e.g., Hilford et al., 2002; Qin et al., 2001; Slotnick & Dodson, 2005). For the more commonly used Old/New recognition memory procedure, we are unaware of a single linear ROC in the human literature.

The linear ROC reported for rats by Fortin et al. (2004) was obtained with a procedure that was necessarily quite different from the confidence-based method so widely used with humans. In their procedure, rats were required to sniff a cup filled with scented sand on each recognition test trial. If the test odor did not match a scent that had been presented on an earlier list (i.e., if the odor was new), then digging in the sand would yield a food reward. If instead the odor did match a prior scent (i.e., if the odor was old), then a reward could be obtained by approaching a cup located elsewhere in the chamber. To change bias, the magnitude of reward for correct Old and New responses, and the difficulty of obtaining reward, were varied across conditions. An ideal ROC procedure would manipulate bias without affecting memory strength. Yet providing differential reward outcomes with experimental animals sometimes does affect memory strength as well as bias (e.g., Savage, Pitkin & Careri, 1999), and it would be important to determine if the novel procedure used by Fortin et al. (2004) succeeded in holding memory strength constant across the varying biasing conditions. If memory strength were affected by the biasing manipulations, then the shape of the ROC would be affected. In any case, the phenomenon observed by Fortin et al. (2004) -- that is, a linear ROC after a long retention interval -- is not observed with humans.

Another study by Yonelinas et al. (1998) involved ROC data from 3 memory-impaired patients and found slopes of .90 and 1.06 for a strong and weak memory condition, respectively, similar to what we found with our hippocampal patients (H-10 vs. H-50). Like Fortin et al. (2004), these authors also tested healthy controls in a weak memory condition, so that the ROC slopes produced by patients and controls could be compared when the overall strength of memory was comparable. Even then, the slope of the ROC was substantially more asymmetric (slope = 0.55) than that of the patients, leading to the suggestion that patients lacked the recollection component that was revealed in the controls. However, the patients in that study were, on average, greater than 70 years of age, whereas the control subjects tested in the weak memory condition were undergraduates. Our own findings show as well that older subjects have a more symmetric ROC than undergraduates when memory strength is equated. For example, the mean d' scores of the older controls at a 3-m retention interval was similar to that of the young adults at the 1-h retention interval (2.07 and 2.14, respectively), yet the slopes of their corresponding ROCs differed markedly (0.83 vs. 0.63, respectively, $p < .05$). When we eliminated the confound of age by comparing patients and age-matched controls (H-10 vs. C-50), the slope difference was eliminated and the ROCs exhibited a similar degree of asymmetry.

Our conclusion that recollection and familiarity are similarly impaired after hippocampal damage is consistent with work reporting that recall and recognition are impaired to a similar degree in patients with hippocampal lesions (Manns et al., 2003). Recall is thought to depend only on recollection, whereas recognition is thought to depend on both recollection and familiarity. Yonelinas et al. (2002) compared recall and recognition performance in a large group of cardiac arrest patients who were assumed to have hippocampal damage. Although it was reported that recall (and therefore recollection) was differentially impaired in these patients, Wixted and Squire (2005) pointed out that this conclusion rested entirely on the obviously aberrant recognition performance of one of 55 control subjects. When that single outlier was removed from the analysis, recall and recognition were impaired to a similar degree.

Several recent single-case studies have also addressed questions about recollection and familiarity in patients with hippocampal damage, but the findings are mixed and do not yield a consistent view. Two patients had similarly impaired recall and recognition for verbal material, but relatively good performance on one or more tests of visual recognition (Barbeau et al., 2005; Cipolotti et al., in press). Two other patients were reported to have impaired recall but performed relatively well on both verbal and visual recognition tests (Mayes et al., 2002; Bastin et al., 2004). Finally, Aggleton et al. (2005) described a patient whose ROC was more symmetric than that of controls, even when memory strength was equated. This result was interpreted to mean that recollection was impaired and familiarity spared, but it is not clear that the difference between the patient and the controls was reliable. One of the 7 controls yielded a recollection estimate even lower than that of the patient. Further, the patient's performance after shallow or deep encoding conditions suggests a different conclusion. The benefits to memory of deep encoding conditions are thought to depend especially on recollection. Yet, the patient's recognition performance was equally impaired in both conditions. Specifically, the patient's d' scores were 64% and 58% of the control d' scores in the deep and shallow conditions, respectively.

One possible reason for the discrepancy among these case studies is that the patients differ in how much damage has occurred to structures beyond the hippocampus as well as in how much damage has occurred on the left and right sides. These factors complicate attempts to interpret individual patient data. We suggest that questions about the relative importance of the hippocampus for recollection and familiarity are best addressed by group studies of patients with thoroughly documented lesions limited to the hippocampus.

In the 5 patients we studied with MRI (all but AB), the hippocampus was reduced in volume bilaterally by a mean of 44%. Two patients with similar volume loss in the hippocampus, as measured by MRI, were found in post-mortem neurohistology to have a nearly complete loss of hippocampal neurons (Rempel-Clower, Zola, Squire & Amaral, 1996). Thus, it is reasonable to suppose that there was little or no preserved hippocampal function in our patients. If so, and if the slope of the ROC is an indicator of recollection, then the idea that the hippocampus subserves a recollection process is discounted by our findings.

Recollection and familiarity remain useful constructs that help to explain a number of findings. For example, fast recognition responses (putatively based on familiarity) are not affected by the degree to which a list of items is semantically organized by the subject, whereas slower recognition responses (putatively based on recollection) are affected by semantic organization (Mandler & Boeck, 1974). However, the simple idea that these processes can be dichotomized and assigned to separate brain structures is challenged by our results. Both processes appear to be supported by the hippocampus and by the structures in the adjacent parahippocampal gyrus. The recollection process may be additionally reinforced by strategic, effortful search directed by the frontal lobes (Buckner & Wheeler, 2001; Wheeler et al. , 1995). We suggest that the processes of recollection and familiarity are better viewed as related to memory strength and as contributing jointly to recognition memory performance (Wixted & Stretch, 2004). Within the medial temporal lobe, the hippocampus and the adjacent cortex do not exclusively support one process or the other.

Experimental Procedures

Participants

The young adults were 115 undergraduates (37 males) who received class credit for their participation. The memory-impaired patients were 5 males and 1 female (AB, KE, LJ, RS, GW, JRW; mean age = 56 years, range = 46-67; mean education =13.5 years). Estimates of the extent of medial temporal lobe damage were based on quantitative analysis of magnetic resonance images (MRI) for 5 of the 6 patients (all but AB) and either 19 controls (for KE, RS, GW, JRW) or 11 controls (for the female patient, LJ) (Gold & Squire, 2005). The hippocampus was reduced in volume bilaterally by a mean of 44 ± 2.9% (SEM), and all values were more than 3 SDs below the control mean. The adjacent parahippocampal gyrus was intact (mean volume reduction + 5.6 ± 4.3%; all values were within 2SDs of the control mean). On the basis of two patients (LM and WH) with similar bilateral volume loss in the hippocampus for whom detailed post-mortem neurohistological information was obtained (Rempel-Clower et al., 1996), this degree of volume loss likely reflects nearly complete loss of hippocampal neurons (also see Gold & Squire, 2005). Additional measurements, based on 4 controls for each patient, were carried out for the fusiform gyrus, insular cortex, and the lateral temporal, frontal, parietal, and occipital lobes (Bayley et al., 2005). With one exception (parietal lobe for RS), all values were within 1.3 SDs of the control mean. Additional information about the etiology of the memory impairment, volumetric measurements, and neuropsychological test performance appears in previous reports (Smith & Squire, 2005; Bayley et al., 2005). The controls for the patients were 8 adults (6 male) averaging 60.5 ± 3.6 years of age and 13.9 ± 1.0 years of education.

Stimuli

One hundred common English nouns were divided into two similar lists of 50 words each. Words were presented on a computer screen at both study and test. The two lists were counter-balanced within each retention-interval group so that across participants words were equally likely to be encountered as targets at study and as lures at test.

Procedure

Following a 250ms fixation cross, each word was presented for 2.5 sec and rated as pleasant or unpleasant on the keyboard. After studying 50 words, the young adults were assigned to one of 5 retention interval conditions (19-24 subjects at retention intervals of 1 h, 1 d, 1 w, 2 w, and 8 w). They returned later for a surprise memory test. For the test, the 50 target words were intermixed with 50 lures, and participants decided whether they recognized each item as having been presented before using a confidence scale of 1 (definitely New) to 6 (definitely Old). Following standard procedure, 5 pairs of hit and false alarm rates were computed for purposes of ROC analysis by cumulating responses from different points on the confidence scale (Macmillan & Creelman, 2005). The first hit and false alarm rate pair consisted of the proportion of targets and the proportion of lures that received a confidence rating of 6; the second pair consisted of the proportion of targets and the proportion of lures that received a confidence rating of 5 or 6, and so on down to the fifth pair, which consisted of the proportion of targets and the proportion of lures that received a confidence rating of 2 or more (confidence ratings of 1 are not included in an ROC analysis because 100% of the targets and 100% of the lures received a confidence rating of 1 or more). Before both the study and test sessions, participants acquainted themselves with the procedure by completing a brief practice run with novel items.

The memory-impaired patients and their controls followed the same procedure, except that the study-test interval was 3 minutes. The patients were also tested with shorter (10-item) study lists. Specifically, the patients studied 4 different lists of 10 words each, and a recognition test was administered 3 min after each study list. The study lists included 4 untested filler items (2 at the beginning and 2 at the end of the list) to reduce primacy and recency effects. The retention interval was filled with continuous conversation.

ROC Analysis

The group ROC data were analyzed by means of maximum likelihood estimation following standard methods (Ogilvie & Creelman, 1968), and fits to the data were calculated using Microsoft Excel's Solver routine. Fits of the standard unequal-variance detection model (Macmillan & Creelman, 2005) involved estimating 2 theoretically significant parameters (the distance between the target and lure distributions -- a parameter analogous to d' -- and the ratio of the standard deviation of the lure distribution to the target distribution -- which is the slope parameter) and 5 additional parameters, one for each confidence criterion (n criteria allow for n+1 levels of confidence). We also fit the data with the dual-process/detection model, which has been used to interpret ROC data (Yonelinas et al., 1998; 2002). Fits of this model also involved estimating two theoretically significant parameters (probability of recollection and distance between the familiarity distributions) and 5 additional parameters, one for each confidence criteria. Goodness of fit for both models was assessed by the chi-square statistic.

Supplementary Data

Nine coronal MR images from 5 patients and a control, together with a detailed description of the lesions, can be found online at www.neuron.org/cgi/content/full/49/3/459/DC1/ .

Acknowledgments

This work was supported by NIMH Grant 24600 and the Medical Research Service of the Department of Veterans Affairs. We thank Rayshawn Tabaldo, Julie Tran, Jennifer Frascino, Yael Shrager, and Jeffrey Gold for assistance.

Experiment 1, in full, is a reprint of the material as it appears in The Hippocampus Supports both the Recollection and the Familiarity Components of Recognition Memory in *Neuron, 49*. Wais, P. E., Wixted, J. T., Hopkins, R. O. and Squire, L. R. (2006). 459-466. The dissertation author was the primary investigator and author of this paper.

Table 1.1 Parameter estimates obtained by fitting the dual-process/detection model (Yonelinas et al., 1998) to the ROCs produced by the young adults across the 5 retention-interval conditions, the hippocampal patients across the two list-length conditions (H-50 and H-10), and controls for the patients (C-50). The recollection estimate is a probability (representing the probability of all-or-none recollection), and the familiarity estimate is a d' value (representing the standardized distance between the means of the target and lure distributions).

Condition	Recollection	Familiarity
1 hour	0.52	1.26
1 day	0.13	1.21
1 week	0.09	0.74
2 weeks	0.07	0.62
8 weeks	0.02	0.25
H-50	0.00	0.83
H-10	0.22	1.21
C-50	0.23	1.64

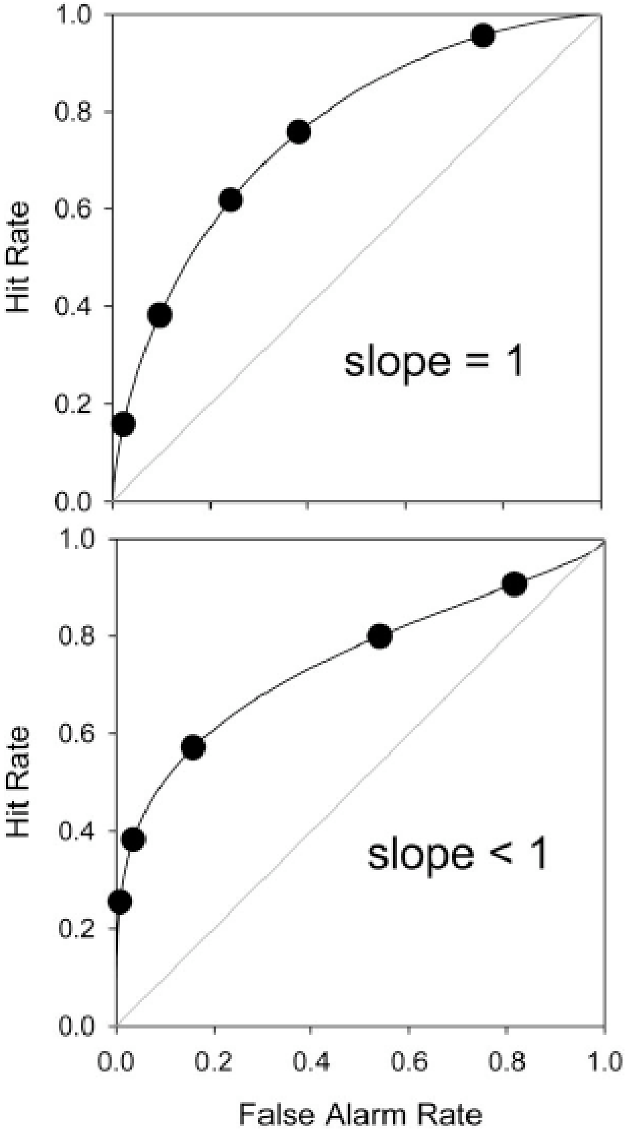


Figure 1.1 Hypothetical ROC data illustrating symmetrical and asymmetrical ROC plots. The degree of asymmetry evident in an ROC is typically quantified by a "slope" parameter obtained by fitting the standard signal detection model (Macmillan and Creelman, 2005) to the data. A slope of 1.0 denotes a symmetrical ROC, whereas a slope less than 1.0 denotes an asymmetrical ROC. The dual process/detection model would yield a recollection parameter estimate of 0 for the symmetrical ROC in the upper panel and an estimate greater than 0 for the asymmetrical ROC in the lower panel.

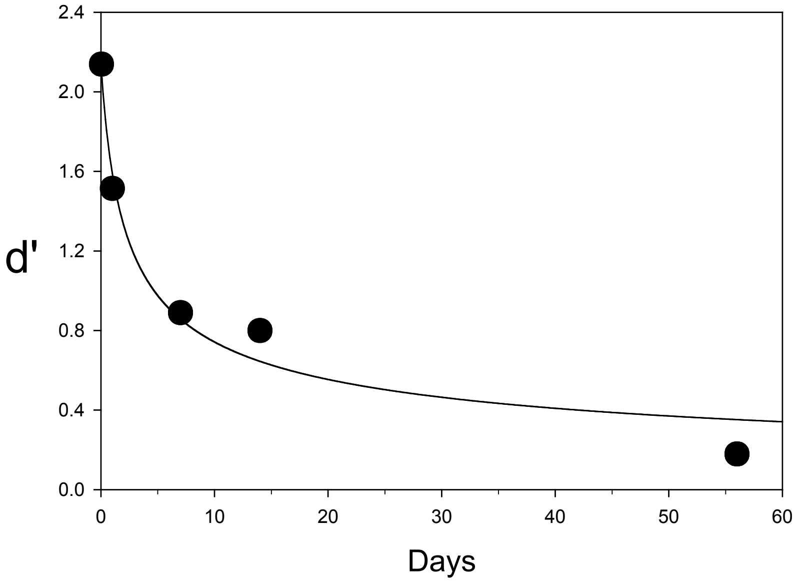


Figure 1.2 Recognition memory performance of young adults (19-24 group), tested with 50-item lists at five different retention intervals (1 hr, 1 day, 1 wk, 2 wk, 8 wk). Performance was quantified using the standard, bias-free measure of recognition memory (d'), as derived from signal-detection theory, where d' = z (Hit Rate) minus z (False Alarm Rate). The solid curve represents the least squares fit of a 3-parameter power function that typically provides a good fit of forgetting data (Wixted, 2004).

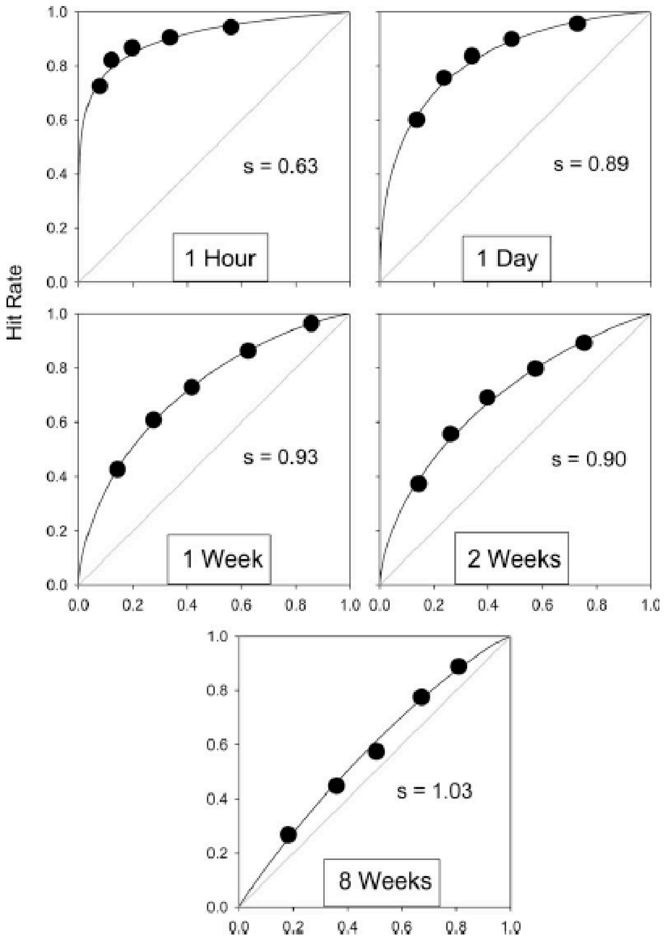


Figure 1.3 ROC data (hit rate vs. false alarm rate) produced by the young adults at each retention interval. Following convention, the smooth curves represent the best fits from the standard signal-detection model (Macmillan and Creelman, 2005), and the slope (s) values represent one of the parameters that is estimated when performing those fits. The chi-square test comparing each slope value to 1.0 was significant for the 1-hr, 1-day, and the 2-wk conditions ($\chi^2(1) \geq 6.21$, $p < .05$) and was marginal for the 1-wk condition, $\chi^2(1) = 2.70$, $p = .10$. For the 8-wk condition, the slope of 1.03 did not differ significantly from 1.0. Previous work using rats suggested that the ROC might be linear following a long retention interval (Fortin et al., 2004). The degree of linearity in the ROC from the 8-wk condition was assessed by comparing the fit of a 1-parameter curvilinear signal-detection model with the slope fixed at 1.0 (to match the data that we obtained at the 8-wk retention interval) and the fit of a 1-parameter pure-recollection version of the dual-process/detection model with the familiarity parameter fixed at 0 (to match the linear plot reported for rats in Fortin et al., 2004). The chi-square goodness-of-fit statistic associated with the former (10.94) was much lower than the latter (22.03), indicating that the curvilinear function offered a better description of the data than the linear function even at the longest retention interval.

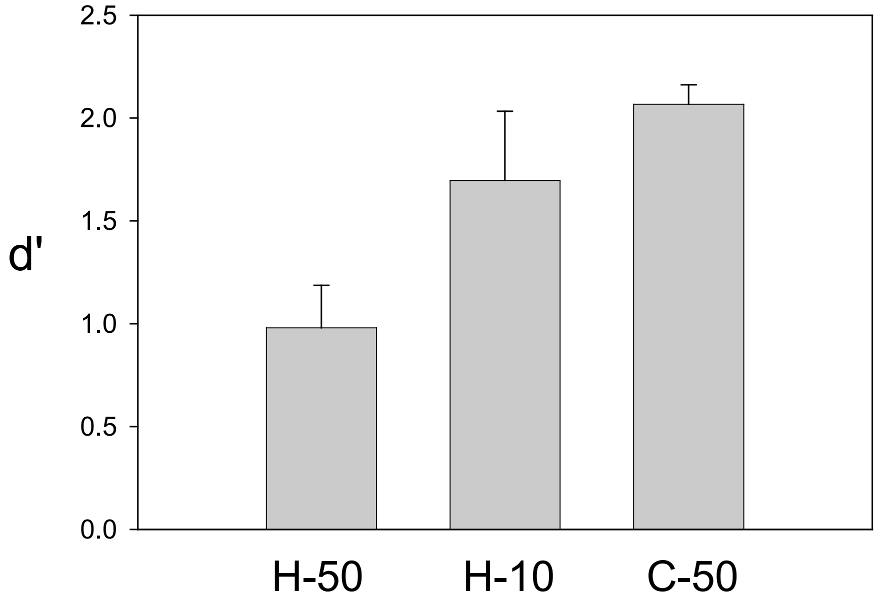


Figure 1.4 Recognition memory performance of the hippocampal patients, who were tested with 50-item (H-50) and 10-item lists (H-10), and controls (C-50), who were tested with 50-item lists (a retention interval of 3 minutes was used in each case). The mean score of the controls (C-50) was greater than that of the patients in the H-50 condition, $t_{(12)} = 5.23$ ($p < .01$), but similar to the d' score obtained by the patients in the H-10 condition ($p > .25$). The d' score in the H-10 condition was also greater than in the H-50 condition, ($t_{(5)} = 4.63$, $p < .01$).

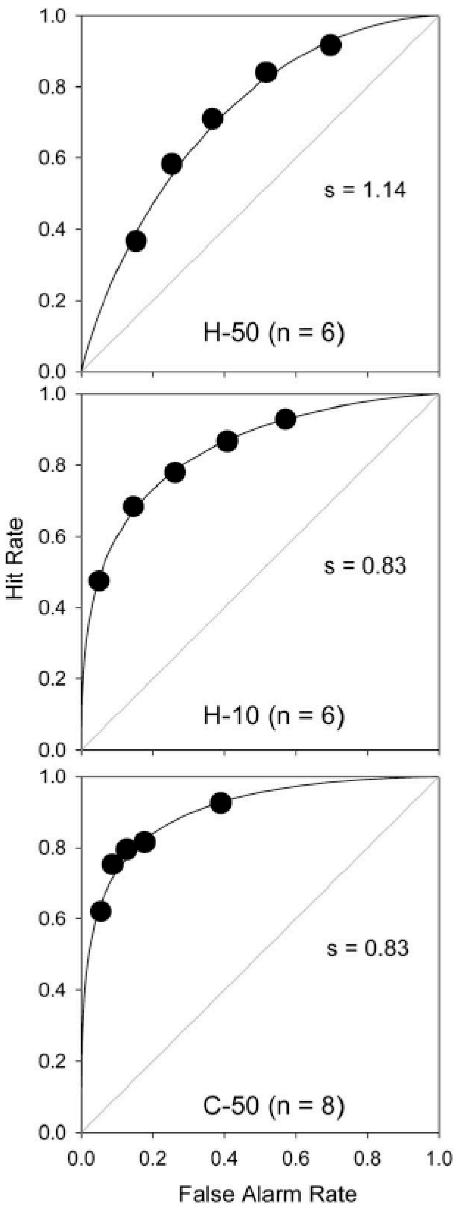


Figure 1.5 ROC data produced by the hippocampal patients in the 50-item condition (top panel) and the 10-item condition (middle panel) and by the controls in the 50-item condition (bottom panel). The slope (s) of 1.14 for the H-50 ROC was not different from 1.0 ($p < .15$), indicating that the ROC was symmetric. The slope of 0.83 for the H-10 ROC and the slope of 0.83 for the C-50 ROC were both less than the slope of 1.14 for the H-50 ROC ($\chi^2(1) \geq 4.70$, $p < .05$) and were significantly less than 1.0 by a one-tailed test ($\chi^2(1) \geq 2.70$, $p \leq .05$, one-tailed).

Experiment 2: Remember/Know Judgments Probe Degrees of Recollection

Summary

Remembering and knowing are states of awareness that accompany the retrieval of facts, faces and experiences from our past. Although originally intended to separate episodic from semantic memory, the dominant view today is that recollection-based decisions underlie remember responses, whereas familiarity-based decisions underlie know responses. Many functional magnetic resonance imaging (fMRI) studies as well as lesion studies have relied on the remember/know procedure to identify the neural correlates of recollection and familiarity. An implicit assumption of this approach is that know responses, which are thought to tap familiarity-based decisions, ought to be devoid of recollection. We investigated this issue by using a source memory procedure and found that the accuracy of source recollection was significantly above chance for studied words that were declared to be Old and Known. This held true even when the source decision was made before the Old/New decision (i.e., even after successful recollection had just occurred). Our results show that although recollection and familiarity may be different processes, the Remember/Know paradigm does not probe them directly. As such, dissociations involving Remember/Know judgments in fMRI studies and in studies involving amnesic patients should be interpreted in terms of memory strength (not memory processes).

Introduction

Dual-process theory holds that some recognition decisions are based on the recollection of contextual detail, whereas other decisions are based on a strong sense of familiarity unaccompanied by contextual information (Mandler, 1980; Curran & Hintzman, 1995). The dominant view in the recognition memory literature today is that recollection-based decisions are identified by remember (R) responses and that familiarity-based decisions are identified by know (K) responses. Many recent neuroimaging studies have used the remember/know (R/K) procedure to investigate the neural correlates of recollection and familiarity (e.g., Brewer et al., 1998; Eldridge et al., 2000; Eldridge et al., 2005; Gonzalves et al., 2006; Henson et al., 1999; Otten, 2006; Uncapher & Rugg, 2005; Wheeler & Buckner, 2004; Woodruff et al., 2005), as have studies that investigate the process-specific effects of hippocampal lesions (e.g., Aggleton et al., 2005; Holdstock, Mayes, Gong, Roberts & Karpur, 2005; Holdstock, Mayes, Isaac, Cezayirli, Roberts, O'Reilly, & Norman, 2002; Moscovitch & McAndrews, 2002; Verfaellie, Cook & Keane, 2003; Yonelinas et al., 1998; Yonelinas et al., 2002).

An explicit assumption underlying the R/K procedure is that individual recognition decisions involve one process or the other (never both processes together). An alternative view is that R/K judgments denote different levels of memory strength, not different processes. According to this view, high-strength memories (associated with R responses) are high in both recollection and familiarity, on average, whereas low-strength memories (associated with K responses) are lower in both processes, on average (Wixted, 2007). Such an account is consistent with the signal-detection interpretation of R/K judgments (Dunn, 2004; Wixted & Stretch, 2004; Donaldson, 1996).

A key difference between these two conceptualizations is how they interpret K judgments. According to most accounts, K judgments reflect familiarity-based decisions that are devoid of recollection. According to the alternative signal-detection account, they instead reflect decisions on the basis of low-strength memories that include lesser degrees of recollection (relative to R responses). One way to differentiate between these two accounts is to use a source recollection procedure. In this procedure, items are presented from one of two sources (e.g., words in either blue or red font). On the recognition test, participants are first asked to make an Old/New decision (along with an R/K judgment for each item that is declared to be old) and are then asked to recollect the item's source. If K responses reflect familiarity-based decisions that are devoid of recollection, then the accuracy of the subsequent source recollection decision ought to be at chance. If they instead reflect decisions that are partially based on recollection, then the accuracy of the subsequent source decision ought to be above chance (i.e., recollection accuracy should fall between that associated with R responses and chance performance).

Conway and Dewhurst (1995) and Perfect, Mayes, Downes and Van Eijk (1996) conducted source memory experiments along these lines and found that source accuracy associated with K responses was generally above chance, but not always significantly so. Eldridge et al. (2005) also found that source recollection success was significantly above chance levels for K responses and was higher still for R responses. In other words, K responses involved less recollective detail than R responses but did not signal the absence of recollective detail.

One way to reconcile above-chance source recollection for K responses with the traditional familiarity-based interpretation is to assume that the initial K response associated with the Old/New decision in these experiments was, indeed, based on recollection-free familiarity but that the subsequent source decision was based on recollection that became available after the Old/New judgment was completed. That is, recollection might have sometimes succeeded after a second query of memory or after additional search time that occurred between the Old/New question and the source question. The purpose of the research we conducted was to investigate that possibility and, more generally, to more clearly establish the relationship between K responses and the availability of recollective information. In the critical test, participants made a source decision *first* and then made an Old/New decision that was accompanied by a R/K judgment.

Method

Participants

The participants were 39 college undergraduates (10 males), who were recruited from the university experimental participants pool, gave their informed consent according to the university IRB protocol and received class credit for completing our experiment. The experiment was run in two versions, with 20 participants assigned to version 1 and 19 to version 2. All participants were native English speakers and free from the effects of any reported medication at the time they completed the experiment.

Stimuli

From a list of 200 English nouns developed in previous experiments (i.e., names of human body parts, American states, foreign countries and international cities), 70 target words were selected and divided into two equal lists such that block A and block B contained words that were as closely thematically matched as possible and balanced for word categories. The 130 remaining words were used as lures during the test session. All stimuli were presented using E-Prime 1.1.4.1 (© Psychology Software Tools, Inc.) scripts on a Dell Dimension 4550 desktop computer and 17-inch liquid crystal display throughout both the encoding and test conditions.

Procedure

Participants were informed that lists of words would be presented in front of them and instructed about how to perform their tasks for each session. Participants ran brief practice scripts before each the encoding and test sessions to ensure their familiarity with their tasks. In the encoding session, each target word was presented for 5.0 seconds while the participant rated each word as pleasant or unpleasant on the computer keyboard. Words in block A were presented above the center of the screen in blue Helvetica font, and words in block B were presented below the center of the screen in red Tahoma font (these were the two sources). During the practice session, each participant was advised that their memory for the words, including the presentation color, would be tested when they returned for their second session.

After a one-hour retention interval, each participant completed a recognition test. The 200 test words were presented in four equal blocks, providing the participant a 10-second rest break in between blocks. Test words were presented in black Courier font for 5.0 seconds during each of two test questions. The recognition test included an old/new question in one step, for which participants could answer Remember, Know, Guess or New as they viewed the test word, and a source recollection question in another step, for which they either entered their confidence rating about the color that the word was presented in during the encoding session, or they entered New. Their source confidence rating was entered on a seven-point scale (e.g., definitely, probably, maybe blue; New; definitely, probably or maybe red). A Guess (G) option was provided during the old/new phase because prior research by R/K theorists has been interpreted to mean that subjects tend to include guesses in their K responses rather than in their R responses, thereby selectively contaminating the former (e.g., Gardiner, Java & Richardson-Klavehn, 1996; Gardiner, Richardson-Klavehn & Ramponi, 1997).

The experiment was run in two versions. The versions were identical in terms of the study phase, but differed in regard to the test phase. In the test phase of version 1, each item was presented for an Old/New decision followed by the source recollection question. In version 2, the question order was reversed so that participants answered the source recollection question first, before answering the old/new question. Before practicing the test session, each participant received specific instructions about the use of the R, K and G responses for the old/new task and heard the descriptions developed by Gardiner and Richardson-Klavehn (2000) verbatim. Those instructions are reproduced here in the Appendix. Participants were encouraged to have these instructions repeated to them until they were completely clear about when to apply each type of recognition response. In both experiments, it was made clear to subjects that the R/K/G judgment pertained to the item's status on the list (i.e., the question pertained to the Old/New decision).

Results

All participants performed well on the item recognition task, but the source recollection task proved to be more difficult. Of the 39 participants tested in the two versions of the experiment, the source recollection performance of 13 participants did not exceed chance (7 participants in version 1 and 6 participants in version 2). Of those, 6 were slightly (and nonsignificantly) below chance, and 7 were slightly (and nonsignificantly) above chance according to a binomial test. Because the data from these participants could not help to address the main question of interest (namely, is source accuracy for K responses greater than chance but less than that for R responses?), their results were analyzed separately.

Old/New Performance

Performance on the Old/New portion of the task is shown in Table 1. The results for version 1 (n =13) and for version 2 (n=13) show the performance of the participants who exhibited above-chance accuracy on the source recollection question. The table also shows the combined performance of the 13 participants from both versions of the experiment who did not exhibit above-chance source-recollection accuracy. The overall hit and false alarm rates (bottom line of the table) were similar for all three groups. In version 1, the mean hit and false alarm rates were .88 and .18, respectively, and the mean d' was 2.22. In version 2 (in which the source recollection question preceded the old/new question), the mean hit and false alarm rates were .90 and .21, respectively, and the mean d' was 2.23. For the 13 participants who failed to exhibit above-chance source recollection, the mean hit and false alarm rates were .86 and .24, respectively, and their mean d' was 2.05. Separate ANOVAs performed on the hit rates, false alarm rates and d' scores from the three groups were all far from significant. Table 2.1 also shows the hit and false alarm rates broken down by response category (R, K and G), and these were similar across groups as well.

Figure 2.1 shows the mean accuracy of Old/New decisions as a function of response category (Guess, Know or Remember) for all 39 participants combined. Remember accuracy for a given participant is equal to the R hit rate divided by the sum of the R hit rate plus the R false alarm rate; Know accuracy is equal to the K hit rate divided by the sum of the K hit rate plus the K false alarm rate; and Guess accuracy is equal to the G hit rate divided by the sum of the G hit rate plus the G false alarm rate. The results show that subjects actually were guessing when they used the Guess option, as their accuracy for those responses was not significantly different from chance. In addition, R responses were highly accurate, while accuracy for K responses fell between these two extremes. This outcome is consistent with both the dual-process interpretation of R/K judgments and with the signal-detection interpretation. According to the dual-process view, R accuracy ought to be high because it is based on recollection, whereas familiarity-based K responses might be expected to be less accurate (and random guesses should obviously be less accurate still). According to the signal-detection view, G, K and R responses reflect gradations of memory strength and so should exhibit precisely the pattern shown in Figure 2.1.

Source Recollection

In version 1, the mean source recollection performance for the 13 participants who exhibited above-chance source accuracy was 68% correct. The corresponding value in version 2 was 65% correct, and these values did not differ significantly. Mean source recollection accuracy for the 13 participants who did not exhibit above-chance source recollection was 51%.

The key findings of this experiment concern source accuracy for Old/New decisions that received G, K or R responses. The mean source accuracy for words that received a G response during the Old/New recognition test was 0.46 (0.09), which did not differ significantly from chance, $t(11)= -0.63$, $p< .55$. For K responses, mean source accuracy was 0.60 (0.06), which was significantly above chance, $t(11)= 3.69$, $p<.01$. One participant who did not make any K responses (and therefore who had no source accuracy score for K responses) was not included in this analysis. For R responses, mean source accuracy was 0.72 (0.03), which was also significantly above chance, $t(12)= 7.45$, $p< .01$.

Similar results were observed in version 2. For G responses, source accuracy was 0.51 (0.08), a value that was not significantly different from chance. For K responses, source accuracy was 0.59 (0.06), which was significantly above chance, $t(11)= 3.70$, $p< .01$. Once again, one participant who did not make any know responses was not included in this analysis. For R responses, source accuracy was 0.68 (0.02), which was also significantly above chance, $t(12)= 7.53$, $p< .01$.

The two versions of the experiment did not produce significantly different source accuracy results for G, K of R responses, so the data from the two versions were collapsed for further analysis. Figure 2.2 shows source accuracy as a function of the judgment associated with the Old/New decision (Guess, Know and Remember) for the 26 participants who exhibited above-chance source recollection. This figure summarizes the main result of our study. The critical finding is that these data show that recollective success increases monotonically across the three judgments. A linear trend analysis as a function of memory strength (with Guess, Know and Remember representing low, medium and high strength) was highly significant, F(1,21) = 12.86, $p<.01$.

Not surprisingly, no such effects were evident for the 13 participants whose overall source accuracy did not exceed chance. Although their Old/New recognition memory performance was similar to that of the other subjects (as shown in Table 1), they clearly did not encode the source information. For these participants, source accuracy for G, K and R responses was .42, .49, and .52, respectively, none of which differed significantly from chance. A linear trend analysis performed on these data was also far from significant, F(1,8) = .166.

Discussion

The question addressed by this research is whether K responses reflect high-confident familiarity-based decisions, as is often assumed (and as standard R/K instructions stipulate), or decisions that are based on relatively low memory strength -- including some degree of recollection. We investigated this issue by using a source memory procedure and found that source recollection accuracy was significantly above chance for items that were declared to be Old and Known. Moreover, this held true even when the source question was asked before the Old/New question (i.e., after participants had often just successfully recollected information about the test item). In a more typical arrangement, the Old/New question is asked first and then the source decision is made. A few prior experiments, like version 1 of the present experiment, found that source recollection accuracy for K responses was usually greater than chance. That finding suggests that K responses might involve recollection after all, but an alternative explanation is that source recollection succeeded after the Old/New decision had been made on the basis of familiarity. Version 2 of our experiment would appear to rule that possibility out. In that version, participants made a source decision first and then made an Old/New decision (along with an R/K/G judgment). Even under those conditions, source accuracy for items declared to be Old and Known was significantly above chance (cf. Hicks, Marsh, & Ritschel, 2002). This result suggests that K responses are associated with low-strength memories (including partial recollection), not with high-strength memories that only involve familiarity. This outcome is entirely consistent with the signal-detection interpretation of R/K judgments (Donaldson, 1996; Dunn, 2004; Wixted & Stretch, 2004; Wixted, 2007).

Dissociations in neural activity between remembering and knowing are often construed as supporting the idea that (a) subjective reports can easily distinguish between recollection and familiarity and (b) different regions of the brain underlie those processes. However, the present results suggest that it may be worth considering what those dissociations would mean if the signal detection account is correct. In the case of functional magnetic resonance imaging, one simple possibility is that the relationship between neural activity and memory strength (as indexed by misses, K responses, and R responses) is nonlinear and that the nature of that nonlinearity differs depending on the brain structure in question. That this might be true should not be surprising given that one class of neurons responds to novelty, whereas another class responds to prior occurrence (Rutishauser, Mamelak, & Schuman, 2006; Viskontas, Knowlton, Steinmetz, & Fried, 2006). The memory strength signal is, presumably, a joint function of the activity of these neurons. If the proportion of novelty-detecting neurons and prior-occurrence-detecting neurons differs across the brain structures of the medial-temporal lobe, then the relationship between memory strength and neural activity is likely to differ as well (perhaps qualitatively). Whatever the reason for the observed dissociations between remembering and knowing, our point is that such dissociations should not be attributed to recollection and familiarity because the R/K procedure probes degrees of recollection, not distinct memory processes.

Appendix

Test response instructions for the Remember/Know paradigm that were read to participants in two experiments which examined process purity (Gardiner & Richardson-Klavehn, 2000):

“Recognition memory is associated with two different kinds of awareness. Sometimes when you recognize a word on the test list as one from the first session, recognition will bring back to mind something you remember thinking about when the word appeared then (on the first session list). You recollect something you consciously experienced at that time. In a case like this, click the Remember button.

But sometimes recognizing a word as one you saw during the first session will not bring back to mind anything you remember about seeing it then. Instead, the word will seem familiar, so that you feel confident it was the one you saw yesterday, even though you don’t recollect anything you experienced when you saw it then. Click the Know button in a case when recognition is accompanied by strong feelings of familiarity in the absence of any recollective experience.

There will also be times when you do not remember the word, nor does it seem familiar, but you might want to guess that it was one of the words you saw during the first session. Click Guess if your response is really just a guess."

Footnotes

[1] Confidence ratings were calculated on the basis of the test instructions to the participants where 3 equaled definitely, 2 equaled probably and 1 equaled maybe.

Acknowledgment

Experiment 2, in full, is a reprint of the material as it appears in Remember/Know Judgments Probe Degrees of Recollection in *Journal of Cognitive Neuroscience, 20*. Wais, P. E., Mickes, L. and Wixted, J. T. (2008). The dissertation author was the primary investigator and author of this paper.

Table 2.1 Mean Hit and False Alarm rates for version 1 (n= 13), version 2 (n= 13) and excluded participants (n= 13) are listed with the standard error of those means. Hits represent the proportion of targets endorsed as old, and false alarms represent the proportion of lures endorsed as old.

	With Source Recollection				**Without Source Recollection**	
	Version 1		**Version 2**		**Combined**	
	hits	***false alarms***	***hits***	***false alarms***	***hits***	***false alarms***
Remember	0.58 (0.06)	0.02 (0.01)	0.66 (0.06)	0.05 (0.01)	0.65 (0.05)	0.06 (0.01)
Know	0.24 (0.06)	0.05 (0.01)	0.15 (0.03)	0.07 (0.02)	0.14 (0.02)	0.08 (0.01)
Guess	0.06 (0.01)	0.11 (0.02)	0.09 (0.02)	0.09 (0.02)	0.07 (0.02)	0.10 (0.03)
OLD/NEW	0.88 (0.02)	0.18 (0.03)	0.90 (0.02)	0.21 (0.03)	0.86 (0.03)	0.24 (0.04)

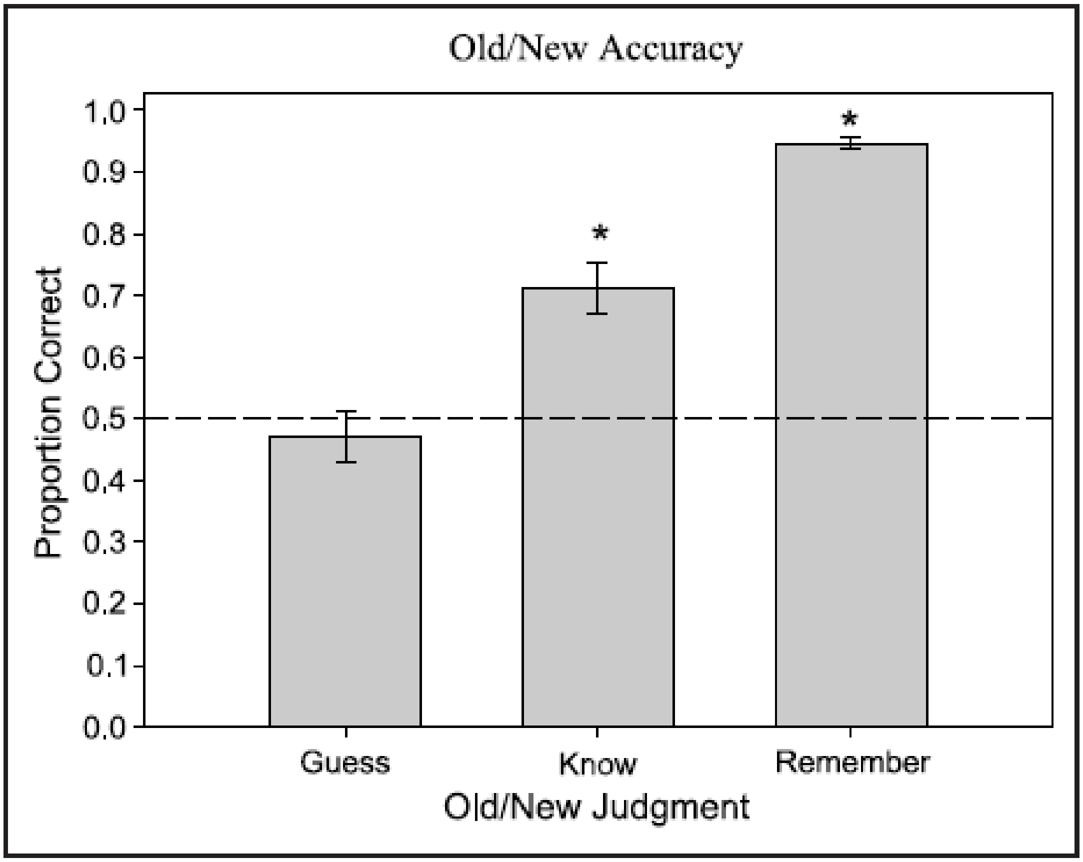


Figure 2.1 Old/New accuracy for Remember, Know and Guess responses collapsed across all subjects (n= 39). For both Remember and Know responses, mean proportions with correct source judgments were significantly above chance (*p*< .01).

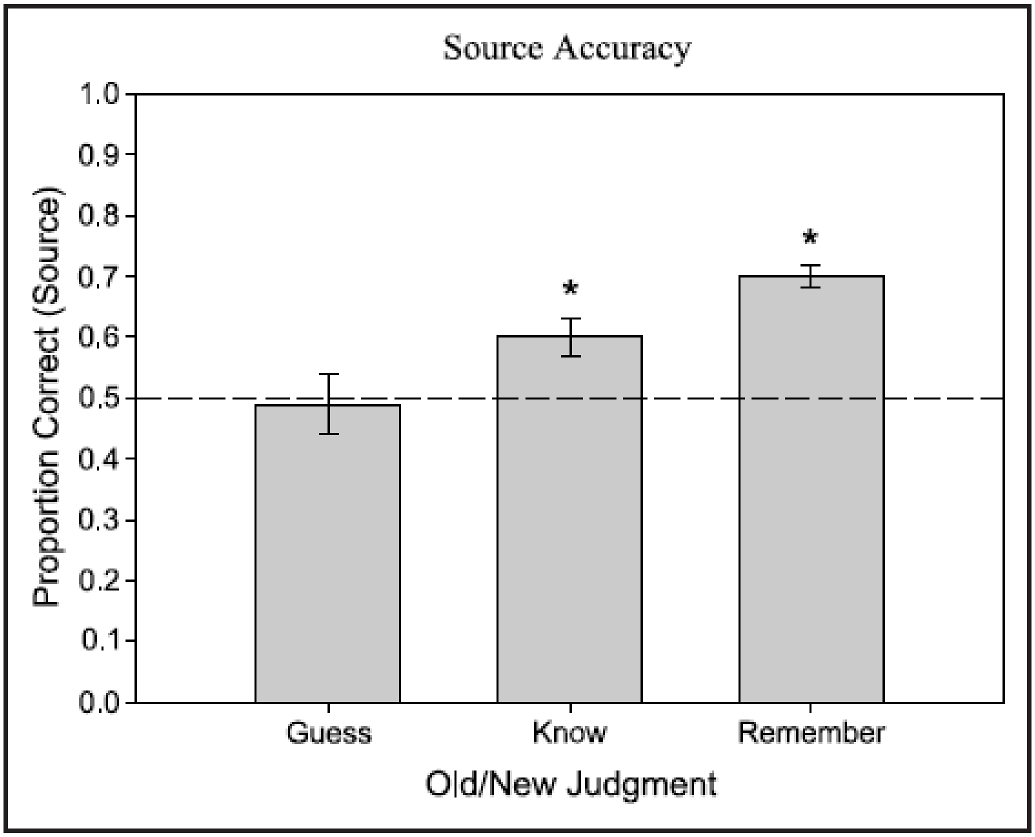


Figure 2.2 Source accuracy for Remember, Know and Guess responses collapsed across version 1 and version 2 (n= 26). For both Remember and Know responses, mean proportions with correct source judgments were significantly above chance (p< .01).

Experiment 3: Recognition Memory Processes in the Medial Temporal Lobe: A Quantitative Meta-Analysis of fMRI Results

Summary

To identify patterns of memory-related neural activity in the medial temporal lobe (MTL), a quantitative meta-analysis of 17 functional magnetic resonance imaging (fMRI) studies was performed. The analysis shows that increased activation in the hippocampus and the perirhinal and parahippocampal cortices predicts subsequent memory strength. During retrieval, activation in the hippocampus increases as memory strength increases, while activation in perirhinal cortex is below the level for misses and inversely correlated with memory strength. The results are consistent with the claim that the hippocampus selectively subserves recollection, whereas adjacent structures subserve familiarity (Eichenbaum, Yonelinas & Ranganath, 2007). However, this conclusion depends on a specific dual-process theory of recognition memory that has been used to interpret the results. An alternative dual-process model holds that the behavioral methods used to differentiate recollection from familiarity instead separate strong memories from weak memories. When the fMRI data are interpreted in terms of the alternative theory, the fMRI results do not point to selective roles for the hippocampus or the adjacent MTL structures. The fMRI data alone cannot distinguish between these two models, so other methods are needed to resolve the issue.

Introduction

We recognize something when we can match it with an experience from our past. Bringing facts and events into a conscious state of mind from our past relies upon the processes of declarative memory (Squire, 1992). Although cognitive models for different declarative memory processes are well defined, the determination of how recognition is supported by the brain remains an open debate. Neuroscience research has demonstrated that the organization of the central nervous system is specialized by behavioral function, but the details of a functional organization in the brain that subserves recognition memory have yet to be completely worked out.

The search for a functional brain map of recognition memory began with the study of patient HM, which uncovered the first empirical data showing how the human brain mediates memory processes (Scoville & Milner, 1957). A large literature has subsequently elucidated the model for a cortical-hippocampal system for declarative memory (Squire & Zola-Morgan, 1991; Eichenbaum, 2000; and Aggleton & Brown, 2006). This research demonstrates how the hippocampal region is critical for recognition (the hippocampal region includes the dentate gyrus, the hippocampus proper and the subicular complex). These studies reach no consensus, however, about how a functional organization of the hippocampal region and the medial temporal lobe (MTL, **Figure 3.1**) support different processes in recognition.

Recognition is described in most memory research as relying on two processes, recollection and familiarity (Mandler, 1980; Curran & Hintzman, 1995). Recollection refers to remembering an event with associated contextual details, whereas familiarity refers to memory absent any contextual information. Neuroanatomical studies in humans and nonhuman primates have traced pathways indicating that the perirhinal and parahippocampal cortices, as well as the hippocampal region, contribute directly to declarative memory (Lavenex & Amaral, 2000; Suzuki & Amaral, 1994; and Amaral & Insausti, 1990). Some findings from comparative psychology suggest a dissociation between how different MTL regions subserve different recognition memory processes. Results from studies with rats, whose MTL anatomy is comparable to humans, have been interpreted to show that recollection depends upon the hippocampus (Fortin, Wright & Eichenbaum, 2004) and that familiarity depends on the perirhinal cortex (Brown & Aggleton, 2001). Some research with humans suggests a similar dissociation and has been interpreted to show that specific MTL regions subserve only selective roles in recognition memory processes (Yonelinas, Kroll, Quamme, Lazzara, Sauve, Widaman & Knight, 2002).

Other research, however, shows that although memory is impaired for amnesic patients in comparison to healthy controls, no functional selectivity for the hippocampus was indicated for either familiarity (Manns, Hopkins, Reed, Kitchener & Squire, 2003) or recollection (Wais, Wixted, Hopkins & Squire, 2006). Evidence from cellular recordings measured in humans suggests that some hippocampal cells are active selectively when stimuli are novel while others are active selectively when stimuli are familiar, whether or not task-relevant source information is recollected (Rutishauser, Mamelak & Schuman, 2006; Rutishauser, Schuman & Mamelak, 2008). The activity associated with familiar items in the absence of source recollection was interpreted to mean that the hippocampus supports familiarity-based decisions, though one cannot exclude the possibility that it instead reflects unmeasured recollection of task-irrelevant information. In any case, such research opportunities with humans are few, however, and a more common approach relies on event-related functional magnetic resonance imaging (fMRI) to measure neural activity in healthy participants during encoding or retrieval tasks. fMRI is capable of fine spatial resolution that can locate these signals to the hippocampal region and the adjacent structures along the parahippocampal gyrus. A dissociation between the activity associated with recollection and the activity associated with familiarity wouild suggest that these separable recognition processes are supported by different structures within the MTL. One caveat about fMRI, however, is that it measures activity associated with performance on a task and does not indicate whether the activity in a particular region is causal for the behavior. fMRI results are therefore best interpreted along with corroborating findings from neuropsychology that are based on direct evidence.

Another issue confusing the fMRI literature for recognition memory is that few of these studies have important details of their experimental designs in common, such as study task or recognition test paradigm, so these different designs may not be testing the same memory processes. More importantly, none of these studies examining recognition have equated confidence (or memory strength) associated with decisions thought to reflect recollection with confidence associated with decisions thought to denote familiarity— these results, therefore, may confound memory strength with memory processes (Squire , Wixted & Clark, 2007).

Citing the many differences between the experimental manipulations in the fMRI studies examining recognition, a recent review concluded that their results were not readily convergent and pointed to only a trend toward a functional network including the hippocampus and other regions in the MTL (Henson, 2005). Two other reviews that examined results from both fMRI and amnesic patient studies (Eichenbaum, Yonelinas & Ranganath, 2007; Skinner & Fernandes, 2007) proposed how these results should be interpreted to find selective roles for the hippocampus (subserving recollection) and the perirhinal cortex (subserving familiarity). That is, Eichenbaum et al. (2007) and Skinner & Fernandes (2007) both held that the fMRI studies they reviewed had effectively isolated the neural correlates of recollection and familiarity. Critically, these two latter reviews interpreted the imaging data from a particular theoretical perspective that assumes that certain behavioral methods are effective in teasing apart recollection and familiarity. An alternative dual-process theory holds that these methods separate strong memories from weak memories (Squire et al., 2007; Wixted, 2007) and that each of these strength categories can include decisions based on recollection and decisions based on familiarity. It is important to consider what recent neuroimaging data might mean when viewed from both perspectives.

The following review provides a quantitative meta-analysis of results from 17 neuroimaging studies and examines how the empirical trends are explained by different psychological models. Therefore, in addition to quantifying empirical trends, this review underscores the point that the interpretation of these trends is always guided by a psychological model of recognition memory and that more than one model can be applied— a fact that is often overlooked.

Across the group of 17 papers in this meta-analysis, most investigators interpreted their findings from the perspective of one model of recognition memory. This model, the high-threshold/dual-process view, holds that individual recognition decisions are based on either recollection, which occurs only above a high-strength threshold, or on familiarity (Yonelinas, 1994, **Table 3.1**). Therefore, according to this account, confidence ratings and Remember/Know judgments can be used to distinguish between the two processes. An alternative perspective holds that recognition decisions are based on a continuous strength variable. This view is compatible with a single-process account of recognition, but it is also compatible with dual-process theory if recollection and familiarity are both assumed to be continuous processes (Wixted, 2007, **Table 3.1**). In that case, both processes could contribute to an aggregated-strength memory signal whether that signal is weak or strong. The important point is that the aggregated-strength/dual-process view holds that individual recognition decisions are not based solely on recollection or solely on familiarity. This view holds that underlying memory processes cannot be inferred from data based on confidence ratings or Remember/Know judgments because some degree of recollection and some degree of familiarity underlies most every recognition decision. Some have argued that the aggregated-strength/dual-process view has been differentially supported in recent behavioral studies when evaluated against the high-threshold/dual-process model that guides the interpretation of many of the current fMRI results (e.g., Slotnick & Dodson, 2005; see Wixted, 2007, for a review), but others disagree (Parks & Yonelinas, 2007). Instead of trying to resolve that debate, this review will consider what the neuroimaging results reveal according to both theoretical perspectives.

Method

A survey of 21 studies, which had applied event-related neuroimaging techniques to examine MTL processes in healthy participants during either the encoding or retrieval phases of recognition tests, were selected for inclusion based on the following criteria:

i) Activation was reported in the hippocampal region and/or the adjacent MTL.

ii) The neuroimaging data were analyzed in one of the following ways:

   a. activity correlated with item-plus-source recognition and with item-without-source recognition was contrasted with activity correlated with misses,
   b. activity was analyzed according to levels of recognition confidence, or
   c. activity was analyzed according to Remember/Know/Guess responses.

These criteria were chosen because they capture the large majority of neuroimaging studies that have been conducted to investigate the neural correlates of recollection and familiarity. Twenty of these studies employed fMRI, and one study additionally employed magnetoencephalography (MEG) to examine a second set of participants in the same experimental design (Gonsalves, Kahn, Curran, Norman & Wagner, 2005).[1] Out of the 21 studies, 17 reported, or the investigators made available by direct request, enough statistical information to make it possible to plot their results as z-scores showing the differences in neural activation between memory success and forgetting (**Table 3.2**).

The significant effects reported by these 17 fMRI studies were placed on a common scale by transforming their results into z-scores. Six studies measured brain

---

[1] Gonsalves et al. recruited two groups of participants and applied the same general design to both fMRI and magnetoencephalography (MEG) versions of their experiment. The fMRI and MEG results show substantially the same pattern, and, for ease of presentation, the term fMRI in the remainder of this review will include this particular MEG study.

activation correlated with the study phase (encoding), while the other 11 studies measured activation during the test phase (retrieval). Results from the encoding studies show MTL activation that predicts subsequent memory (subsequent hit vs. subsequent miss), while results from the retrieval studies show MTL activation correlated with concurrent memory (hits vs. misses).

The meta-analysis begins by separating the results from the 17 studies into comparable categories. These categories include encoding and retrieval phases, brain regions of interest by hemisphere and neuroanatomical convention (ROI), and stimulus types. Because the results did not differ substantially whether the test stimuli employed were words or images (for an example, see Kensinger & Schacter, 2006), data from both stimulus types have been collapsed in the meta-analysis. Each of the studies reported activation in one or more of the neuroanatomical regions of interest in MTL commonly described as subserving declarative memory (Brown & Aggleton, 2001; Eichenbaum, 2000). Two studies reported results from both the encoding and retrieval phases, and all of their results have been included in the meta-analysis (Eldridge, Engel, Zeineh, Bookheimer & Knowlton, 2005; Henson, Hornberger & Rugg, 2005).

The 17 studies reported activation according to functional regions of interest. In an effort to improve the outcome of normalization across their datasets, three studies took the additional step of aligning each of their participant's functional data for the MTL onto templates prescribed by specific anatomical landmarks (Gold, Smith, Bayley, Shrager, Brewer, Stark, Hopkins & Squire, 2006; Eldridge et al., 2005, both encoding and retrieval). The results listed by MTL region in the meta-analysis represent the original authors' characterization of the localization of their fMRI data after the normalization, spatial smoothing and group analyses performed under their respective protocols. The results from the 17 studies are distributed as follows:

i) for the five encoding studies in the meta-analysis:

  a. five reported results for the hippocampus
  b. four reported results for the perirhinal cortex
  c. one reported results for the entorhinal cortex
  d. four reported results for the parahippocampal cortex.

ii) for the 10 retrieval studies in the meta-analysis:

  a. four reported results for the hippocampus
  b. seven reported results for the perirhinal cortex
  c. four reported results for the parahippocampal cortex.

iii) two studies applied a high-resolution scanning technique during fMRI, and their results are reported separately for each of the above categories.

For each ROI, the brain activation results were placed into three categories: Recollection/strong, Familiarity/weak and miss. These labels are applied in order to fairly represent how the different dual-process views introduced above interpret the successful memory categories. In the case of the Recollection/strong category, the results include activation correlated with item-plus-source recognition, highest-confidence hits and Remember responses. The high-threshold view holds that these are all indicative of recollection-based decisions, whereas the aggregated-strength view instead holds they reflect strong memory (which may be based on a combination of strong familiarity and strong recollection). In the case of the Familiarity/weak category, the results include activation correlated with item-without-source recognition, low-confidence hits and

Know responses. The Familiarity/weak category represents solely familiarity-based decisions according to the high-threshold view, but indicates weak memory (weak in both recollection and familiarity) according to the aggregated-strength view. Results for the miss category include activation correlated with responses for stimuli studied but not recognized at test.

Based upon hits in either the Recollection/strong or Familiarity/weak categories (hits are previously studied stimuli that are recognized at test), z-activity for each result was determined by the calculation:

z-activity = (signal for hit – signal for miss) / standard deviation.

The results from each study were given equal weight in the calculation of the mean z-activity for each of the two response categories (i.e., Recollection/strong and Familiarity/weak) in each of the ROI's. The standard deviation used for each calculation was drawn from the statistics reported for that particular contrast. For example, some studies reported t-tests that made comparisons between mean signal for Remember and mean signal for misses, in which case the standard deviation statistic necessary to compute a z-score was obvious.[2] Other studies reported the mean signal amplitude for

---

[2] Eldridge et al. (2005) reported that the mean signal change in the left subiculum that correlated with Remember responses was significantly greater than that for Forgotten responses ($t(8) = 2.70$, $p < 0.03$). From this example, the standard deviation can be computed to equal 0.03 units.

each confidence level (with its standard error),[3] in which case the standard deviation statistic necessary to compute the z-transform was calculated from the error reported for the misses.[4]

As described above, the meta-analysis uses the miss condition as the baseline from which to assess neural activity correlated with memory effects. This approach best fits the 17 fMRI studies in this review because all of the authors have characterized their activation data for the miss condition as being correlated with forgetting, or predicting the subsequent forgetting of, previously-studied stimuli. Neural activity correlated with memory effects is commonly identified in the fMRI literature by the contrast between signal from trials when previously-studied stimuli are endorsed as old (hits) versus trials when previously-studied stimuli are mistaken as new (misses).

It is worth noting that another possible explanation for the signal correlated with the miss condition would make the preceding interpretation of these memory effects more difficult. Neuroimaging studies that have made specific assessments of misses have found that some misses are correlated with increased levels of neural activation that are equal to

---

[3] Kensinger et al. (2006) reported that the mean signal change in the left hippocampus that correlated with subsequent Misses (words) had a standard error of 0.02 units. From this example (n= 21), the standard deviation can be computed to equal 0.09 units.

[4] Most of the studies in this review pooled their error terms per the common approach for within-subjects analysis described by Loftus & Masson (1994). For those few studies that reported an error term for each parameter estimate (i.e., Daselaar, Fleck & Cabeza, 2006), it is possible that their error terms would have been smaller using the pooled approach, although the degree to which this would be the case is uncertain.

or greater than those correlated with weak memories on the one hand, or correct rejections on the other hand (Stark & Okado, 2003; Stark & Squire, 2001). These results suggest that the mean signal for the miss condition actually represents an average of activation ranging from the small signal correlated with very weak memory (i.e., chance judgments in an old/new task) up to the greater activation correlated with novelty effects from correct rejections. These findings from Stark and others raise a concern about whether the hit versus miss contrast commonly applied in the neuroimaging literature is sensitive enough to be interpreted as the difference between recognizing and forgetting. Eleven of the 17 fMRI studies reviewed here did report activation correlated with a correct rejection condition (Daselaar, Fleck & Cabeza, 2006; Montaldi, Spencer, Roberts & Mayes, 2006; Eldridge et al., 2005, both encoding and retrieval; Gonsalves et al., 2005, both fMRI and MEG; Henson et al, 2005, both encoding and retrieval; Kahn, Davachi & Wagner, 2004; Weis, Specht, Klaver, Tendolkar, Willmes, Ruhlmann & Fernandez, 2004; and Rugg, Henson & Robb, 2003), and, in each case, such activation was equal to or greater than the signal change those studies reported for misses. Therefore, it is noted that findings for a null result in the contrasts of activation correlated with weak memory conditions (e.g., item-without-source in some studies, low-confidence hits and Know responses in other studies) versus miss should be interpreted with caution.

As indicated earlier, across the 17 studies, the investigators used three different approaches to identify different recognition processes: item-without-source compared to item-with-source recognition; the Remember/Know procedure; or the high-threshold/dual-process model that interprets the highest confidence level as recollection (Yonelinas, Kroll, Dobbins, Lazzara & Knight, 1998). In 10 studies, the behavioral responses indicated whether studied items were recognized with source information, recognized without source information, or missed (“forgotten”). Four studies used the Remember/Know procedure (Eldridge et al., 2005, encoding and retrieval; Gonsalves et al. 2005, fMRI and MEG), albeit with different interpretations about whether Remember and Know responses are diagnostic for the recollection and familiarity processes, respectively. A fifth study used a variation on the Remember/Know procedure intended to examine degrees of familiarity (Montaldi et al., 2006). One study used the difference between shallow and deep encoding to assess the neural correlates of familiarity in comparison to recollection, respectively (Henson et al., 2005). The remaining study included in the meta-analysis measured only recognition confidence on a seven-point scale (Daselaar et al. 2006) and interpreted the highest-confidence hits as recollection-based responses and the remaining hits as familiarity-based responses.

Results

A review of the results for the studies in the meta-analysis is presented in the following manner:

i) A summary for each region of interest cited by the 15 typical-resolution fMRI studies (i.e., the hippocampal region and the perirhinal, entorhinal and parahippocampal cortices from each hemisphere) shows the z-activity computed from the results for each referenced study (shown in **Table 3.3**).

ii) A summary for the two high-resolution fMRI studies is shown separately (**Table 3.4**).

iii) An overall summary of the observed trends (separately for the left hemisphere and for the right hemisphere) is presented for the encoding phase (**Figure 3.2**) and for the retrieval phase (**Figure 3.3**).

Hippocampal Region.

The results from the five studies in the meta-analysis that collected fMRI data during the encoding phase show that the level of z-activity in the hippocampus (**Table 3.3**, Hippocampal region, see Gold et al., 2006; Kensinger et al., 2006; Henson et al., 2005; Ranganath, Yonelinas, Cohen, Dy, Tom & D'Esposito, 2004; and Davachi, Mitchell & Wagner, 2003) that predicts Recollection/strong responses is significantly greater than the levels predicting either Familiarity/weak or miss responses ($t(8) = 3.58$, $p < 0.01$). The results from these same studies are mixed about whether the level of hippocampal activation that predicts Familiarity/weak responses is significantly different than the level predicting misses.

Four out of 10 of the retrieval studies in the meta-analysis reported results for the hippocampus (**Table 3.3**, Hippocampal region, see Daselaar et al., 2006; Montaldi et al., 2006; Weis et al., 2004; and Dobbins, Rice, Wagner & Schacter, 2003) that found significantly greater activation during the Recollection/strong condition than the Familiarity/weak condition ($t(8) = 3.86$, $p < 0.01$). This pattern is supported by two other fMRI studies that did not publish sufficient data to transform their data into z-scores (Yonelinas, Otten, Shaw & Rugg, 2005; and Wheeler & Buckner, 2003). By contrast, the results from these four studies are equivocal whether z-activity in the hippocampus associated with Familiarity/weak responses is different than that associated with misses.

Z-activity for this condition was above the level of activation for misses in two studies, but below the level for misses in the other two studies.

These mixed results for activation in the hippocampus correlated with Familiarity/weak responses may simply represent the normal variability that could be expected across experiments if the true results were negative. If that is the case, then a reasonable conclusion about the equivocal z-activity evoked during Familiarity/weak responses is that the hippocampus is not a contributor to the familiarity process. An alternative interpretation is that the data in these contrasts included only weaker memories that correlated with a blood-oxygen-level-dependent (BOLD) signal not quantifiable as different than the signal correlated with misses in typical-resolution fMRI (Stark et al., 2003; Stark et al., 2001).

A unique study acquired fMRI data at a high level of spatial resolution within the MTL and isolated differences in activation between three sub-structures that are combined as the hippocampus in the studies in the meta-analysis: the dentate gyrus, CA fields and subiculum (**Table 3.4**, Hippocampal region, Eldridge et al., 2005). This project collected data during both the encoding and retrieval phases from each participant. The activity Eldridge et al. reported in the hippocampus shows a different pattern in comparison to the results from the studies scanned at typical resolution: increased activation in certain subregions of the hippocampus was correlated with both Remember and Know responses. The authors interpreted their results according to the Remember/Know procedure that assumes that Remember responses denote recollection and that Know responses denote familiarity and, therefore, concluded that activation in the hippocampal region during encoding was correlated with both recollection and familiarity.

During retrieval, Eldridge et al. (2005) found that activation in the hippocampus followed the same gradient as the four typical-resolution fMRI studies discussed above. These results are difficult to interpret, however, because z-activity correlated with Remember responses and with Know responses was greater than for misses in three hippocampal subregions, but less than for the misses in the other three hippocampal sub-regions.

Perirhinal Cortex.

Eleven studies report results in or immediately adjacent to the perirhinal cortex that can be transformed into z-activity for the meta-analysis: four during encoding (**Table 3.3**, Perirhinal cortex, see Gold et al., 2006; Henson et al., 2005; Ranganath et al., 2004; and Davachi et al., 2003) and seven during recognition tests (**Table 3.3**, Perirhinal cortex, see Montaldi et al., 2006; Gonsalves et al., 2005, fMRI and MEG; Henson et al., 2005; Weis et al., 2004; Rugg et al., 2003; and Casino, Maquet, Dolan & Rugg, 2002). It is clear from the encoding studies that perirhinal activation is predictive of subsequent memory, given that mean z-activity during encoding is greater for items subsequently recognized than missed ($t(7) = 3.19$, $p < 0.02$). It is not clear whether the level of perirhinal activation increases, or actually decreases, as a predictor of subsequent memory in the Recollection/strong condition as compared to the Familiarity/weak condition. Two experiments found that activation increased or remained constant during the encoding of words that were subsequently recollected, while two other studies found that z-activity decreased from the level for subsequent Familiarity/weak responses to the level for subsequent Recollection/strong responses.

Ranganath et al. (2004) presented two analyses from their results for perirhinal activation during encoding: one plotted parameter estimates indexing response amplitudes as a function of subsequent recognition confidence (for which activation was positively correlated with old/new confidence), and the other compared the difference between activation predicting subsequent correct versus subsequent incorrect source judgments (for which activation was negatively correlated with subsequent source memory). The meta-analysis includes the results presented by Ranganath et al. "to show relative magnitudes of subsequent familiarity and subsequent recollection effects observed in each ROI."

Kensinger et al. (2006) presented both words and images as study targets and found that activation in entorhinal cortex predicted subsequent memory in a pattern and location similar to Davachi et al. (2003) for perirhinal cortex (**Table 3.3**, Entorhinal cortex). These results are also consistent with data reported by Henson et al. (2005) that show a linear trend in entorhinal/perirhinal activation, increasing from Familiarity/weak toward Recollection/strong, that predicts subsequent memory.

During retrieval, the meta-analysis of perirhinal activation from seven experiments shows a clearer pattern than the comparable encoding results (**Table 3.3**, Perirhinal cortex, see Montaldi et al., 2006; Gonsalves et al., 2005, fMRI and MEG; Henson et al., 2005; Weis et al., 2004; Rugg et al., 2003; and Casino et al., 2002). All seven of the studies show that activation is significantly suppressed ($t(17) = 7.23$, $p < 0.001$) in perirhinal cortex when studied images, words or faces are recognized in the

Familiarity/weak condition, meaning that z-activity decreases for hits compared to misses. The four results for the left perirhinal cortex show a trend ($t(3) = 1.80$, $p < 0.09$) for a gradient in z-activity decreasing from the Familiarity/weak condition toward the Recollection/strong condition (**Table 3.3**). Further evidence for this gradient comes from the fine temporal resolution available in the data from the Gonsalves et al. MEG experiment: these results showed that the suppression correlated with Recollection/strong responses, compared to activation for Familiarity/weak responses, occurred at significantly longer latency.

An eighth study, scanned at high resolution (**Table 3.4**, Eldridge et al., 2005), found yet a different pattern in which perirhinal activation correlated with recognition of studied words is suppressed below miss during Know responses (the Familiarity/weak condition), but is greater than miss during Remember responses (the Recollection/strong condition).

Parahippocampal Cortex.

Four encoding studies in the meta-analysis reported fMRI data for the parahippocampal cortex that predicted subsequent recognition (**Table 3.3**, Parahippocampal cortex, see Gold et al., 2006; Henson et al., 2005; Ranganath et al., 2004; and Davachi et al., 2003). In all four studies, z-activity that predicted subsequent Recollection/strong responses was significantly greater than for Familiarity/weak responses ($t(4) = 3.01$, $p < 0.04$), as well as for misses ($t(4) = 4.28$, $p < 0.02$). In three of these four studies, activation that predicted subsequent Familiarity/weak responses was greater than for misses, although the meta-analysis did not find a significant difference between z-activity that predicted Familiarity/weak responses versus misses. This activation pattern is very similar to that for the hippocampus, which is the structure to which the parahippocampal cortex projects via the entorhinal cortex.

The findings from four studies in the meta-analysis that report results for the parahippocampal cortex during retrieval do not converge in a clear pattern (**Table 3.3**, Parahippocampal cortex, see Daselaar et al., 2006; Gonsalves et al., 2005, fMRI and MEG; and Kahn et al., 2004). Considering the multiple conditions reported in Kahn et al. (2004), it was possible to analyze a total of five z-transforms that compare parahippocampal cortex activation correlated with responses in the Familiarity/weak, Recollection/strong or miss conditions. The face recognition results reported by Gonsalves et al. and words that had been encoded in the shallow task in Kahn et al. (but not the deep task) both exhibited the same pattern of repetition suppression that was evident in the meta-analysis for the perirhinal cortex at retrieval. Z-activity from the other two results, however, followed a positive gradient (Daselaar et al., 2006; Kahn et al., 2004, see deep task).

Also different from the other studies, Eldridge et al. (2005) reported a laterality effect in parahippocampal cortex correlated with successful retrieval-- more active than miss on the left, and substantially suppressed below miss on the right (**Table 3.4**).

Summary of Results.

During encoding (**Figure 3.2**), five studies show that activity is increased differentially in association with subsequent Recollection/strong responses in the hippocampus and parahippocampal cortex. In these regions, z-activity predicting subsequent Recollection/strong responses is greater than activity predicting subsequent Familiarity/weak responses and subsequent misses. Four studies show that activation in perirhinal cortex predicting subsequent recognition is greater than that predicting subsequent misses.

During retrieval (**Figure 3.3**), four studies show that activity in the hippocampus is differentially increased in association with Recollection/strong responses. Seven studies show that activation in the perirhinal cortex decreases significantly from miss to Familiarity/weak responses and, left-lateralized, continues a trend in decreasing activation toward to Recollection/strong responses. In the parahippocampal cortex, although all the retrieval results show differences in z-activity between miss, Familiarity/weak and Recollection/strong responses, a flat pattern of activation is suggested by the meta-analysis comparing these different conditions.

The meta-analysis presents empirical evidence, which are bilateral in five of six comparisons (none of the retrieval studies in the meta-analysis reported activation in right parahippocampal cortex), that can be interpreted by two dual-process models. How this evidence can be interpreted as support for the division of labor in the MTL associated with recollection or familairity, or alternatively as dividing recognition responses by strength but not underlying processes, is the matter of the discussion below.

Discussion

This meta-analysis of 17 fMRI studies shows that activity associated with Recollection/strong responses differed from the level of activation associated with misses in all three MTL regions reviewed here (the hippocampus, and the perirhinal and parahippocampal cortices). The empirical pattern in the meta-analysis contrasts with the equivocal findings from the Henson review (2005). Specifically, the present results show that increased encoding activity (relative to that associated with misses) in both the parahippocampal cortex and the hippocampus predicts subsequent Recollection/strong responses but does not predict subsequent Familiarity/weak responses. The same pattern is evident during retrieval in the hippocampus and, to a lesser extent, in the parahippocampal cortex as well. In the perirhinal cortex, increased activation during encoding predicts recognition, and this pattern does not differ whether predicting subsequent Familiarity/weak responses or Recollection/strong responses. During retrieval, activation in the perirhinal cortex associated with Familiarity/weak responses and with Recollection/strong responses decreases below the level for forgotten items. The degree to which activation is reduced does not clearly differ between Familiarity/weak responses and Recollection/strong responses.

The fMRI data from these 17 studies tell a fairly consistent empirical story that can be interpreted, from the perspective of the high-threshold view, to separate recollection from familiarity (Eichenbaum et al., 2007; Skinner & Fernandes, 2007). What has yet to be fully appreciated is the interpretation of these results from the perspective of the aggregated-strength view. This alternative perspective suggests that the typical behavioral methods designed to separate recollection from familiarity instead separate strong memories from weak memories. Moreover, the fMRI data alone cannot distinguish between these two possible interpretations. With this issue in mind, it is important to understand how these two psychological models (discussed in the introduction) interpret the fMRI data.

Model-Based Interpretations.

The high-threshold/dual-process model (Yonelinas, 1998) assumes that responses based on recollection and responses based on familiarity can be easily isolated from each other because they are independent processes that contribute to different recognition decisions. More specifically, the high-threshold model views the strength of familiarity as being continuous (i.e., ranging from weak confidence based on familiarity to strong confidence based on familiarity), whereas it views recollection as a categorical process that, when it occurs, only gives rise to the strongest confidence. Because recollection reliably yields responses with the highest memory confidence, this model assumes that the occurrence of recollection preempts familiarity and that such responses are based exclusively on recollection. If recollection does not occur, then the response is exclusively based on familiarity instead (Parks & Yonelinas, 2007, **Table 3.1**). Accordingly, recognition decisions made with the highest confidence can be taken to primarily denote recollection, whereas recognition decisions made with confidence below that threshold can be taken to denote familiarity.

Similar considerations apply to experiments that use the Remember/Know/New procedure (Gardiner & Richardson-Klavehn, 2000; Tulving, 1985). Standard instructions for this procedure ask subjects to respond “Remember” based on recollection whenever it occurs and to otherwise respond “Know” based on a strong sense of familiarity. The Remember/Know procedure assumes that responses are based exclusively on one process or the other and that the recollection process will preempt the familiarity process, just as the high-threshold view does.

Interpreted in terms of high-threshold/dual-process models like these, the results of the present meta-analysis suggest that the hippocampus selectively subserves the recollection process (e.g., Daselaar et al., 2006; Montaldi et al., 2006; Henson et al., 2005; Yonelinas et al., 2005; and Ranganath et al., 2004). That is because activity, as shown in **Figures 3.2** and **3.3**, associated with responses that are assumed to be based exclusively on recollection is reliably elevated compared to misses, during both encoding and retrieval. By contrast, activity associated with responses that are assumed to be based exclusively on familiarity is not elevated compared to misses, during either encoding or retrieval. The high-threshold view interprets the pattern of activity observed in the perirhinal cortex to suggest that this region subserves familiarity. That is because activity associated with responses that are assumed to be based exclusively on familiarity is elevated compared to misses but is not further elevated for responses that are assumed to be based exclusively on recollection. The activity associated with the latter responses presumably reflects the fact that these items are relatively familiar. Thus, familiarity is at least partially redundant with recollection even though, theoretically, familiarity did not participate in the decision process. According to this view, patients with bilateral hippocampal lesions would be able to form memories based only on familiarity (e.g., Yonelinas et al., 2002).

The aggregated-strength/dual-process model assumes that recollecting the contextual details about an experience is a separable process from recognizing the familiarity of an item. However, this model, which is compatible with standard signal-detection theory, uniquely holds that both processes contribute to individual recognition decisions (Kelley & Wixted, 2001; Wixted, 2007; **Table 3.1**). According to this view, the strength of recollection underlying recognition responses varies from weak to strong, just as the strength of underlying familiarity varies from weak to strong (Slotnick & Dodson, 2005). In addition, it assumes that recollection and familiarity are aggregated to determine the memory strength of a particular item.

Such a view of how recognition processes work means that the strength of memory *per se* cannot be interpreted as a sign of underlying recollection or familiarity (Wixted, 2007). If the aggregated-strength view is correct, then the interpretations by the studies in the meta-analysis that have adopted the high-threshold view (Daselaar et al., 2006; Montaldi et al., 2006; Henson et al., 2005; Ranganath et al., 2004; Weis et al., 2004; Rugg et al., 2003; Casino et al., 2002) are drawn from fMRI results that may confound memory processes and memory strength. For example, according to the aggregated-strength view, the highest confidence decisions in an old/new task (e.g., the ”6’s” in Daselaar et al., 2006, and Ranganath et al., 2004) or the Remember responses in similar strength-based test procedures (e.g., the “R’s” in Montaldi et al. 2006, or Remember in Eldridge et al., 2005) indicate strong memory, but do not offer evidence whether such high-strength responses are based exclusively on recollection. Strong memory might instead be based on a combination of moderately strong recollection and moderately strong familiarity. Similarly, the aggregated-strength view assumes that the weaker confidence decisions in an old/new task (e.g., the”5’s” and “4’s” in Daselaar et al., 2006, and Ranganath et al., 2004) or similar strength-based test procedures (e.g., the F1, F2 and F3 responses in Montaldi et al. 2006, or Know responses in Eldridge et al., 2005) indicate weaker memory, yet nevertheless can be based on some degree of recollection as well a some degree of familiarity. Indeed, using the Remember/Know procedure, Eldridge et al. (2005) conducted a post-test session to separately examine the accuracy of their participants’ recollection of detail learned during the encoding procedure. The post-test found that the proportion of the participants' Remember responses that included recollection of correct study cues was 70%, and the proportion of Know responses that included recollection of correct study cues was 58% (a value that was reliably above chance). This latter result is uniquely consistent with the aggregated-strength view that weaker memory strength, as expressed by Know responses, does not exclude source recollection. Instead, according to this view, Know responses reflect weak memories that are made with relatively low confidence and that are associated with above-chance recollection (Wais, Mickes & Wixted, 2008).

From the perspective of the aggregated strength model, the simplest interpretation of the pattern of activity summarized in **Figures 3.2** and **3.3** is that hippocampal activity is associated with strong memory. That is, if the hippocampus is differentially active during encoding, the resulting memory is likely to be strong, and if the hippocampus is active at retrieval, it is contributing to a strong memory that was associated with hippocampal activity during encoding. Furthermore, the strong memory that is subserved by hippocampal activity can be associated with relatively high levels of *both* recollection and familiarity. Perirhinal activity, by contrast, is not associated with strong memory, but it can contribute to a weak memory (one that can be based on relatively low levels of both recollection and familiarity). Therefore, the aggregated-strength view makes interpretations about how MTL structures differ in terms of their memory-making efficacy whereas the high-threshold view makes interpretations about how MTL structures differ in terms of the memory processes they subserve. The aggregated-strength view assumes that the hippocampus, when differentially active, subserves strong memory and that the perirhinal cortex, when differentially active, subserves weak memory. According to this view, patients with bilateral hippocampal lesions would be able to form only weaker memories, in comparison to healthy controls, but these weaker memories would nevertheless be associated with some degree of both recollection and familiarity (e.g., Wais et al., 2006).

Other Interpretations.

There are other explanations for how the level of z-activity in the hippocampus associated with the Familiarity/weak condition could be misinterpreted in comparison to the level for the misses. One explanation suggests that the miss condition may not serve as an effective baseline to contrast with activation correlated with weaker memory (Stark et al., 2001) given evidence that the mean signal for the miss condition includes some unknown amount of retrieval activity, as well as incidental-encoding activity (Stark et al., 2003). A second alternative explanation is based on the view that the magnitude of the BOLD signal in functional regions of interest, in this case localized to the hippocampus and associated with Familiarity/weak responses, is not always distinct from the noise inherent in fMRI (Poldrack, 2007). Specifically, because the uniformity of the high-intensity magnetic field upon which MRI depends is distorted in the ventromedial regions of cortex, measuring small differences in activity in MTL may be difficult (Greicius, Krasnow, Boyett-Anderson, Eliez, Schatzberg, Reiss & Menon, 2003). During fMRI, the inhomogeneity of the magnetic field in the hippocampal region means that the signal to noise ratio in this region is reduced significantly, thus weakening the power to analyze subtle changes in metabolic rates correlated with neural activation. Improvements in the effective resolution of fMRI that helped to mitigate this loss of signal were applied by

Gold et al. (2006)[5] and Eldridge et al. (2005)[6] amongst the 17 fMRI studies in this review. Notably, these studies reported activation in the hippocampal region (**Table 3.2**, see Gold et al., 2006; and **Table 3.3**, Hippocampal region) for both Familiarity/weak and Recollection/strong responses that was different than miss.

It is important to note that, in addition to Gold et al. (2006), seven of the nine studies in the meta-analysis of hippocampal activation (Daselaar et al., 2006; Kensinger et al., 2006; Montaldi et al., 2006; Henson et al., 2005; Ranganath et al., 2004; Weis et al., 2004; Davachi et al., 2003) did report significant differences between the Familiarity/weak condition and miss in regions of the MTL adjacent to the hippocampus. If one assumes that the measurement of neural activity in the hippocampus and the adjacent MTL structures is equally efficacious, then it makes sense to interpret these fMRI results for the hippocampus as supporting the null hypothesis (e.g. activation in the hippocampus correlated with the Familiarity/weak condition is not different than for misses). This assumption, however, also counts on a constant relationship across different brain regions between the level of the blood-oxygen-dependent-level (BOLD) signal and the level of correlated neural activity. Logothetis & Wandell (2004) noted that the BOLD signal might depend nonlinearly on the neural signal even for structures that lie in close proximity.

---

[5] Gold et al. (2006) improved the resolution of their functional MRI data by applying the ROI-AL alignment method during their analysis (Stark & Okado, 2003).

[6] Eldridge et al. (2006) applied a high resolution technique in their fMRI echo-planar-image (EPI) pulse sequence to sample a selective field, FOV 20, twice as often, NEX-4, as compared to typical whole-brain fMRI.

Conclusions.

Based on interpretations that strong memory denotes recollection and weaker memory denotes familiarity, the high-threshold/dual-process view concludes that the pattern of MTL activity shown in the meta-analysis (**Figures 3.2** and **3.3**) shows selective roles for the hippocampus (subserving recollection) and the perirhinal cortex (subserving familiarity). The aggregated-strength/dual-process view concludes from these same data that when the hippocampus is differentially engaged, strong memory results and that when the perirhinal cortex is differentially engaged, weaker memory results.

One way to test these different conclusions would be to compare fMRI data associated with specific conditions that are compatible with the interpretations of both the high-threshold view and the aggregated-strength view. For example, both models would interpret high-confidence recognition with correct source judgments as based on recollection and high-confidence recognition with incorrect source judgments as based on familiarity. Critically for this comparison, observations would need to be equated for recognition strength. Unfortunately, such data are yet available in the literature. Although Ranganath et al. (2004) and Gold et al. (2006) tested recognition memory separately from source memory, their analyses did not make comparisons between encoding activity associated with correct source decisions and activity associated with incorrect source decisions that were equated in memory strength. Future fMRI research is needed to test the conclusions of both dual-process views toward the aim of defining the neural correlates of recollection and familiarity in the MTL, but the important points from this review are that (a) a reliable pattern of activity in the MTL can be identified across studies and (b) that pattern is consistent with at least two interpretations.

Acknowledgment

Experiment 3, in full, has been submitted for publication of the material as it may appear in Recognition Memory Processes in the Medial Temporal Lobe: A Quantitative Meta-Analysis of fMRI Results in *Neuropsychologia*. Wais, P. E. (2008). The dissertation author was the investigator and author of this paper.

Table 3.1 The comparison two models for recognition memory.

	High-threshold view	**Aggregated-strength view**
Dual-process view	yes	yes
Familiarity (continuous strength)	yes	yes
Recollection (continuous strength)	no	yes
Recollection threshold	yes	no
Patient studies	yes *(a)*	yes *(b)*
fMRI studies	yes *(c)*	no *(d)*

(a) Yonelinas et al. (2002); *(b)* Wais et al. (2006); *(c)* see Table 1;
(d) no studies have equated memory strength for recollection and familiarity

Table 3.2 fMRI studies examining recognition memory processes: 21 studies published results showing activation in the hippocampal region and/or the adjacent MTL correlated with behavioral responses based on item-plus-source or item-without-source recognition, levels of recognition confidence, or Remember/Know/Guess responses. 17 out of 21 studies made enough statistical information available to be discussed in the review (15 in the meta-analysis).

<u>Studies in the meta-analysis</u>

Encoding:
Davachi, Mitchell and Wagner (2003)
Gold, Smith, Bayley, Shrager, Brewer, Stark, Hopkins and Squire (2006)
Henson, Hornberger, and Rugg, (2005)
Kensinger, and Schacter (2006)
Ranganath, Yonelinas, Cohen, Dy, Tom and D'Esposito (2004)

Retrieval:
Casino, Maquet, Dolan, and Rugg, (2002)
Daselaar, Fleck and Cabeza (2006)*
Dobbins, Rice, Wagner and Schacter, (2003)
Gonsalves, Kahn, Curran, Norman and Wagner (2005)*** *results from fMRI*
Gonsalves, Kahn, Curran, Norman and Wagner (2005)*** *results from MEG*
Henson, Hornberger, and Rugg (2005)
Kahn, Davachi, and Wagner (2004)
Montaldi, Spencer, Roberts, and Mayes (2006)**
Rugg, Henson, and Robb (2003)
Weis, Specht, Klaver, Tendolkar, Willmes, Ruhlmann and Fernandez (2004)

<u>Studies scanned at high-resolution fMRI and shown separately</u>

Eldridge, Engel, Zeineh, Bookheimer and Knowlton (2005)** during encoding
Eldridge, Engel, Zeineh, Bookheimer and Knowlton (2005)** during retrieval

<u>Studies which could not be analyzed by the meta-analysis</u>

Morcom, Good, Frackowiak and Rugg (2003)
Otten Henson, and Rugg (2001)
Wheeler and Buckner (2003)
Yonelinas, Otten, Shaw, and Rugg (2005)

* this study measured recognition responses on a seven-point confidence
** these studies measured recognition responses with the Remember/Know procedure
*** this study measured recognition responses with the Remember/Know procedure and reported results separately for participants in either fMRI or MEG sessions

Table 3.3 Meta-analysis of z-activity by region of interest for 15 fMRI studies.

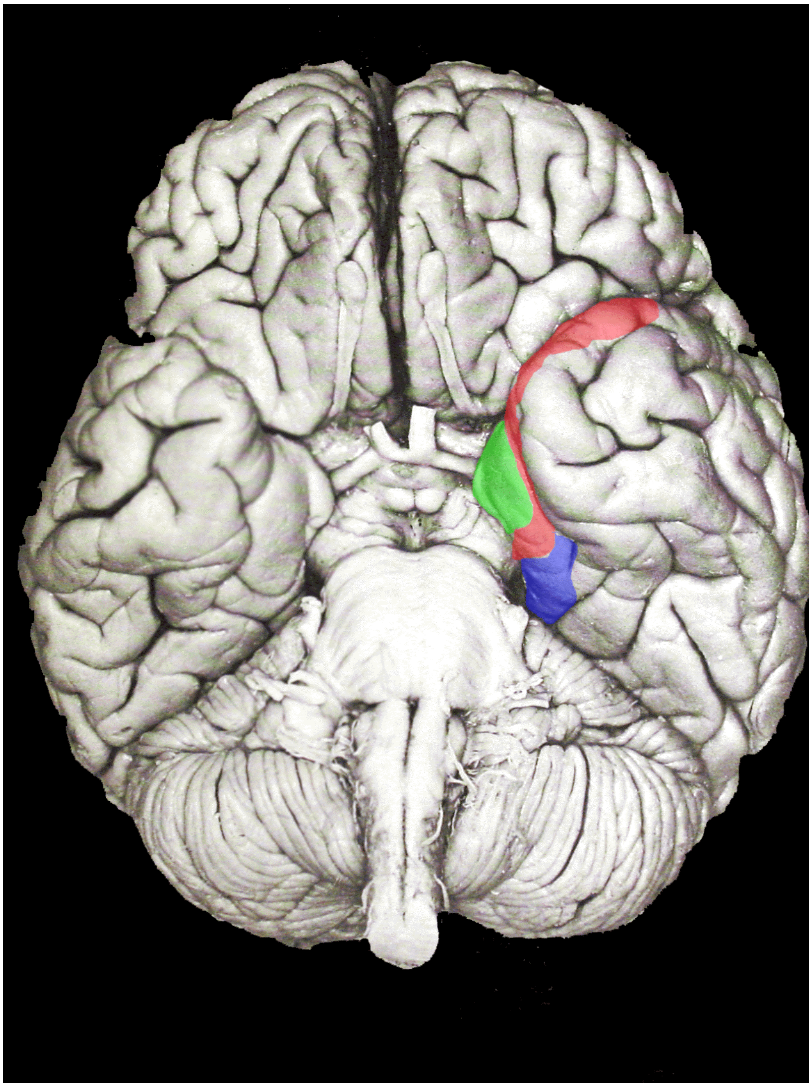
Z-activity equals (mean signal for hit - mean signal for miss) / standard deviation for miss

	Left Familiarity/ weak	Left Recollection/ strong	Right Familiarity/ weak	Right Recollection/ strong
Hippocampal region:				
encoding				
Gold et al.	0.7	0.9		
Kensinger et al. -words	0.8	3.2	0.1	0.4
Kensinger et al. -images	-0.6	1.6	-0.1	1.0
Davachi et al.	-0.1	0.2	-0.3	0.3
Henson et al.	0.0	0.9		
Ranganath et al.			0.5	2.2
averages	0.2	1.4	0.0	0.9
retrieval				
Daselaar et al.	-0.1	0.9		
Montaldi et al.	0.4	1.5	0.2	0.8
Weia et al.	-0.4	1.2		
Dobbins et al.	-0.1	1.1		
average	0.0	1.2		
Perirhinal cortex:				
encoding				
Gold et al.			1.0	0.7
Davachi et al.	0.8	0.8		
Henson et al.	0.1	0.7		
Ranganath et al.	1.5	-0.4		
average	0.8	0.4		
retrieval				
Montaldi et al.	-0.8	-1.4	-1.4	-2.0
Gonzalves et al. -fMRI	-0.4	-1.0	-0.6	-1.2
Gonzalves et al. -MEG	-0.2	-0.6		
Henson et al.	-0.3	-0.1		
Weis et al.			-1.2	-0.5
Casino et al.			-0.6	-0.7
Rugg et al.			-1.0	-1.2
averages	-0.4	-0.8	-1.0	-1.1
Entorhinal cortex:				
encoding				
Kensinger et al. -words	0.3	0.8		
Kensinger et al. -images	0.2	0.4		
average	0.3	0.6		
Parahippocampal cortex:				
encoding				
Gold et al.	0.3	0.6	0.6	0.6
Davachi et al.	-0.6	0.6		
Henson et al.	0.2	1.6		
Ranganath et al.			0.3	1.5
averages	0.0	0.9	0.4	1.1
retrieval				
Kahn et al. -imagine	0.1	2.0		
Kahn et al. -read	0.7	0.4		
Gonzalves et al. -fMRI	-0.2	-0.6		
Gonzalves et al. -MEG	-0.2	-0.4		
Daselaar et al.	0.2	0.4		
average	0.1	0.3		

Table 3.4 Analysis of z-activity by region of interest reported by Eldridge et al. (2005).

Z-activity equals (mean signal for hit - mean signal for miss) / standard deviation

	Left Familiarity/ weak	Left Recollection/ strong	Right Familiarity/ weak	Right Recollection/ strong
Hippocampal region:				
encoding				
dentate gyrus	1.3	0.7	0.1	0.1
subiculum	1.4	-0.1	0.4	-0.3
averages	1.3	0.3	0.2	-0.1
retrieval				
dentate gyrus	-1.5	-0.8	-2.1	-1.3
CA1	-0.4	0.1	0.3	0.9
subiculum	0.0	0.9	0.2	0.8
averages	-0.6	0.1	-0.6	0.1
Perirhinal cortex:				
retrieval	-1.4	1.0	-0.7	1.4
Parahippocampal cortex:				
encoding			0.3	1.1
retrieval	0.4	0.4	-1.3	-1.1



(Clark, 2006)

Figure 3.1 Viewed from the ventral perspective of the human medial temporal lobe (MTL): the **Perirhinal**, **Entorhinal** and **Parahippocampal** cortices.

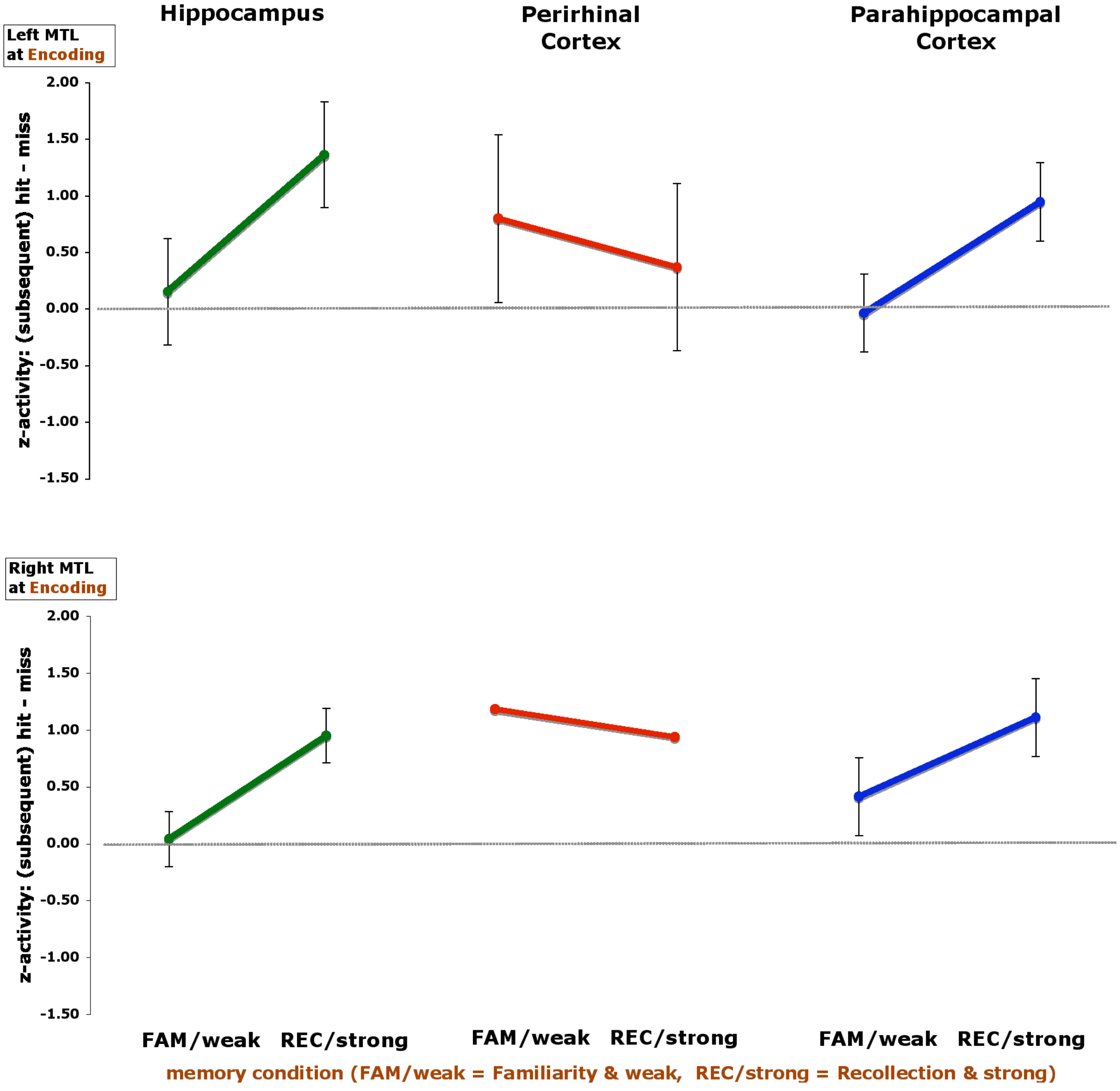


Figure 3.2 Meta-analysis of activity in MTL regions during encoding (for each region, error bars represent the standard error of the mean differences between z-activity for Familiarity/weak and z-activity for Recollection/strong). Five studies contributed results to one or more of the ROIs described below.

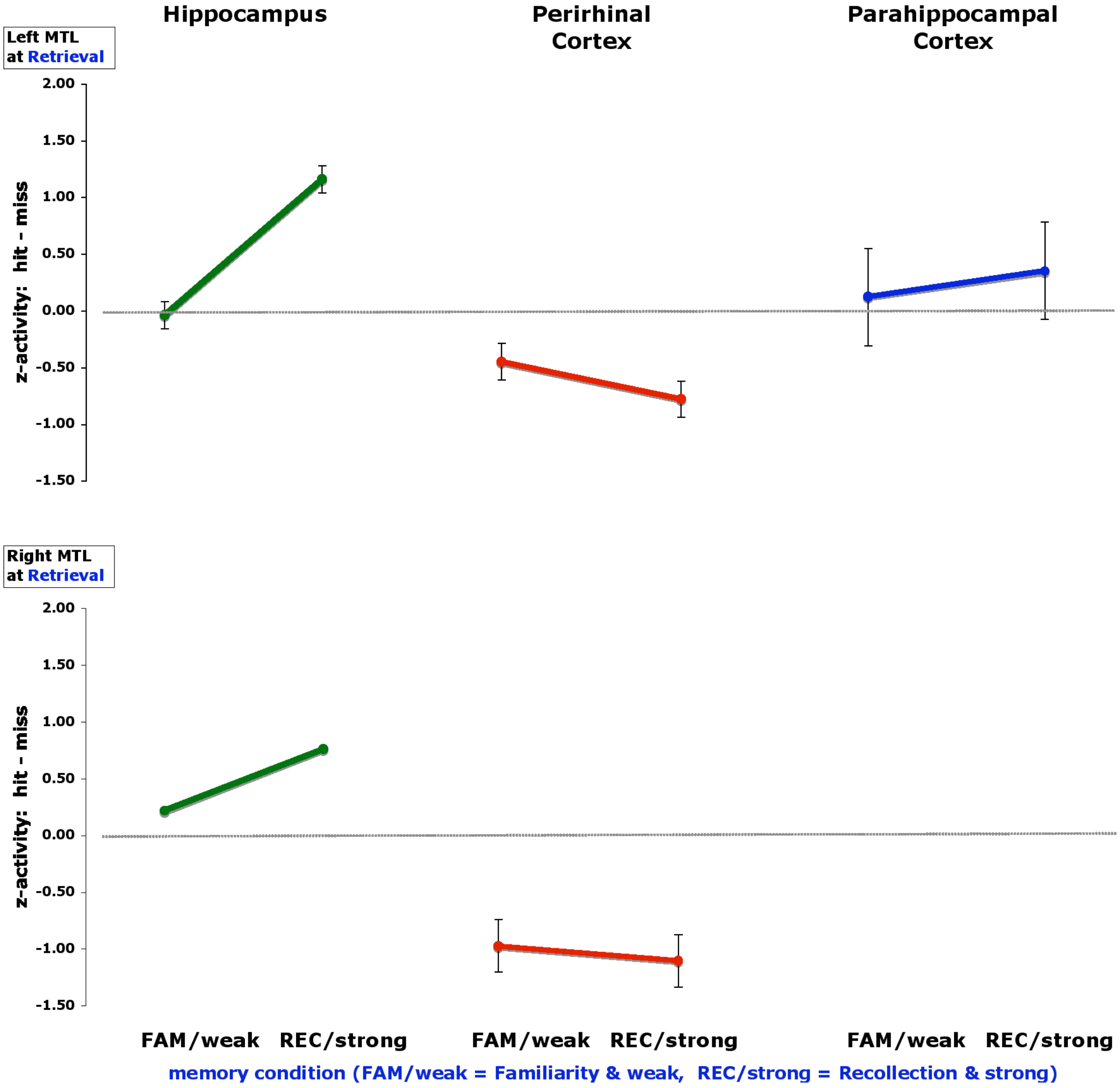


Figure 3.3 Meta-analysis of activity in MTL regions during retrieval (for each region, error bars represent the standard error of the mean differences between z-activity for Familiarity/weak and z-activity for Recollection/strong). Ten studies contributed results to one or more of the ROIs described below.

Experiment 4: fMRI Evidence for Recollection and Familiarity Signals in the Hippocampus

Summary.

fMRI studies of recognition memory have often been interpreted to mean that the hippocampus selectively subserves recollection and that adjacent regions selectively subserve familiarity. Other research suggests that these studies have confounded recollection and familiarity with strong and weak memories. In a source memory experiment, we compared correct source judgments (recollection) and incorrect source judgments (familiarity) while equating for old/new memory strength by including only high-confidence hits in the analysis. Hippocampal activity associated with both correct source judgments and incorrect source judgments exceeded the activity associated with forgotten items and did so to a similar extent. Further, hippocampal activity was greater for high-confidence old decisions relative to forgotten items even when source decisions were at chance. These results identify both recollection and familiarity signals in the hippocampus. Similar results were obtained in parahippocampal gyrus. Unlike in the medial temporal lobe, prefrontal activity increased differentially in association with task-relevant recollection.

Introduction

Dual-process theories of recognition memory hold that two distinct memory processes, recollection and familiarity, underlie one's ability to recognize an item as having been previously encountered (Mandler, 1980; Curran & Hintzman, 1995). Recollection involves the retrieval of contextual detail associated with the test item, whereas familiarity involves simply knowing that the item was encountered before. An important and unresolved issue concerns how the level of confidence expressed in a recognition decision is related to these two memory processes. According to one view (the high-threshold/signal-detection model), high confidence in a recognition decision strongly implies that the decision was based on recollection, whereas lower confidence necessarily implies that the decision was based on familiarity (Yonelinas, 1994). Following this perspective, functional magnetic resonance imaging (fMRI) studies have often interpreted activity correlated with highly confident responses (or Remember responses) as a neural signal of recollection, and activity correlated with less confident responses (or Know responses) has often been interpreted as a neural signal of familiarity (Daselaar, Fleck & Cabeza, 2006; Montaldi, Spencer, Roberts & Mayes, 2006; Ranganath, Yonelinas, Cohen, Dy, Tom & D"Esposito, 2004; Yonelinas, Otten, Shaw & Rugg, 2005).

An alternative view holds that the level of confidence is related to memory strength and that memory strength reflects varying degrees of both recollection and familiarity (Squire, Wixted & Clark, 2007; Wixted, 2007). By this view, the strength of memory *per se* cannot be taken to indicate whether a recognition decision was based on one process or the other. Further, in the fMRI studies just cited, one cannot determine whether the reported effects were due to differences in memory strength or to differences between recollection and familiarity (Squire et al., 2007).

Other fMRI studies have assessed recollection and familiarity by probing differences between source memory and item memory. In a typical source memory experiment, items are presented for study from one of two sources (e.g., at the top or bottom of the screen). On a subsequent memory test, items are presented first for an old/new decision (did this item appear on the list or not?) followed by a source memory decision for items declared to be old (was the item presented at the top or bottom of the screen?). Correctly identifying an item as old and with correct source information is thought to denote a recollection-based decision, whereas identifying an item as old but with incorrect source information is thought to denote a decision based mainly on familiarity and much less on recollection. A typical finding from fMRI studies is that hippocampal activity associated with source-correct responses exceeds the activity associated with forgotten items, whereas the activity associated with source-incorrect responses does not (Kensinger & Schacter, 2006; Davachi, Mitchell & Wagner, 2003; Weis, Specht, Klaver, Tendolkar, Willmes, Ruhlmann, Elger & Fernandez, 2004; Gold, Smith, Bayley, Shrager, Brewer, Stark, Hopkins & Squire, 2006). This pattern has been interpreted to mean that the hippocampus selectively subserves recollection (Eichenbaum, Yonelinas & Ranganath, 2007).

Yet, these studies confound memory strength with source-correct and source-incorrect decisions. Specifically, confidence is typically higher for old/new decisions that are subsequently associated with correct source judgments than for old/new decisions that are subsequently associated with incorrect source judgments (Gold et al., 2006; Slotnick

& Dodson, 2005). This difference in old/new confidence suggests that, in prior source-memory studies using fMRI, the activity associated with relatively strong, recollection-based decisions was compared with the activity associated with relatively weak, familiarity-based decisions. The strength confound is problematic because the distinction between recollection and familiarity is independent of memory strength. That is, strong memories can be based on a strong sense of familiarity (Mandler, 1980), and weak memories can be based on a limited amount of recollection (Slotnick & Dodson, 2005). Thus, if the intention is to compare recollection-based decisions (as indicated by source-correct decisions) with familiarity-based decisions (as indicated by source-incorrect decisions), then it is important to equate for memory strength.

In our fMRI study, we used a source memory procedure and obtained confidence ratings for both old/new and source memory decisions (**Figure 4.1**). We then measured activity associated with source-correct vs. source-incorrect decisions using only old decisions that were made with relatively high confidence. That is, we compared decisions based on a strong sense of recollection (source-correct) with decisions based on an equivalently strong sense of familiarity (source-incorrect). The question of interest was whether hippocampal activity associated with recollection would exceed the level of activity associated with familiarity, once memory strength was equated.

In a second analysis, we compared high-confidence old decisions to forgotten items when the accuracy of source decisions was at chance (source guesses). That is, we compared decisions based on a strong sense of familiarity (source guesses) with decisions based on a weak sense of familiarity (forgotten items), independently of source memory. The question of interest was whether hippocampal activity would be detected in this contrast, when the contribution of recollection was minimal. Lastly, using high-confidence old decisions, we also tested directly for a selective recollection signal by comparing correct source judgments made with high source confidence (strong recollection) with source guesses (strong familiarity). If the hippocampus selectively subserves recollection, as some have argued (Eichenbaum et al., 2007; Brown & Aggleton, 2001), then a recollection signal, but not a familiarity signal, should be evident in the hippocampus. If instead, the hippocampus is sensitive to memory strength, then when memory is strong, both recollection-based and familiarity-based activity should be evident in the hippocampus to a similar extent.

Results

Behavioral Results

The participants demonstrated good old/new recognition memory for the target words (d' = 1.93 ± 0.15; and 79 ± 2% correct for the old/new response). Words studied in the “common” cue condition were recognized as readily as words studied in the “discuss” cue condition (d' = 1.98 ± 0.17 vs. *d'* = 1.89 ± 0.16). The distribution of responses for hits and false alarms across the six-level old/new confidence scale revealed a bias to respond “old” (**Figure 4.2**). As a result, responses to targets given a confidence level 4 (maybe old) were at chance accuracy overall (56% ± 6% correct), whereas responses to foils given a confidence level 3 (maybe new) were much more accurate (80% ± 4% correct). The accuracy of responses to targets given a confidence rating of 5 or 6 was also high (71% ± 6% correct and 87% ± 3% correct, respectively). The old/new accuracy calculations for each rating included scores of participants who had at least 5 observations for that rating (e.g., at least 5 ratings of 3).

Overall source accuracy was 64 ± 2% correct, and source d' was 0.71 ± 0.10. As has been observed in prior studies, source accuracy varied as a function of confidence in the old/new decision for targets. Source accuracy was highest for items that received an old/new confidence rating of 6 (67% correct, significantly above chance, $p < .05$), next highest for items that received an old/new confidence rating of 5 (63% correct, significantly above chance, $p < .05$), and lowest for items that received an old/new confidence rating of 4 (50% correct).

For target items that were correctly declared to be old (i.e., targets that received a rating of 4, 5, or 6), we computed the mean old/new confidence rating separately depending on whether the subsequent source decision was correct or incorrect. The mean old/new confidence associated with source-correct decisions (**Table 4.1**) was significantly higher than the mean old/new confidence associated with source-incorrect decisions ($p < .02$). Thus, our results exhibit the typical memory strength confound that has been observed in prior source memory studies (Gold et al., 2006; Slotnick & Dodson, 2005).

The most straightforward way to eliminate this confound would be to use only items that received a confidence rating of 6 during the old/new stage (ensuring that only strong memories were involved in the analysis) and to then separate those decisions into two categories depending on the accuracy of the source decision (source-correct and source-incorrect). In our fMRI analyses, the use of Old decisions made with a confidence rating of 6 yielded too few observations to detect MTL activity reliably. Thus, to increase power, we combined old/new hits that had been given confidence ratings of 5 or 6 and then divided those responses into source-correct and source-incorrect categories. A possible difficulty with this approach is that it could introduce the strength confound we sought to avoid (i.e., the old/new confidence ratings for incorrect source judgments could be lower, on average, than the old/new confidence ratings for source-correct judgments). However, in our study, this did not in fact occur. As shown in Table 1, for old/new decisions made with a confidence rating of 5 or 6, the mean old/new confidence for source-incorrect decisions (5.82) was virtually identical to the mean old/new confidence for source-correct decisions (5.84), and the small difference between them did not approach significance. Thus, a comparison of activity associated with these source-correct and source-incorrect decisions provides a test of activity associated with recollection and familiarity that is not confounded with memory strength.

To allow for a further analysis of neural activity associated with source recollection, we also partitioned correct old decisions in a more fine-grained manner. Specifically, instead of separating them into 2 categories (namely, source-correct and source-incorrect), we separated them into 3 categories: true source judgments (i.e., correct source judgments made with medium or high confidence), source guesses (source judgments made with low confidence, whether correct or incorrect), and false source judgments (incorrect source judgments made with medium or high confidence). **Table 4.1** shows that there is an old/new strength confound if all of the correct old decisions are used, so we included only old decisions made with a confidence rating of 5 or 6 (which eliminated the confound). For these high-strength old decisions, 44% were followed by true source judgments, 37% were followed by source guesses, and 19% were followed by false source judgments. The source accuracy of the guesses was 55 ± 2%, which did not differ significantly from chance ($p = 0.12$). Thus, source information was, in fact, absent when items were recognized as old with high confidence and the source judgment was a guess.

In the fMRI analyses described below, we compared the activity associated with either two or three categories of source judgments (equated for old/new confidence) against the activity associated with forgotten items. Typically, a target item is considered to be forgotten if it is incorrectly declared to be new (i.e., if it receives a confidence rating of 1, 2 or 3). However, as indicated above, many of the participants in our experiment exhibited a liberal response bias such that ratings of 4 were as likely to be given to targets as to foils (**Figure 4.2**). In that case, a confidence rating of 4 for a target indicates a forgotten item as well. In all of the analyses described below, we considered old/new confidence ratings of 1, 2, 3 or 4 to reflect forgotten words for the 11 of 16 participants who exhibited no better than chance accuracy when responding 4 (maybe old), and we considered responses of 1, 2 or 3 to denote forgotten words for the remaining 5 participants whose old/new confidence ratings of 4 were associated with greater than chance accuracy.

fMRI Results

Our objective was to measure activity associated with recollection-based decisions and familiarity-based decisions after eliminating the typical memory strength confound. To that end, we first measured activity associated with source-correct and source-incorrect judgments using only those old decisions that were made with relatively high confidence (i.e., 5 or 6). In one voxel-based t-test (thresholded at $p < 0.001$), we found that, in the left hippocampus, activity associated with source-correct decisions was significantly greater than the activity associated with forgotten items (**Figure 4.3**). In the same region of the left hippocampus, a second, independent voxel-based t-test revealed that activity associated with source-incorrect decisions was also significantly greater than activity associated with forgotten items (**Figure 4.3**). We also directly contrasted source-correct decisions vs. source-incorrect decisions, but no statistically significant regions ($p < 0.001$) were identified in the MTL. These results suggest that increased activation in the left hippocampus is associated with increased memory strength (i.e., high-confidence hits versus forgotten items) and does not differ whether the decision is based on strong recollection or strong familiarity (i.e., source-correct versus source-incorrect involving high-confidence hits).

The analysis summarized in Figure 3 assumes that source-correct decisions were based on recollection and that source-incorrect decisions were based on familiarity. However, both of these categories included source memory judgments made with low, medium and high confidence (i.e., “maybe,” “probably,” or “definitely”). Thus, some source-incorrect decisions were made with high source confidence and may have reflected false recollection. Conceivably, the hippocampal activity associated with source incorrect decisions in the analysis described above reflects false recollection, as has been reported in other paradigms (Schacter & Slotnick, 2004; Cabeza, Rao, Wagner, Mayer & Schacter, 2001). To address this issue, we used voxel-based t-tests (thresholded at $p < 0.001$) to contrast activity associated with true source judgments, source guesses, and false source judgments against the activity associated with forgotten items. Once again, in order to eliminate a strength confound that would otherwise exist, only old decisions made with high-confidence (5 or 6) were included in the following analyses. For each identified cluster (p-corrected< 0.05), signal data were also extracted for the other source conditions.

Regions in the posterior hippocampus, bilaterally, exhibited significantly greater activity associated with true source decisions than for forgotten items (**Figure 4.4a**). In signal data extracted from this cluster, the activity levels for source guesses and false source decisions were both numerically higher than the level associated with forgotten items and did not differ significantly from the level associated with true source decisions. In a region of the right posterior hippocampus, activity associated with source guesses was significantly greater than the activity associated with forgotten items (**Figure 4.4b**). The location of this cluster was virtually identical to the location of the cluster in the right hippocampus identified by the comparison between true source decisions and forgotten items (shown in **Figure 4.4a**). The activity levels extracted from this cluster for true source decisions and false source decisions were numerically higher than the level associated with forgotten items and did not differ from the level associated with true source decisions.

The findings presented in **Figures 4.4a** and **4.4b** provide evidence for both a recollection and a familiarity signal in the hippocampus when memory is strong. Evidence for a recollection signal comes from the fact that the activity associated with true source memories significantly exceeded the activity associated with forgotten items (**Figure 4.4a**). Such an interpretation is consistent with much prior evidence suggesting that the hippocampus plays an important role in recollection. For example, Manns, Hopkins, Reed, Kitchener and Squire (2003) found that selective hippocampal lesions were associated with clear deficits in recall performance, which is generally assumed to be based exclusively on recollection.

Evidence for a familiarity signal in the hippocampus comes from the fact that the activity associated with source guesses (using only old decisions made with high confidence) significantly exceeded the activity associated with forgotten items (**Figure 4.4b**). This finding has not been previously reported, perhaps because when old decisions made with lower confidence are included in the analysis, rather than only old decisions made with high confidence, then memories associated with incorrect source decisions (or source guesses) are too weak, on average, to elicit an fMRI signal in the hippocampus (Squire et al., 2007).

In order to test for activity in the hippocampus that might be selectively associated with recollection-based decisions (relative to equally-strong familiarity-based decisions), we also contrasted activity associated with true source decisions against activity associated with source guesses (again using only old decisions made with high confidence). No statistically significant regions ($p< 0.001$) were identified for this contrast in the hippocampus. Taken together, these results suggest that hippocampal activity signals strong memories, whether they are based on recollection or on familiarity.

With the same analysis just described, the voxel-based t-tests also revealed several areas of activity in the parahippocampal gyrus. Specifically, in left parahippocampal cortex, activity associated with true source decisions was significantly greater than activity associated with forgotten items (**Figure 4.5a**), just as was the case in the hippocampus bilaterally (**Figure 4.4a**). Also as in the hippocampus, in signal data extracted from this cluster, the activity levels for source guesses and false source memories were both numerically greater than that associated with forgotten items and did not differ significantly from the level associated with true source decisions. In left perirhinal cortex, the activity associated with source guesses was significantly greater than the activity associated with forgotten items (**Figure 4.5b**), just as was the case in right hippocampus (**Figure 4.4b**). Also as in the right hippocampus, the activity levels associated with true source decisions and false source decisions extracted from this cluster were both numerically greater than that associated with forgotten items and did not differ significantly from the level for source guesses. Lastly, a contrast between activity associated with true source decisions (i.e., strong recollection) vs. activity associated with source guesses (i.e., strong familiarity) identified no significant regions within the parahippocampal gyrus. Thus, the pattern in the parahippocampal gyrus was similar to that seen in the hippocampus in that there is evidence for both a recollection signal and a familiarity signal.

Next, because both the dorsolateral and the ventrolateral regions of the prefrontal cortex (DLPFC and VLPFC, respectively) have been associated with source memory processes in prior fMRI studies (Badre & Wagner, 2007; Ranganath & Blumenfeld, 2007), we first examined the whole-brain data to determine whether activity in the PFC associated with true source judgments, source guesses, and false source judgments was greater than activity associated with forgotten items. Voxel-based t-tests (thresholded at $p < 0.001$) identified one region in the left DLPFC (approximately BA47/BA11) and one region in the left VLPFC (approximately BA44) where the activity associated with true source judgments was significantly greater than for forgotten items. To test whether activity associated with recollection-based decisions was greater than the activity associated with equally strong familiarity based decisions, we next performed the contrast of true source decisions versus source guesses in the whole brain data (again using only old decisions made with high confidence). Unlike in the MTL, this contrast identified two areas that were significantly more active when source information was recollected. Activation in left VLPFC (**Figure 4.6a**), approximately BA45, and right DLPFC (**Figure 4.6b**), approximately BA46, increased significantly during responses correlated with true source memory as compared to source guesses. Thus, even when memories were equated for strength, a recollection signal was identified in left VLPFC and right DLPFC.

All of the preceding analyses were designed to test for activity correlated with recollection-based and familiarity-based decisions that had been equated for memory strength. To determine whether our findings would be similar to those reported in previous studies that did not take steps to equate for memory strength, we also conducted an analysis that was based on the notion that old/new confidence ratings of 6 denote recollection-based decisions, whereas confidence ratings of less than 6 denote familiarity-based decisions (Yonelinas, 1994). This theory has often been used to guide fMRI analyses in the past (Daselaar et al., 2006; Montaldi et al., 2006; Ranganath et al., 2004; Yonelinas et al., 2005) even though considerable evidence suggests that weak memories are associated with lower degrees of recollection, not with the absence of recollection (Slotnick & Dodson, 2005). Voxel-based t-tests of the LDDMM data for the MTL (thresholded at $p< 0.005$) identified a region in the right hippocampus where the activity correlated with hits rated 6 was greater than the activity associated with forgotten items (**Figure 4.7**). By contrast, no regions were identified in which the activity associated with hits rated 5 differed significantly from the activity associated with forgotten items. This result is similar to the pattern of data that has been interpreted previously to indicate that the hippocampus selectively serves recollection (Daselaar et al., 2006; Montaldi et al., 2006; Ranganath et al., 2004; Yonelinas et al., 2005). An alternative interpretation suggested by all of the other data reported above is that this result indicates instead that hippocampal activity is readily detectable when memory is strong.

Discussion

This study is the first to investigate neural activity associated with recollection and familiarity after equating for possible differences in memory strength. Previous research on this issue, which has suggested a functional dissociation within the MTL, relied on methods to distinguish between recollection and familiarity by separating strong recollection-based memories from weak familiarity-based memories (Squire et al. 2007). We removed this confound by taking old/new decisions made with relatively high confidence and then separating them into categories according to whether source memory was correct (in which case the old decision was likely based on recollection) or incorrect (in which case the old decision was likely based on familiarity). Under those conditions, hippocampal activity was elevated (and equally so) for both kinds of decision relative to forgotten items.

We also partitioned high-confidence old/new decisions into three categories to address the possibility that some decisions in the source incorrect condition were based on false recollection (which might have accounted for the elevated hippocampal activity associated with those decisions). The three categories were: true source memory (correct source decisions made with relatively high confidence), source guesses (correct and incorrect source decisions made with low confidence and low accuracy), and false source memory (incorrect source decisions made with relatively high confidence). Our results showed that hippocampal activity was higher for true source memories (strong recollection) and for source guesses (strong familiarity uncontaminated by false recollection) relative to forgotten items but did not differ from each other. This finding again suggests that the hippocampus plays a role in both familiarity-based and recollection-based memories. Finally, whole brain analyses showed greater activity for recollection-based decisions (true source) compared to familiarity-based decisions (source guesses) in the frontal lobes even when strength was equated. Overall, the results suggest that activity in the MTL is mainly determined by memory strength (whether the memory is based on recollection or familiarity), whereas a specific recollection signal is evident in the frontal lobes.

The strength confound that our procedure avoids is common in the neuroimaging literature where there has been interest in identifying the neural correlates of recollection and familiarity. This confound is particularly apparent in studies that have compared activity for old/new decisions made with high confidence to activity for old/new decisions made with lower confidence (Daselaar et al., 2006; Ranganath et al., 2004). The assumption in those studies was that high confidence in an old/new decision reflects recollection and that lower confidence reflects familiarity even though much evidence suggests that varying degrees of source recollection accompany varying levels of old/new confidence (Slotnick &Dodson, 2005). If recollection is distributed across different levels of confidence (as familiarity is), then confidence, per se, cannot be used to separate recollection from familiarity.

According to a related view, recollection and familiarity can be probed directly by the Remember/Know procedure (Gardiner, Richardson-Klavehn & Ramponi, 1997). This view holds that Remember responses denote recollection-based decisions and that Know responses denote familiarity-based decisions, regardless of the level of confidence that is associated with a recognition decision. In practice, however, confidence ratings for Know responses are substantially lower than those associated with Remember responses (Wixted & Stretch, 2004). Indeed, there is considerable evidence that Remember and Know judgments are tantamount to high and low confidence ratings, respectively, and are not reliable markers of qualitatively-different processes, such as recollection and familiarity (Wixted & Stretch, 2004; Dunn, 2004; Wasi, Mickes & Wixted, 2008).

Even in a source memory procedure, where activity associated with source-correct responses is compared with the activity associated with source-incorrect responses, a memory strength confound exists unless steps are taken to eliminate it, as we did here. When old/new memory strength was equated, elevated hippocampal activity was evident for both recollection-based and familiarity-based decisions (i.e., true source decisions and source guesses, respectively).

The failure of prior fMRI studies to detect increased hippocampal activity associated with familiarity-based responses may have more to do with the failure to detect a weak memory than with the absence of familiarity-related hippocampal activity. An implication of this view is that the typical relationship between memory strength and neural activity in the hippocampus, as measured by fMRI, is nonlinear (Squire et al., 2007). Indeed, evidence from cellular recordings of single hippocampal neurons in humans indicates that some cells are more active when an item is correctly declared to be old (compared to forgotten items) even when source recollection fails, and they are more active still when source recollection succeeds (Rutishauser, Mamelak & Schuman, 2006; Rutishauser, Schuman & Mamelak, 2008). Thus, successful recollection was not required for hippocampal neurons to exhibit familiarity-based item recognition. This study did not equate old/new memory strength for source-correct and source-incorrect items as we did, but it nevertheless detected elevated hippocampal activity for weak, source-incorrect items. This result suggests that single-unit recordings may be better able to detect hippocampal activity associated with weak memory than fMRI is. Our findings suggest that familiarity-based and recollection-based hippocampal activity can be detected by fMRI when memory is strong.

Our findings are at odds with a prominent view that accords to the hippocampus a selective role for recollection and the perirhinal cortex a selective role in familiarity (Eichenbaum et al., 2007; Brown & Aggleton, 2001). Perhaps the only way to account for our results from that point of view is to speculate that all of the high-confidence hits in our experiment were based on recollection, whether or not source recollection was successful. According to this idea, the responses that we interpreted to be familiarity-based (i.e., source guesses) were actually based on the participants' recollection of idiosyncratic contextual cues (cues not related to the source question that was asked). Consequently, according to this view, the elevated hippocampal activity associated with what we interpreted to be familiarity-based responses is, instead, associated with task-irrelevant recollection. If such task-irrelevant recollection occurred on virtually all source guess trials, then our results would not weigh against the notion that the hippocampus selectively subserves recollection. However, under this same assumption that task-irrelevant recollection occurred on all source guess trials, our results would also weigh against the related notion that the perirhinal cortex selectively subserves familiarity. This is because activity associated with the source guesses, which are hypothetically contaminated by task-irrelevant recollection, was significantly elevated in perirhinal cortex compared to forgotten items, just as it was in the hippocampus.

The view that source memory guesses represent task-irrelevant recollection has not been raised in prior fMRI studies of source memory. These studies have interpreted source-incorrect responses, categorically, to be based on familiarity, even though some of the recognition decisions associated with these source-incorrect responses were likely made with high confidence (Ranganath et al., 2004; Kensinger & Schacter, 2006; Weis et al., 2004; Davachi et al., 2003; Cabeza et al., 2001). There is no suggestion in any of these studies that high-confidence recognition responses with incorrect source judgments are based on task-irrelevant recollection, whereas weaker confidence responses with incorrect source judgments are based on familiarity. According to this perspective, the true source decisions in our experiment were associated with successful recollection and the source guesses were associated mainly with familiarity (because task-relevant recollection is absent and task-irrelevant recollection is likely to be infrequent).

Prior investigations of neural activity in the hippocampus and perirhinal cortex have often used the high-threshold/signal-detection model (Yonelinas, 1994) to interpret their findings (Daselaar et al., 2006; Ranganath et al., 2004). This model has also been used to extract quantitative estimates of recollection and familiarity from confidence-based receiver operating characteristic (ROC) data (Sauvage, Fortin, Owens, Yonelinas & Eichenbaum, 2008; Yonelinas, Kroll, Quamme, Lazzara, Sauve, Widaman & Knight, 2002). We therefore used this model to estimate task-irrelevant recollection from our Old/New and source confidence ratings. As described by Yonelinas (1999), the high-threshold/signal-detection model can be fit to Old/New ROC data to obtain an estimate of overall (i.e., task-relevant plus task-irrelevant) recollection. The model can then be fit to the source ROC data to estimate task-relevant recollection. The difference between the two recollection estimates provides a model-based estimate of task-irrelevant recollection. When the model was fit to our group Old/New ROC data, recollection was estimated to be zero (suggesting purely familiarity-based responding). This occurred because the ROC was symmetrically curvilinear. When the model was fit to our source ROC data, the recollection estimates for both source A (common) and source B (discuss) were also both equal to zero. This occurred because our source ROC was also symmetrically curvilinear. The idea that a source memory task can yield familiarity-based responding was espoused by Parks & Yonelinas (2007), who argued that it is the natural interpretation whenever the source ROC data are curvilinear. Thus, from the point of view of this model, our task elicited purely familiarity-based responding, and all of the hippocampal activity we observed reflected the familiarity process.

In contrast to the interpretation offered by the high-threshold/signal-detection model, we suggest that our findings indicate that the hippocampus supports both recollection (true source decisions) and familiarity (source guesses), and it does so equally when strength is equated. An obvious question that arises from our results is this: if not the hippocampus, then what region(s) of the brain selectively subserve recollection? Our finding that the right DLPFC (BA46) was more active when participants made a true source decision than when they made a source guess decision extends earlier work showing that this prefrontal region is recruited during discrimination of context-dependent information in order to recollect the correct source cue (Rugg, Henson & Robb, 2003; Wagner, Desmond, Glover & Gabrieli, 1998). Similarly, Ranganath, Heller & Wilding (2007) showed that activation in the DLPFC (BA46) is greater when specific contextual information about a study word (whether spoken by a male or female voice during study) is recollected than when the word is recognized as old but the context-based decision is incorrect. Additionally, our finding that the activity associated with true source memories was greater than that associated with source guess memories in the left mid-VLPFC (BA45) supports the conclusion from Dobbins & Wagner (2005) that this region is recruited during the selection of goal-relevant details. Our results are also consistent with lesion studies showing that frontal patients exhibit selective source memory deficits (Janowsky, Shimamura & Squire, 1989), whereas item and source memory are comparably impaired in patients with hippocampal lesions (Gold et al., 2006).

A great deal of research has demonstrated that the MTL is critically involved in the encoding and retrieval of declarative memories. Our study extends recent work using fMRI to show that the hippocampus supports declarative memory whether memory is based on recollection or on familiarity. When items are equated for memory strength, differential activity associated with recollection is identified in the DLPFC (BA46) and mid-VLPFC (BA45), rather than in the hippocampus.

Materials and Methods

Participants

Informed consent was obtained from 18 students (6 females) at the University of California, San Diego. All participants were right-handed. Two participants who did not score above chance levels for their source memory judgments were excluded from further analysis.

Stimuli

240 English nouns were selected from the MRC Psycholinguistic Database with the following constraints: word frequency of 50 to 300, length of five to twelve letters, and two to four phonemes. The words were randomly divided into one list of 192 targets and another list of 48 foils.

Behavioral Procedure & Data Analysis

Participants studied a list of words presented on a desktop computer. Words were presented in six blocks of 32 words each. Words in each block were randomly ordered for each participant. During each 2.5 sec trial in the study session, participants responded to one of two contextual-cue questions posed for each word, the *common* question or the *discuss* question (common: does the word describe something you expect to encounter in a typical week?; or discuss: does the word describe something you would discuss with a close friend?). The contextual-cue question was the same for all trials within a block so that participants studied the target words as alternating blocks with either the “common” or “discuss” cues. Participants were instructed to read each word, enter a yes or no answer to the cued question, and to remember the word, including its contextual cue, for a memory test during their subsequent scanning session.

The memory test for each participant was conducted in the MRI scanner approximately three hours after the study session. Participants saw test items in six blocks of 40 words (5.0 sec per word). Each test block included 32 targets from the study session, plus eight foils. The test items were presented in a random order to each participant and intermixed with trials from an odd-even digit task described below (fMRI Procedure and Data Analysis). For each word presented in the test phase, participants first gave a confidence judgment as to whether the word was old or new (1 = definitely new, 2 = probably new, 3 = maybe new, 4 = maybe old, 5 = probably old, 6 = definitely old) and then gave a confidence judgment for their source decision (1 = definitely discuss, 2 = probably discuss, 3 = maybe discuss, 4 = maybe common, 5 = probably common, 6 = definitely common). For clarity, we will refer to old/new confidence ratings in terms of the 1-through-6 numerical scale, but we will refer to source confidence ratings in terms of correct and incorrect decisions that were made with low, medium or high confidence (e.g., correct source confidence ratings of 1 for "discuss" items and 6 for "common" items will both be referred to as correct source decisions made with high confidence).

Participants were instructed not to enter a source judgment for words endorsed as new. The old/new scale and the source decision scale were each presented for 2.5 sec beneath the test word on each trial. In order to facilitate fMRI analysis (see below), participants also performed an odd/even classification task (Stark & Squire, 2001) on trials randomly intermixed with the memory task. For this baseline task, the digits 1-9 were presented for 1.25 sec each in blocks of 2, 4, 6, or 12.

fMRI Scanning Parameters, Procedure and Data Analysis. Imaging was carried out in a GE Signa Excite 3T scanner at the Center for Functional MRI (University of California, San Diego). Functional images were acquired using a gradient-echo, echo-planar, T2*-

weighted pulse sequence (TR = 2.5 sec, TE = 30, 90° flip angle, bandwidth = 250 MHz, FOV = 22cm). 42 slices covering the whole brain were acquired perpendicular to the long axis of the hippocampus (matrix size = 64x64, slice thickness = 5mm). Following six functional runs, high-resolution structural images were acquired using a T1-weighted, fast-spoiled-gradient-echo (FSPGR) pulse sequence (TE = 3.1; 12° flip angle; FOV = 25cm; 172 slices; 1mm slice thickness; matrix size = 256x256).

Between word presentations, participants were given 0, 2, 4, 6 or 12 of the 1.25 sec baseline task that served to jitter the MR signal acquired for subsequent deconvolution of the hemodynamic response function (hrf). For each participant, the fMRI data were partitioned into ten categories (see Results for an explanation of the trials in each category). The first seven categories were based on the old/new confidence ratings provided on each trial: (a) correct old responses to targets (i.e., hits) that were rated 6; (b) hits that were rated 5; (c) high-confidence hits (rated 5 or 6) that were subsequently associated with correct source decisions; (d) high-confidence hits (5's or 6's) that were subsequently associated with incorrect source decisions; (e) misses (targets rated 1, 2 , 3, or in some cases, 4); (f) false alarms (foils rated 4, 5, or 6); and (g) correct rejections (foils rated 1, 2, or 3). Additionally, the high-confidence hits (those associated with an old/new confidence rating of 5 or 6) were subdivided into three additional categories based on the confidence ratings for the source decision: (h) "true source" decisions (correct source decisions made with medium or high confidence on the source confidence scale); (i) "source guesses" (correct and incorrect source decisions made with low confidence); and (j) "false source" decisions (incorrect source decisions made with medium or high confidence).

For each of the ten categories, a hemodynamic response (relative to the baseline condition) was estimated for the 25 seconds following the presentation of the word by using signal deconvolution and the AFNI suite of programs (Cox, 1996). Data analysis was then based on the area under the hrf from 0 to 15 seconds following the presentation of the word (at about 15 seconds, the hrf returned to baseline). The anatomical scans and the fMRI data were normalized to the Talairach template (Talairach & Tournoux, 1998). Functional data were resampled to 2x2x2mm and blurred with a 4mm FWHM Gaussian kernel. These data were used for the whole brain analysis. For the analysis of MTL activity, the ROI-LDDMM alignment method (Miller, Beg, Ceritoglu & Stark, 2005) was used to improve cross-participant alignment and increase statistical reliability (Kirwan, Jones, Miller & Stark, 2007).

Voxel-based t-tests (threshold of $p < 0.001$, two-tailed) were then carried out as group analyses across all 16 participants for both the whole brain and MTL analyses based on the area under the hrf for contrasts of interest (described below). Monte Carlo simulations were then used to correct for multiple comparisons and to determine how large a cluster of voxels was needed in order to be statistically significant ($p < 0.05$). The coordinates of all of the regions of activity we identified that were statistically significant (p-corrected< 0.05) are listed in Table S1 as supplementary information.

Acknowledgments

Supported by an Innovative Research Grant from the Kavli Institute for Brain and Mind at the University of California, San Diego, the Medical Research Service of the Department of Veteran Affairs, NIMH, and the Metropolitan Life Foundation. Experiment 4, in full, has been submitted for publication of the material as it may appear in fMRI Evidence for Recollection and Familiarity Signals in the Hippocampus in *Journal of Cognitive Neuroscience.* Wais, P. E., Squire, L. R. and Wixted, J. T. (2008). The dissertation author was the primary investigator and author of this paper.

Table 4.1 Mean old/new confidence (s.e.m.) for different source accuracy conditions and different levels of source confidence when all hits were included (old/new confidence ratings of 4, 5 or 6) and when only relatively high-confident hits were included (old/new confidence ratings of 5 or 6).

	By Two Source Categories		By Three Source Categories		
Old/New Ratings Partitioned	Source Correct	Source Incorrect	True Source	Source Guess	False Source
4,5,6	5.62 (0.08)*	5.44 (0.09)*	5.73 (0.07) †	5.37 (0.10) †,‡	5.58 (0.07) ‡,†
5,6	5.84 (0.04)	5.82 (0.04)	5.85 (0.05)	5.81 (0.04)	5.81 (0.04)

Values that share symbols (e.g., *) differ significantly from each other (p < .05).

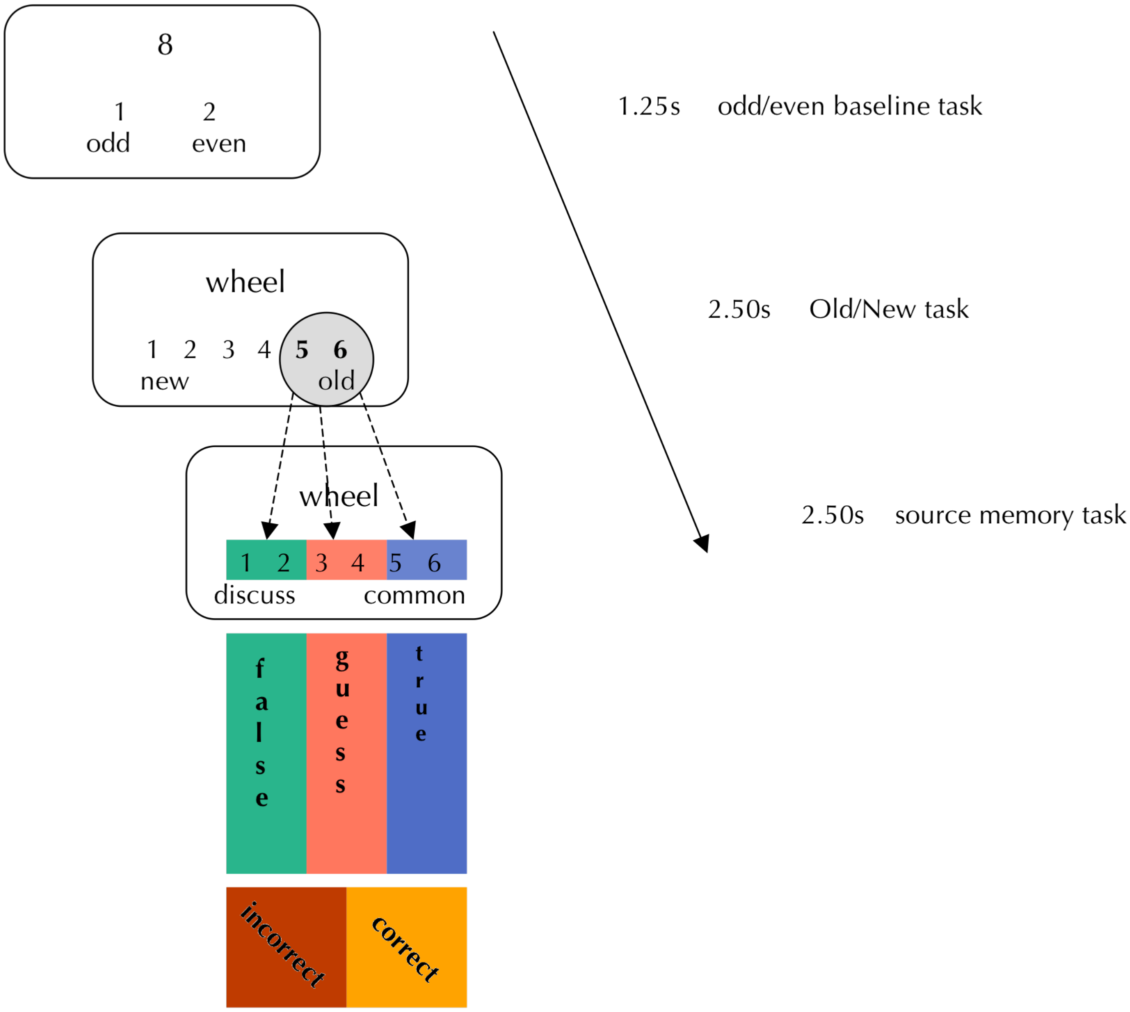


Figure 4.1. Example of test procedure and behavioral analysis: the stimulus “wheel” was studied under the *common* contextual-cue condition and endorsed as a high-confidence hit (5 or 6) in the old/new recognition task. For the subsequent source memory task, a response of 1 or 2 indicates false source memory, a response of 3 or 4 indicates source guesses and a response of 5 or 6 indicates true source memory (source 1, 2 & 3 are incorrect and source 4, 5 & 6 are correct).

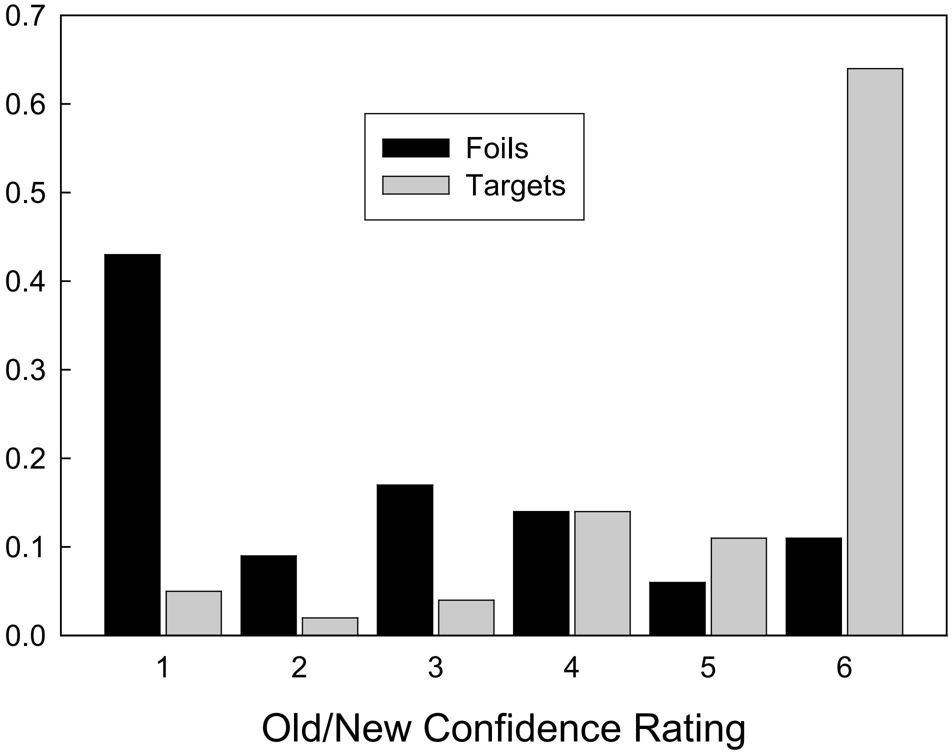


Figure 4.2 Proportion of responses to targets and foils for each confidence level in the old/new task, n= 16, mean recognition d' = 1.93 (0.15).

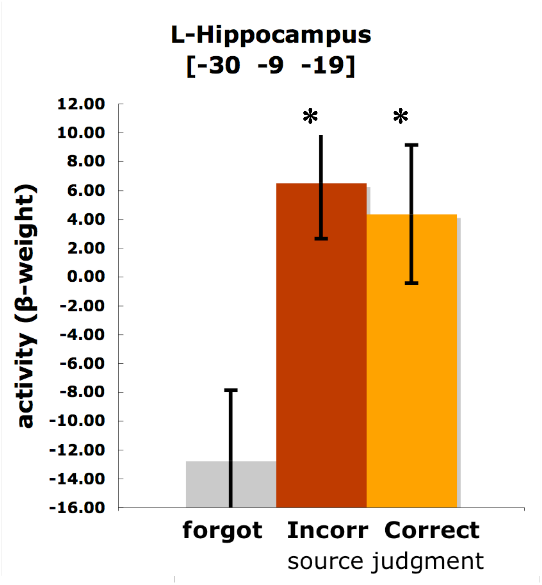


Figure 4.3 Activation identified for separate contrasts of correct source judgments vs. forgotten items and incorrect source judgments vs. forgotten items. To equate for memory strength, the source correct and source incorrect data were based on old decisions made with high confidence. Error bars for the two source categories represent the s.e.m. of the difference scores for each comparison, whereas the error bar for the forgotten items represents the root mean square of the s.e.m. values associated with the two individual comparisons (* denotes a significant difference relative to forgotten items, p-corrected< 0.05).

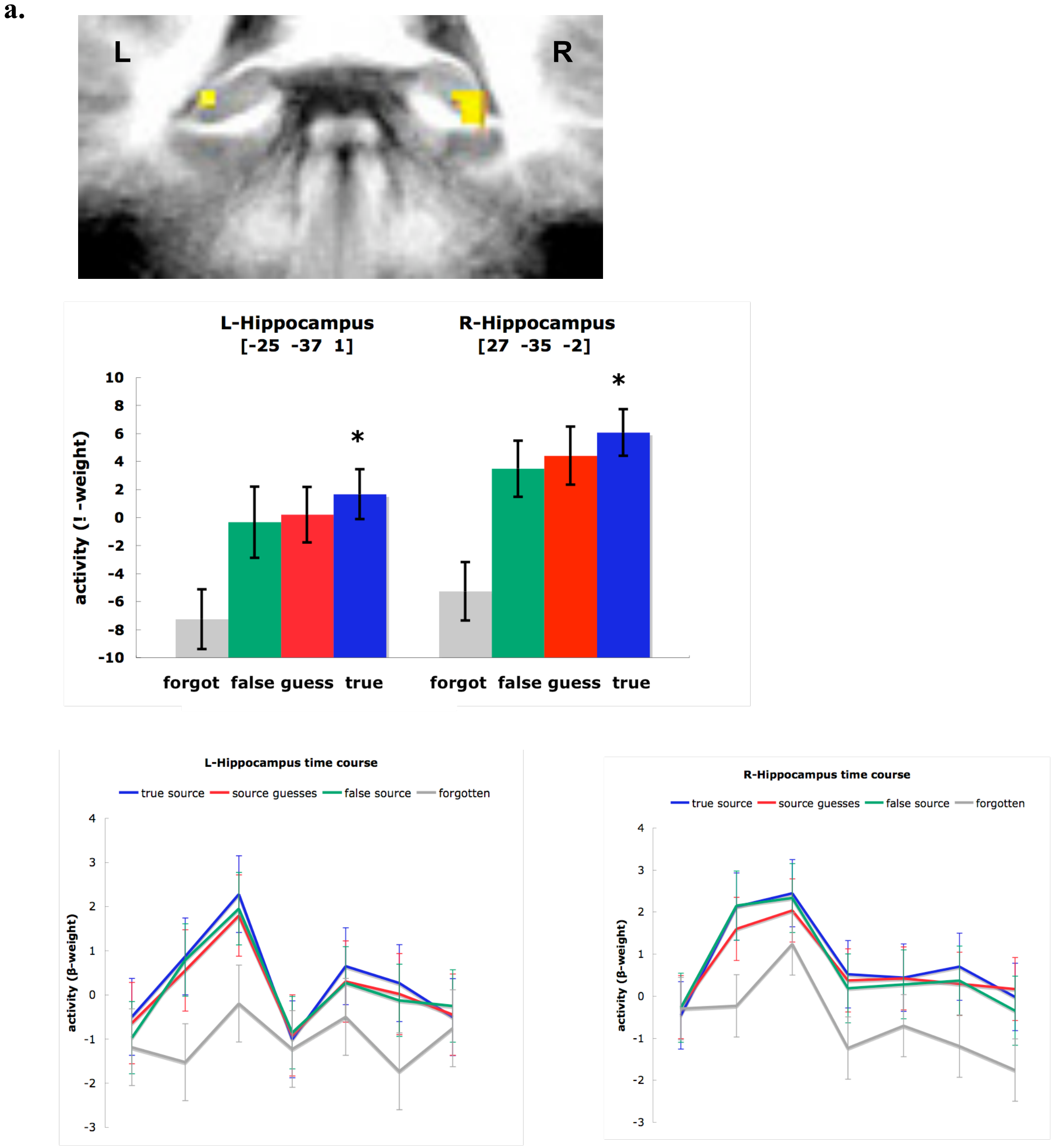


Figure 4.4a MRI section locating activity identified in the hippocampus (on averaged anatomical images for our participants) for the contrast of true source vs. forgotten items. Bar graphs show signal correlated with forgotten items and with recognition decisions that were accompanied by true, guess or false source judgments. Also illustrated are the timecourses of the hrf correlated with these results. Error bars for the three source categories represent the s.e.m. of the difference scores for each comparison (relative to forgotten items), whereas the error bar for the forgotten items represents the root mean square of the s.e.m. values associated with the three individual comparisons (* denotes a significant difference relative to forgotten items, p-corrected< 0.05).

b.

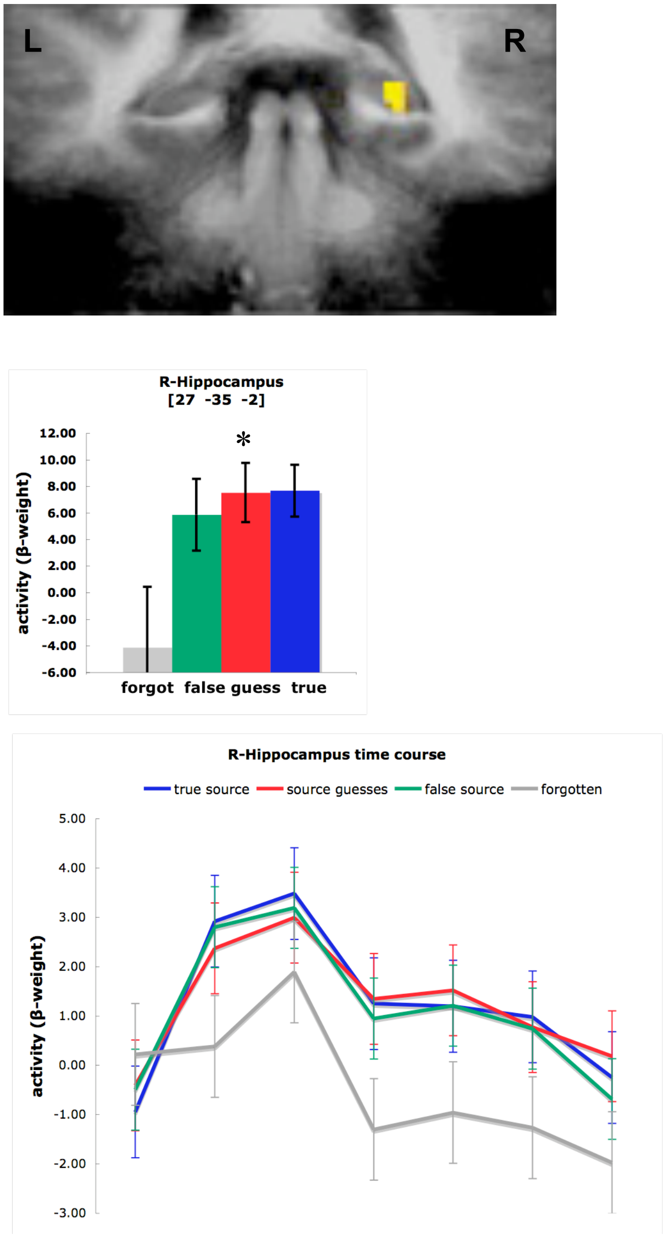


Figure 4.4b MRI section locating activity identified in the hippocampus (on averaged anatomical images for our participants) for the contrast of source guesses vs. forgotten items. Bar graphs show signal correlated with forgotten items and with recognition decisions that were accompanied by true, guess or false source judgments. Also illustrated are the timecourses of the hrf correlated with these results. Error bars for the three source categories represent the s.e.m. of the difference scores for each comparison (relative to forgotten items), whereas the error bar for the forgotten items represents the root mean square of the s.e.m. values associated with the three individual comparisons (* denotes a significant difference relative to forgotten items, p-corrected< 0.05).

a.

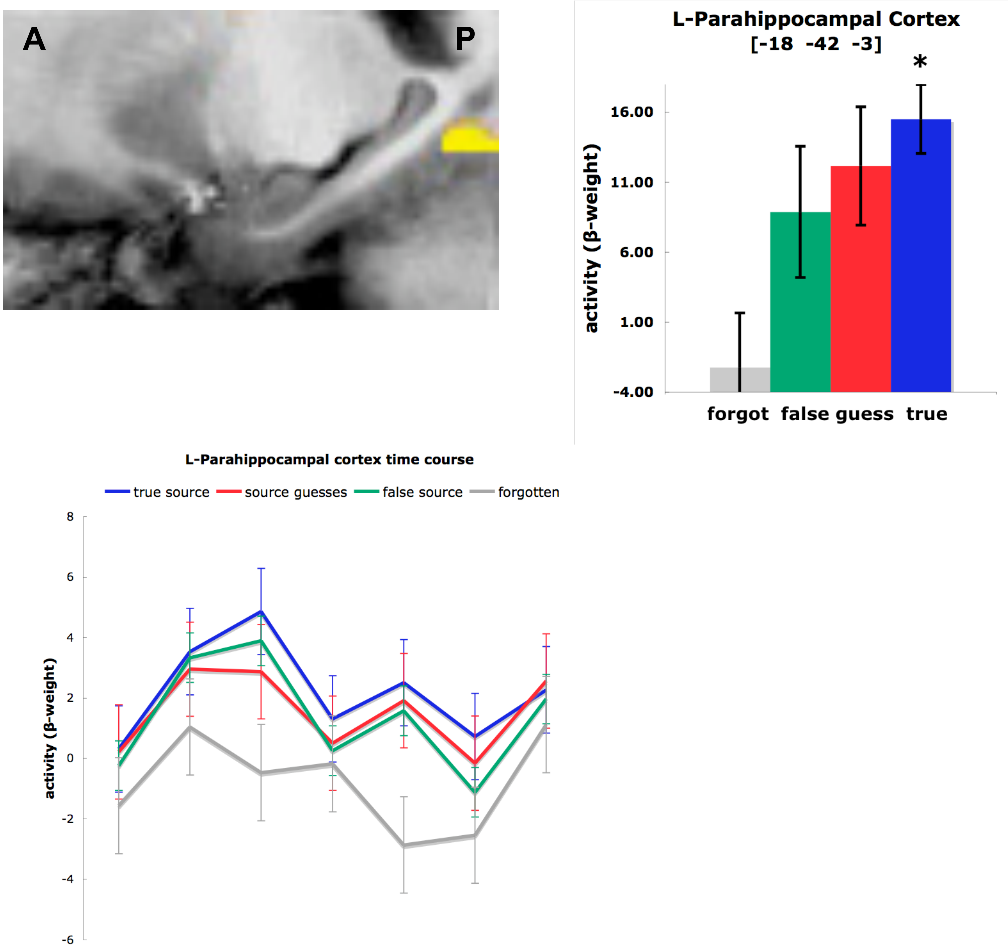


Figure 4.5a MRI sagittal section locating activity identified in left parahippocampal cortex (averaged anatomical images for our participants) for the contrast of true source decisions vs. forgotten items. Bar graphs show signal correlated with forgotten items and with recognition decisions that were accompanied by true, guess or false source judgments. Also illustrated are the timecourses of the hrf correlated with these results. Error bars for the three source categories represent the s.e.m. of the difference scores for each comparison (relative to forgotten items), whereas the error bar for the forgotten items represents the root mean square of the s.e.m. values associated with the three individual comparisons (* denotes a significant difference relative to forgotten items, p-corrected < 0.05).

b.

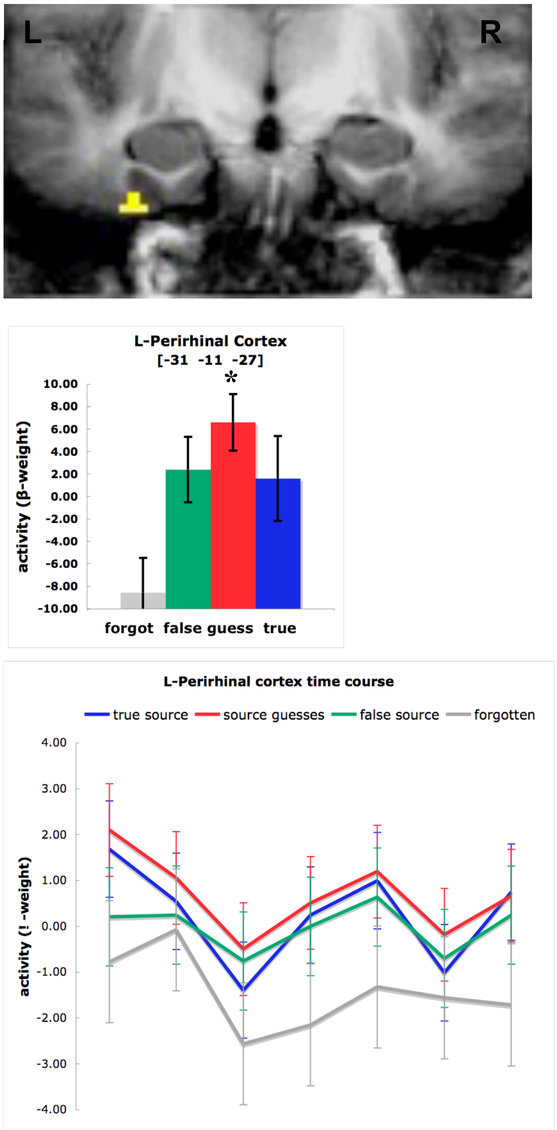


Figure 4.5b MRI section locating activity identified in left perirhinal cortex (averaged anatomical images for our participants) for the contrast of true source decisions vs. forgotten items. Bar graphs show signal correlated with forgotten items and with recognition decisions that were accompanied by true, guess or false source judgments. Also illustrated are the timecourses of the hrf correlated with these results. Error bars for the three source categories represent the s.e.m. of the difference scores for each comparison (relative to forgotten items), whereas the error bar for the forgotten items represents the root mean square of the s.e.m. values associated with the three individual comparisons (* denotes a significant difference relative to forgotten items, p-corrected < 0.05).

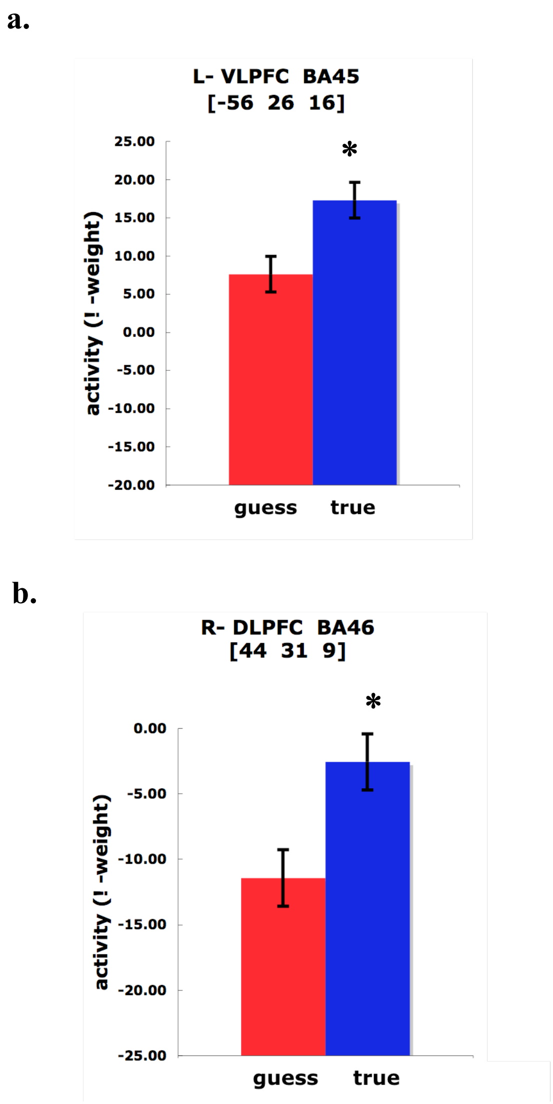


Figure 4.6 Activation identified in pre-frontal cortex for the contrast of high-confidence hits with true source vs. high-confidence hits with source guesses. **a**. left VLPFC (BA45) and **b**. right DLPFC (BA46). Error bars represent the s.e.m. of the difference scores (* denotes a significant difference between true source and source guesses, p-corrected< 0.05).

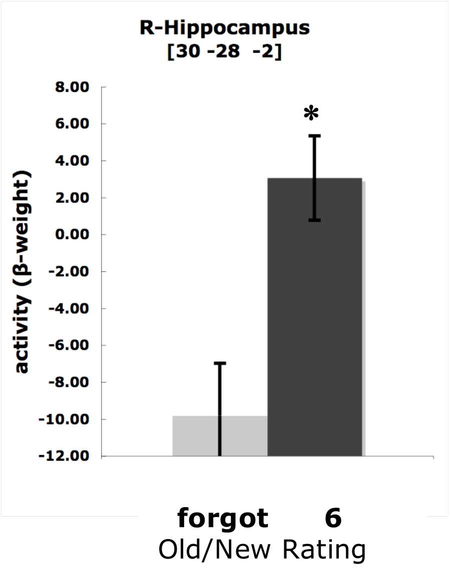


Figure 4.7 Activation identified for the contrast of hits rated as old/new "6" vs. forgotten item. Error bars represent the s.e.m. of the difference scores (* denotes a significant difference relative to forgotten items, p-corrected< 0.05).

Table S1. Supplementary information: clusters of activation (p-corrected< 0.05) identified in LDDMM analyses by the contrasts listed below. Talairach coordinates are for the peak voxel in each cluster.

Region	Brodmann area	Hemisphere	Talairach coordinates (x,y,z)
All highest confidence hits ("6's") vs. forgot:			
Temporal pole	38	R	22, 13, -22
Hippocampus		R	32, -24, -2
High-confidence hits with correct source vs. forgot:			
Inferior frontal gyrus	13	L	-45, 7, 6
Precentral gyrus	6	R	54, -1, 10
Postcentral gyrus		L	-48, -10, 16
Insula		L	-31, 2, 16
Hippocampus		L	-29, -10, -19
Thalamus		L	-5, -14, 0
Cerebellum		R	17, -42, -34
High-confidence hits with incorrect source vs. forgot:			
Inferior Frontal Gyrus	47	L	-28, 29, -14
Precentral gyrus	13	L	-46, 3, 7
	13	L	-48, -12, 14
	6	R	54, -1, 9
Hippocampus		L	-28, -9, -19
Caudate		L	-6, 6, 9
		R	12, 19, 4
Lentiform Nucleus		L	-20, 14, -4
		R	20, 6, -7
Thalamus		L	-4, -14, -1
		L	-18, -32, 11
		R	10, -19, 16
Cerebellum		R	32, -39, -24
High-confidence hits with true source vs. forgot:			
Precentral gyrus	4	L	-53, -4, 16
	6	R	54, 2, 14
Temporal pole	38	R	46, 6, -9
Superior temporal gyrus	22	L	-50, -9, 1
Insula	13	L	-33, -9, 17
Hippocampus		L	-28, -34, 1
		R	28, -35, 0
	42	R	60, -16, 11
Fusiform gyrus	37	R	28, -49, -11
Parahippocampal gyrus	19	L	-18, -42, -3
Caudate		L	-16, -4, 18
Putamen		L	-25, 6, 4
		R	24, 1, 3
Thalamus		R	7, -22, -3
Cerebellum		L	-23, -47, -14
High-confidence hits with absent source vs. forgot:			
Hippocampus		R	26, -34, -2
Parahippocampal gyrus	20	L	-33, -14, -29

Supplementary information (continued):
The clusters of activation (p-corrected< 0.05) identified in the whole-brain analyses by the contrast listed below. Talairach coordinates are for the peak voxel in each cluster.

Region	Brodmann area	Hemisphere	Talairach coordinates (x,y,z)
High-confidence hits with true source vs. high-confidence hits with absent source:			
Medial frontal gyrus	11	L	-9, 35, -16
Middle frontal gyrus	9	L	-51, 33, 21
Inferior frontal gyrus	46	R	44, 31, 8
Medial frontal gyrus	11/25	R	6, 26, 21
Inferior frontal gyrus	45	L	-54, 23, 14
Medial frontal gyrus	25	L	-12, 23, -16
Inferior frontal gyrus	47	L	-27, 22, -17
Middle frontal gyrus	6	L	-48, 9, 51
Precentral gyrus	6	L	-33, -11, 71
	6	R	29, -14, 61
	4	L	-31, -24, 51
Postcentral gyrus	3	L	-46, -19, 49
	3	L	-36, -31, 58
Insula	13	R	29, 21, 16
Inferior parietal lobule	40	L	-41, -24, 24
Middle temporal gyrus	19	L	-46, -61, 16
Lingual gyrus	19	L	-15, -61, -4
	19	R	17, -51, -9
Middle occipital gyrus		L	-34, -64, 1
Calcarine sulcus		R	24, -66, 11
Cuneus	19	L	-7, -99, 29
Cuneus	19	R	16, -86, 36
Caudate		L	-13, -1, 221
		L	-18, -14, 14
Putamen		L	-19, 11, 4
Globus Pallidus		R	29, -9, -8
Thalamus		L	-23, -29, 11
		R	2, -24, 1
Cerebellum		L	-4, -61, -3
		R	16, -42, -22
		R	21, -69, -31

General Discussion

The conclusion drawn from the four experiments here is that the hippocampus serves a broader role than selectively supporting recollection.

Developments from 50 years of memory research show that the hippocampus serves a critical role in recognition, yet there is no consensus about what the hippocampus does and does not do in this role. Cognitive neuroscience has addressed this question by applying psychological models to interpret data from patients with hippocampal lesions and from fMRI studies. The psychological models that have been applied are based on how recognition is experienced, including an awareness of confidence and an awareness of whether recollection succeeded or failed. The intent of these models is to separate memories based on recollection from memories based on familiarity and, when applied to neuroscience studies, to separate the neural correlates of recollection from the neural correlates of familiarity.

Particular models have proposed how the qualitative experience of remembering contextual details about an episode reflects a different class of behavioral response than the qualitative experience of context-free recognition. The high-threshold/dual-process view and the related Remember/Know procedure assume that recollection is a categorical process— it succeeds or it fails. When recollection succeeds, according to these views, confidence is always strong. Accordingly, the high-threshold view interprets recognition decisions made with high confidence as being based on recollection and recognition decisions made with less confidence as being based on familiarity. Taking a similar approach, the Remember/Know procedure instructs participants to make Remember responses when they are confident about recollection and to make Know responses when they are confident about the prior occurrence of an item because of its high familiarity and despite the failure of recollection.

Experiments 1 and 2 tested the estimates provided by the high-threshold/dual-process model and the related Remember/Know procedure that have been assumed to determine whether recognition was based on recollection or on familiarity. The results from Experiment 1 in this dissertation show that the high-threshold view does not reliably predict whether recognition responses are based on recollection or on familiarity. The results from Experiment 2 in this dissertation show that the Remember/Know procedure does not reliably separate recognition responses based solely on recollection from those based solely on familiarity. These new experiments showed that recollection is not a categorical process, that the contributions of recollection and familiarity to a recognition decision cannot be inferred from the memory strength associated with the decision, and that recollection is not selectively impaired in patients with hippocampal lesions. Furthermore, the data from Experiment 2 show that confidence in recollection varies (e.g., Remember responses are based on strong recollection and Know responses are based on weak recollection). The conclusions from these experiments support the view that recognition decisions are made as an aggregate of input from the recollection process and input from the familiarity process.

FMRI studies have typically applied the high-threshold/dual-process view and the Remember/Know procedure/model to make interpretations about the correlates of recollection and familiarity in the MTL. Both models have been used extensively to interpret fMRI data because they assume a simple, categorical basis by which activity correlated with recollection can be dissociated from activity correlated with familiarity.

The typical results across 21 recent fMRI studies show that activity in the hippocampus is differentially increased for the highest confidence responses in recognition tasks, yet it is no different than misses for the weaker confidence responses. According to the high-threshold view and the Remember/Know procedure, the inescapable conclusion from this pattern of activity is that the job of the hippocampus is to support recollection and only recollection. This conclusion is typical in the relevant fMRI literature.

The analysis of this literature in Experiment 3, however, found that although these studies intended to dissociate MTL activity on the basis of recognition processes, their interpretations dissociated activity on the basis of memory strength. In other words, all of these fMRI studies confounded memory strength with memory processes in their analyses. This is a critical point because other research in the cognitive literature has demonstrated that:

> i. Memories thought to be associated with recollection (e.g., Remember responses) are typically strong and memories thought to be associated with familiarity (e.g., Know responses) are typically weaker (Donaldson, 1996).
>
> ii. The strength of recollection is continuous, just as the strength of familiarity is continuous (Slotnick & Dodson, 2005).

This means that the pattern of activity in the hippocampus, which has typically been interpreted as evidence for a selective role in recollection, can be explained equally well as evidence that the hippocampus subserves high-strength memory whether based on recollection or familiarity. Because the aggregated-strength view explains the fMRI results equally well, a new approach was needed to examine of the neural correlates of recollection and familiarity.

Experiment 4 followed a procedure that allowed for the parametric analysis of recognition memory strength separately from the parametric analysis of source memory strength and equated recognition strength for decisions based on recollection with decisions based on familiarity (usually denoted by recollection failure in the relevant fMRI literature). After equating for memory strength, activity in the hippocampus in association with high-confidence hits was greater than for forgotten items, regardless whether source judgments were correct (recollection succeeded) or incorrect (recollection failed). Specifically, these data show that the hippocampus subserves recollection and familiarity when memory strength is uniformly high. An analysis of weaker strength responses in this experiment did not show significantly elevated activity. Results from Experiment 3 also show that the hippocampus is differentially engaged in association with strong memory, but the level of activity in association with weaker memory is not different from that associated with forgotten items. The convergence of the results from Experiments 3 and 4 suggests that the hippocampus subserves strong memory, but may not play a role in weaker memory (or, if it does, then its role in weak memories may not be detectable using fMRI).

Does the Hippocampus mediate recognition on the basis of strength, salience or both?

The view that activity in the hippocampus is selective for strong memory accounts for the fMRI data and also for results with patients who have suffered hippocampal lesions. These patients are capable of forming new declarative memories, but these memories are weak, in comparison to controls, and therefore not durable (Haist, Shimamura & Squire, 1992; Wais et al., 2006). If the hippocampus is necessary for strong memory (i.e., recall, or recognition based on strong recollection or strong familiarity) but not for weaker memory, then hippocampal patients can be expected to show recognition impairment related to strength (Yonelinas et al., 2002; Manns et al., 2003; Wais et al., 2006; Kan, Giovanello, Schnyer, Makris, & Verfaellie, 2007). The view that the hippocampus serves only strong memory suggests a framework for understanding functional differences in the medial temporal lobe. Specifically, when input from regions that project onto the hippocampus summates above a threshold, consolidation may be instigated, thereby leading to a strong memory trace.

The hippocampus receives projections from regions of the parahippocampal gyrus (primarily via the entorrhinal cortex) that integrate input from the ventral and dorsal streams of the association cortex (Suzuki & Amaral, 2004) and receives projections from the amygdala, which directly mediates aspects of emotional learning (McGaugh, 2000; LaBar & Cabeza, 2006) and is associated with memory for emotional events (Canli, Zhao, Brewer, Gabrieli & Cahill, 2000; Mather, Canli, English, Whitfield, Wais, Ochsner, Gabrieli & Carstensen, 2004). In a strength-based framework, it is input afferent from these MTL regions to the hippocampus that signals some degree of simple item recognition, elaborating details and arousal for an experience that instigates (or is reconstructed as) a salient memory. Significantly, the salience of a declarative memory is heightened by arousal in this framework whether arousal modulates memory for items (Mather, 2007) or episodes (Anderson, Wais & Gabrieli, 2006). The idea is that the hippocampus, as the nexus for signaling from other MTL structures, is positioned to aggregate input from the regions associated with item identification (perirhinal cortex, Aggleton & Brown, 2001) and contextual information (parahippocampal cortex, Eichenbaum et al., 2007) with input from the region associated with arousal (amygdala, McGaugh, 2000). The strength-based framework suggests that any one of these attributes of memory by itself is not typically sufficient to produce a strong memory and that the role of the hippocampus is to serve as a capacitor of sorts to enhance the encoding and retrieval of salient experiences.

The results from Experiment 4 are consistent with the notion that the hippocampus is differentially engaged only when memory is strong, but it is important to emphasize that those findings alone are not sufficient to confidently draw the conclusion that the hippocampus is selective for strong memory. A common mistake in the interpretation of fMRI data is to accept a null result as evidence that a particular region is not engaged in a task (Poldrack, 2007), and the implications of this sort of misjudgment are significant and complex in terms of sorting out activity associated with weak memory (Stark & Squire, 2001). Therefore, other research is worth considering in relation to the finding from some fMRI studies that the hippocampus serves only strong memory, given that the fMRI studies may have misinterpreted the equivalence of the levels of the BOLD signal correlated with weak memory and with the misses.

There is evidence from high-resolution fMRI and single-cell recordings that argues against the view that the hippocampus is engaged only in association with strong memory. Although the literature examined in Experiment 3 shows that fMRI acquired at typical resolution may not be sensitive enough to distinguish changes in the BOLD signal correlated with different levels of weak memory in the hippocampus, fMRI studies that focused increased resolving power on the MTL have found differentially-increased activity in the hippocampus in association with weaker strength recognition (Eldridge et al., 2005; Johnson, Muftuler and Rugg, 2008). Additionally, single-cell recordings from the human hippocampus have identified two classes of neurons with firing rates correlated with the strength of recognition memory (Rustihauser et al., 2006, Rutishauser et al., 2008). During responses to a source memory test, one class of neurons increased spiking activity when a studied image was recognized and increased spiking further if source information was also available. A second class of neurons signaled the novelty of lure images during the test with spiking frequency that was inversely correlated with familiarity. Both classes of neurons spiked differentially when recognition of test images was accompanied with recollection in comparison to when recognition was absent recollection. Because recognition accompanied by recollection typically reflects stronger memory than recognition absent recollection, the patterns of activity observed by Rutishauser et al. (2008) suggest that hippocampal neurons are sensitive to strong as well as weaker memory.

Squire et al. (2007) considered these neuroimaging data and proposed that the hippocampus subserves a broad role in recognition that is not selective for either processes or strength. This view suggests that the hippocampus abstracts bits of information from prior experience that are related to spatial, frequency, recency, modality, semantic class or other stimulus-based associations (such as arousal). As such, the abstraction process subserved by the hippocampus does not map onto specific recognition processes (i.e., recollection and familiarity) or measurements of memory strength. This view is compatible with new work from high-resolution fMRI that identified hippocampal activity associated with the sort of computational role necessary for abstraction (Bakker, Kirwan, Miller & Stark, 2008). This view also accounts well for the cause of memory impairment suffered by patients with hippocampal lesions.

The results from this dissertation extend our understanding of the different roles that the hippocampus serves in recognition. Empirical evidence presented and discussed here identified an important confound in prior research that suggested a selective role for the hippocampus. A new approach avoided the memory-strength confound that compromised previous studies and found evidence from fMRI that the hippocampus subserves both the recollection and familiarity processes. These fMRI data also suggest that the hippocampus, uniquely in the MTL, signals strong memory. Other recent research shows that the hippocampus is sensitive for recollection, familiarity and increasing gradations in memory strength, although further work is needed to examine its range of sensitivity for memory strength. Taken as a whole, these developments elucidate a critical role for the hippocampus in recognition and not solely in recollection.

References

Aggleton, J. and Brown, M. (2006). Interleaving brain systems for episodic and recognition memory. *Trends in Cognitive Sciences*, 455-463.

Aggleton, J. P., Vann, S. D., Denby, C., Dix, S., Mayes, A. R., Roberts, N. & Yonelinas, A. P. (2005). Sparing of the familiarity component of recognition memory in a patient with hippocampal pathology. *Neuropsychologia*, *43*, 1810-1823.

Amaral, D. and Insausti, R. (1990). Chapter 21: Hippocampal formation. *The Human Nervous System, Academic Press, New York, NY*, 711-755.

Anderson, A., Wais, P. & Gabrieli, J. (2006). Emotion enhances remembrance of neutral events past. *Proceedings of the National Academy of Sciences, 103.* 1599-1604.

Badre, D. & Wagner, A. (2007). Left ventrolateral prefrontal cortex and the cognitive control of memory. *Neuropsychologia, 45*. 2883-2901.

Bakker, A., Kirwan, C., Miller, M. and Stark, C. (2008). Pattern separation in the human hippocampal CA3 and dentate gyrus. *Science, 319*. 1640-1642.

Barbeau E, Felician O, Joubert S, Sontheimer A, Ceccaldi M, Poncet M. (2005). Preserved visual recognition memory without the hippocampus: evidence from a case study. *Hippocampus, 15.* 587-96.

Bastin, Ch., Van der Linden, M., Charnallet, A., Denby, Ch., Montaldi, D., Roberts, N., & Mayes, A. (2004). Dissociation between recall and recognition memory performance in an amnesic patient with hippocampal damage following carbon monoxide poisoning. *Neurocase*, *10.* 330-344.

Bayley, P.J., Gold, J.J., Hopkins, R.O. and Squire, L.R. (2005). The neuroanatomy of remote memory. *Neuron 46.* 799-810.

Brewer, J. et al. (1998). Making memories: brain activity that predicts how well visual experience will be remembered. *Science, 281*. 1185-1187.

Brown, M. and Aggleton, J. (2001). Recognition memory: what are the roles of the perirhinal cortex and hippocampus? *Nature Reviews Neuroscience, 2*. 51-61.

Buckner, R.L. and Wheeler, M.E. (2001). The cognitive neuroscience of remembering. *Nature Reviews Neuroscience, 2*. 624-634.

Cabeza, R., Rao, S., Wagner, A., Mayer, A., & Schacter, D. (2001) Can medial temporal lobe regions distinguish true from false? An event-related functional MRI study of veridical and illusory recognition memory. *Proceedings of the National Academy of Sciences***,** *98*. 4805-4810.

Canli, T., Zhao, Z., Brewer, J., Gabrieli, J. and Cahill, L. (2000). Event-related activation in the human amygdala associates with later memory for individual emotional experience. *Journal of Neuroscience, 20.* RC99.

Casino, S., Maquet, P., Dolan, R. and Rugg, M. (2002). Brain activity underlying encoding and retrieval of source memory. *Cerebral Cortex, 12*. 1048-1056.

Cipolotti, L., Bird, C., Good, T., Macmanus, D., Rudge, P., and Shallice, T. (2006). Recollection and familiarity in dense hippocampal amnesia: A case study. *Neuropsychologia, 44*. 489-506.

Conway, M. A., & Dewhurst, S. A. (1995). Remembering, familiarity, and source monitoring. *Quarterly Journal of Experimental Psychology: Human Experimental Psychology, 48,* 125-140.

Curran, T. and Hintzman, D. (1995). Violations of the independence assumption in process dissociation*. Journal of Experimental Psychology: Learning, Memory & Cognition, 21.* 531-547.

Daselaar, S., Fleck, M. and Cabeza, R. (2006). Triple dissociation in the medial temporal lobes: recollection, familiarity and novelty. *Journal of Neurophysiology, 96*, 1902-1911.

Davachi, L., Mitchell, J. and Wagner, A. (2003). Multiple routes to memory: distinct medial temporal lobe processes build item and source memories. *Proceedings of the National Academy of Sciences, 100.* 2157-2162.

Diana, R., Yonelinas, A. and Ranganath, C. (2007). Imaging recollection and familiarity in the medial temporal lobe: a three-component model. *Trends in Cognitive Sciences, 11*. 379-386.

Dobbins, I. and Wagner, A. (2005). Domain-general and domain-sensitive prefrontal mechanisms for recollecting events and detecting novelty. *Cerebral Cortex, 15*. 1768-1778.

Dobbins, I., Rice, H., Wagner, A. and Schacter, D. (2003). Memory orientation and success: separable neurocognitive components underlying episodic recognition. *Neuropsychologia, 41*. 318-333.

Donaldson, W. (1996). The role of decision processes in remembering and knowing. *Memory & Cognition, 24,* 523–533.

Dunn, J. (2008). The dimensionality of the remember-know task: A state-trace analysis. *Psychological Review, 115*, 426-446.

Dunn, J. (2004). Remember-Know: A matter of confidence. *Psychological Review, 111*, 524-542.

Eichenbaum, H., Yonelinas, A., and Ranganath, C. (2007). The medial temporal lobe and recognition memory. *The Annual Review of Neuroscience, 30*. 123-152.

Eichenbaum, H. (2000). A cortical-hippocampal system for declarative memory. *Nature Reviews Neuroscience, 1,* 41-50.

Eldridge, L., Engel, S., Zeineh, M., Bookheimer, S. and Knowlton, B. (2005). A dissociation of encoding and retrieval processes in the human hippocampus. *Journal of Neuroscience, 25*. 3280-3286.

Fortin, N., Wright, S. and Eichenbaum, H. (2004). Recollection-like memory retrieval in rats is dependent on the hippocampus. *Nature, 431*. 188-191.

Gardiner, J. (1988). Functional aspects of recollective experience. *Memory & Cognition, 16*. 309-313.

Gardiner, J.M., Java, R.I., & Richardson-Klavehn, A. (1996). How levels of processing really influence awareness in recognition memory. *Canadian Journal of Experimental Psychology. 50*, 114–122.

Gardiner, J. M., Richardson-Klavehn, A. & Ramponi, C. (1997) On reporting recollective experiences and "direct access to memory systems'. *Psychological Science, 8*, 391-394.

Gardiner, J. and Richardson-Klavehn, A. (2000). Remembering and knowing. *The Oxford Handbook of Memory*. Oxford University Press. New York.

Glanzer, M., Kim, K., Hilford, A. and Adams, J. K. (1999). Slope of the receiver-operating characteristic in recognition memory. . *Journal of Experimental Psychology: Learning, Memory & Cognition, 25*. 500-513.

Gold, J., Smith, C., Bayley, P., Shrager, Y., Brewer, J., Stark, C., Hopkins, R. and Squire, L. (2006). Item memory, source memory, and the medial temporal lobe : concordant findings from fMRI and memory-impaired patients. *Proceedings of the National Academy of Sciences, 103*. 9351-9356.

Gonsalves, B., Kahn, I., Curran, T., Norman, K. and Wagner, A. (2005). Memory strength and repetition suppression: multimodal imaging of medial temporal cortical contributions to recognition. *Neuron, 47*, 751-761.

Greicius, M., Krasnow, B., Boyett-Anderson, J., Eliez, S., Schatzberg, A., Reiss, A. and Menon, V. (2003). Regional analysis of hippocampal activation during memory encoding and retrieval: fMRI study. *Hippocampus, 13*. 164-174.

Haist, F., Shimamura, A. and Squire, L. (1992). On the relationship between recall and recognition memory. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 18*, 691-702.

Heathcote, A. (2003). Item recognition memory and the receiver operating characteristic. . *Journal of Experimental Psychology: Learning, Memory & Cognition, 29*. 1210-1230.

Henson, R. (2005). A mini-review of fMRI studies of human medial temporal lobe activity associated with recognition memory. *The Quarterly Journal of Experimental Psychology, 58B,* 340-360.

Henson, R., Hornberger, M. and Rugg, M. (2005). Further dissociating the processes involved in recognition memory: an fMRI study. *The Journal of Cognitive Neuroscience, 17*, 1058-1073.

Henson, R., Rugg, M., Shallice, T., Josephs, O. and Dolan, R. (1999). Recollection and familiarity in recognition memory: an event-related fMRI study. *Journal of Neuroscience, 19*. 3962-3972.

Hicks, J. L., Marsh, R. L., & Ritschel, L. (2002). The role of recollection and partial information in source monitoring. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 28*, 503-508.

Hilford, A., Glanzer, M., Kim, K., and DeCarlo, L. T. (2002) Regularities of source recognition: ROC analysis. *Journal of Experimental Psychology: General, 131*, 494-510.

Holdstock, J. S., Mayes, A.R., Roberts, N., Cezayirli, E., Isaac, C.L., O'Reilly, R.C. & Norman, K.A. (2002). Under what conditions is recognition spared relative to recall after selective hippocampal damage in humans? *Hippocampus 12*, 341–351.

Holdstock, J. S., Mayes, A.R., Gong, Q. Y., Roberts, N. & Karpur, N. (2005). Item recognition is less impaired than recall and associative recognition in a patient with selective hippocampal damage. *Hippocampus, 15*, 203-215.

Jacoby, L. (1991). A process dissociation framework: separating automatic from intentional uses of memory. *Journal of Memory and Language, 30*. 513-541.

Jacoby, L., Yonelinas, A., & Jennings, J. (1997). The relation between conscious and unconscious (automatic) influences: a declaration of independence. *Scientific Approaches* *to the Question of Consciousness*, J. D. Cohen & J. W. Schooler (eds.). Erlbaum. Hillsdale, NJ.

James, William. (1890). *The Principles of Psychology*. Henry Holt. New York.

Janowsky, J., Shimamura, A. and Squire, L. (1989). Source memory impairment in patients with frontal lobe regions. *Neuropsychologia, 27.* 1043-1056.

Johnson, J., Muftuler, L. and Rugg, M. (2008). Multiple repetitions reveal functionally- and anatomically-distinct patterns of hippocampal activity during continuous recognition memory. *Hippocampus,* in press

Kahn, I., Davachi, L. and Wagner. A. (2004). Functional-neuroanatomical correlates of recollection: implications for models of recognition memory. *Journal of Neuroscience, 24.* 4172-4180.

Kan, I., Giovanello, K., Schnyer, D., Makris, N. and Verfaellie, M. (2007). Role of the medial temporal lobes in relational memory: Neuropsychological evidence from a cued recognition paradigm. *Neuropsychologia, 45.* 2589-2597.

Keane, M. & Gabrieli, J. (1991). Evidence for a Dissociation Between Perceptual and Conceptual Priming in Alzheimer's Disease. *Behavioral Neuroscience, 105.* 326-342.

Kelley, R. and Wixted, J. (2001). On the nature of associative information in recognition memory. *Journal of Experimental Psychology: Learning, Memory and Cognition, 27.* 701-722.

Kensinger, E. and Schacter, D. (2006). Amygdala activity is associated with the successful encoding of item, but not source, information for positive and negative stimuli. *Journal of Neuroscience, 26.* 2564-2570.

Kirwan, C., Jones, C., Miller, M. and Stark, C. (2007). High-resolution investigation of the medial temporal lobe. *Human Brain Mapping, 10.* 959-966.

Kroll, N., Knight, R., Metcalf, J., Wolf, E. and Tulving, E. (1996). Cohesion failure as a source of memory illusions. *Journal of Memory and Language, 35*. 176-196.

LaBar, K. & Cabeza, R. (2006). Cognitive neuroscience of emotional memory. *Nature Reviews Neuroscience, 7*. 54-64.

Lavenex, P. and Amaral, D. (2000). Hippocampal-neocortical interactions: a hierarchy of associativity. *Hippocampus, 10*. 420-430.

Logothetis, N. and Wandell, B. (2004). Interpreting the BOLD signal. *Annual Review of Physiology, 66*. 735–769.

Loftus, G. and Masson, M. (1994). Using confidence intervals in within-subject designs. *Psychonomic Bulletin & Review, 1*. 476-490.

Macmillan, N. A. and Creelman, C. D. (2005). *Detection theory: A user's guide* (2nd Edition): New York, NY, USA.

Mandler, G. (1980). Recognizing: the judgment of previous occurrence. *Psychological Review, 87*. 252-271.

Mandler, G. and Boeck, W. J. (1974). Retrieval processes in recognition memory. *Memory & Cognition, 2*. 613-615.

Manns, J., Hopkins, R., Reed, J., Kitchener, E. and Squire, L. (2003). Recognition memory and the human hippocampus. *Neuron, 37*. 171-180.

Mather, M. (2007). Emotional arousal and memory binding. *Perspectives on Psychological Science, 2*. 33-52.

Mather, M., Canli, T., English, T., Whitfield, S., Wais, P., Ochsner, K., Gabrieli, J. & Carstensen, L. (2004). Amygdala responses to emotionally valenced stimuli in older and younger adults. *Psychological Science 15, 4*. 259-263.

Mayes, A.R., Holdstock, J.S., Isaac, C.L., Hunkin, N.M. & Roberts, N. (2002). Relative sparing of item recognition memory in a patient with adult-onset damage limited to the hippocampus. *Hippocampus*, *12*. 325-340.

McGaugh, J. (2000). Memory—a century of consolidation. *Science, 287,* 248–251.

Miller, M., Beg, M., Ceritoglu, C. and Stark, C. (2005). Increasing the power of functional maps of the medial temporal lobe by using large deformation diffeomorphic metric mapping. *Proceedings of the National Academy of Sciences, 102*. 9685-9690.

Montaldi, D., Spencer, T., Roberts, N. and Mayes, A. (2006). The neural system that mediates familiarity memory. *Hippocampus, 16*. 504-520.

Morcom, A., Good, C., Frackowiak, R. and Rugg, M . (2003). Age effects on the neural correlates of successful memory encoding. *Brain, 126*. 213-229.

Moscovitch, D. and McAndrews, M. (2002). Material-specific deficits in "remembering" in patients with unilateral temporal lobe epilepsy and excisions. *Neuropsychologia, 40*. 1335-1342.

Ogilvie J.C. and Creelman C.D. (1968). Maximum-likelihood estimation of receiver operating characteristic curve parameters. *Journal of Mathematical Psychology, 5*. 377-391.

Otten, L. (2007). Fragments of a larger whole: retrieval cues constrain observed neural correlates of memory encoding. *Cerebral Cortex, 17.* 2030-2038.

Otten, L., Henson, R. and Rugg, M. (2001). Depth of processing effects on neural correlates of memory encoding: relationship between findings from across- and within-task comparisons. *Brain, 124*. 399-412.

Parks, C. and Yonelinas, A. (2007). Moving beyond pure signal-detection models: comment on Wixted (2007). *Psychological Review, 114.* 188-202.

Poldrack, R. (2007). Region of interest analysis for fMRI. *Social, Cognitive & Affective Neuroscience, 2.* 67-70.

Qin, J., Raye, C. L., Johnson, M. K., and Mitchell, K. J. (2001). Source ROCs are (typically) curvilinear: Comment on Yonelinas (1999). *Journal of Experimental Psychology: Learning, Memory and Cognition, 27***.** 1110-1115.

Rajaram, S. (1993). Remembering and knowing: two means of access to the personal past. *Memory & Cognition, 21.* 89-102.

Ranganath, C. and Blumenfeld, R. (2007). Prefrontal cortex and human memory: an integrative review of findings from neuropsychology and neuroimaging. *Neuroscientist, 13*. 280-291.

Ranganath, C., Heller, A. and Wilding, E. (2007). Dissociable correlates of two classes of retrieval processing in prefrontal cortex. *Neuroimage, 35*. 1663-1673.

Ranganath, C., Yonelinas, A., Cohen, M., Dy, C., Tom, S. and D'Esposito, M. (2004). Dissociable correlates of recollection and familiarity within the medial temporal lobes. *Neuropsychologia, 42*. 2-13.

Rempel-Clower, N., Zola, S.M., Squire, L.R. and Amaral, D.G. (1996). Three cases of enduring memory impairment following bilateral damage limited to the hippocampal formation. *Journal of Neuroscience, 16*. 5233-5255.

Rotello, C. M., Macmillan, N. A., & Reeder, J. A. (2004). Sum-Difference Theory of Remembering and Knowing: A Two-Dimensional Signal Detection Model. *Psychological Review, 111*, 588–616.

Rugg, M., Henson, R. and Robb, W. (2003). Neural Correlates of retrieval success in the prefrontal cortex in recognition and exclusion tasks. *Neuropsychologia, 41*. 40-52.

Rutishauser, U., Mamelak, A. and Schuman, E. (2006). Single-trial learning of novel stimuli by individual neurons of the human hippocampus-amygdala complex. *Neuron, 49,* 805-813.

Rutishauser, U., Schuman, E. and Mamelak, A. (2008). Activity of human hippocampal and amygdala neurons during retrieval of declarative memories. *Proceedings of the National Academy of Sciences, 105.* 329-334.

Sauvage, M., Fortin, N., Owens, C., Yonelinas, A. & Eichenbaum, H. (2008). Recognition memory: opposite effects of hippocampal damage on recollection and familiarity. *Nature Neuroscience, 11*, 16-18.

Savage, L., Pitkin, S. and Careri, J. (1999). Memory enhancement in aged rats: the differential outcomes effect. *Developmental Psychobiol*ogy, *35*, 318-27.

Schacter, D. and Slotnick, S. (2004). The cognitive neuroscience of memory distortion. *Neuron, 44*. 149-160.

Schmolck, H., Kensinger, E., Corkin, S. and Squire, L. (2002). Semantic knowledge in patient H.M. and other patients with medial and lateral temporal lobe lesions. *Hippocampus, 12*, 520-33.

Scoville, W. and Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. *Journal of Neurology, Neurosurgery and Psychiatry, 20*, 11-21.

Skinner, E., and Fernandes, M. (2007). Neural correlates of recollection and familiarity: a review of neuroimaging and patient data. *Neuropsychologia, 45*. 2163-2179.

Slotnick, S. and Dodson, C. (2005). Support for a continuous (single-process) model of recognition memory and source memory. *Memory & Cognition, 33*. 151-170.

Smith, C., and Squire, L. (2005). Declarative memory, awareness, and transitive inference. *Journal of Neuroscience., 25*, 10138-10146.

Squire, L, Wixted, J. and Clark, R. (2007). Recognition memory and the medial temporal lobe: a new perspective. *Nature Reviews Neuroscience, 8*. 872-884.

Squire, L. (1992). Declarative and non-declarative memory: multiple brain systems supporting learning and memory. *Journal of Cognitive Neuroscience, 4*, 232-243.

Squire, L. and Zola-Morgan, S. (1991). Medial temporal lobe memory system. *Science, 253,* 1380-1386.

Stark, C. and Okado, Y. (2003). Making memories without trying: medial temporal lobe activity associated with incidental memory formation during recognition. *Journal of Neuroscience, 23.* 6748-6753.

Stark, C. and Squire, L. (2001). When zero is not zero: the problem of ambiguous baseline conditions in fMRI. *The Proceedings of the National Academy of Sciences, 98.* 12760-12766.

Suzuki, W. and Amaral, D. (2004). Functional neuroanatomy of the medial temporal lobe memory system. *Cortex, 40.* 220-222.

Suzuki, W. and Amaral, D. (1994). Topographical organization of the reciprocal connections between monkey entorhinal cortex and the perirhinal and parahippocampal cortices. *Journal of Neuroscience, 14.* 1856-1877.

Tulving, E. (1985). Memory and consciousness. *Canadian Journal of Psychology, 26.* 1-12.

Uncapher, M. and Rugg, M. (2005). Encoding and the durability of episodic memory: a functional magnetic resonance imaging study. *Journal of Neuroscience, 25.* 7260-7267.

Verfaellie, M., Cook, S. and Keane, M. (2003). Absence of size congruency effects in amnesic patients' recognition: a failure of perceptually based recollection. *Neuropsychology, 17*, 108-14.

Wagner, A., Desmond, J., Glover, G. and Gabrieli, J. (1998). Prefrontal cortex and recognition memory: functional-MRI evidence for context-dependent retrieval processes. *Brain, 121.* 1985-2002.

Wais, P., Mickes, L. and Wixted, J. (2008). Remember/Know judgments probe degrees of recollection. *Journal of Cognitive Neuroscience, 20.* 400-405.

Wais, P., Wixted, J., Hopkins, R. and Squire, L. (2006). The Hippocampus supports both the recollection and the familiarity components of recognition memory. *Neuron, 49*, 459-466.

Weis, S., Specht, K., Klaver, P., Tendolkar, I., Willmes, K., Ruhlmann, J., Elger, C. and Fernandez, G. (2004). Process dissociation between contextual retrieval and item recognition. *Neuroreport, 15.* 2729-2733.

Wheeler, M., Stuss, D. and Tulving, E. (1995). Frontal lobe damage produces episodic memory impairment. *Journal of the International Neuropsychological Society, 1.* 525-536.

Wheeler, M. and Buckner, R. (2003). Functional dissociation among components of remembering: control, perceived oldness, and content. *Journal of Neuroscience, 23.* 3869-3880.

Wheeler, M. and Buckner, R. (2004). Functional-anatomic correlates of remembering and knowing. *Neuroimage, 21.* 1337-49.

Wixted, J. (2007). Dual-process theory and signal-detection theory of recognition memory. *Psychological Review, 114.* 152-76.

Wixted, J. T. (2004). On common ground: Jost's (1897) law of forgetting and Ribot's (1881) law of retrograde amnesia. *Psychological Review, 111.* 864-879.

Wixted, J. and Squire, L. (2004). Recall and recognition are equally impaired in patients with selective hippocampal damage. *Cognitive, Affective & Behavioral Neuroscience, 4.* 58-66.

Wixted, J. T. and Stretch, V. (2004). In defense of the signal detection interpretation of Remember/Know judgments. *Psychonomic Bulletin & Review, 11.* 616-641.

Woodruff, C., Johnson, D., Uncapher, M. and Rugg, M. (2005). Content-specificity of the neural correlates of recollection. *Neuropsychologia, 43.* 1022-1032.

Yonelinas, A. (1994). Receiver operating characteristics in recognition memory: evidence for a dual process model. *Journal of Experimental Psychology: Learning, Memory & Cognition, 20.* 1341-1354.

Yonelinas, A.P. (1997). Recognition memory ROCs for item and associative information: The contribution of recollection and familiarity. *Memory & Cognition, 25,* 747-763.

Yonelinas, A., Kroll, N., Dobbins, I., Lazarra, M. and Knight, R. (1998). Recollection and familiarity deficits in amnesia: convergence of remember/know, process dissociation and receiver operating characteristic data. *Neuropsychology, 12.* 323-339.

Yonelinas, A.P. (1999). The contribution of recollection and familiarity to recognition and source memory: an analysis of receiver operating characteristics and a formal model. *Journal of Experimental Psychology: Learning, Memory and Cognition, 25.* 1415-1434.

Yonelinas, A., Kroll, N., Quamme, J., Lazzara, M., Sauve, M., Widaman, K. and Knight, R. (2002). Effects of extensive temporal lobe damage or mild hypoxia on recollection and familiarity. *Nature Neuroscience, 5.* 1236-1241.

Yonelinas, A., Otten, L., Shaw, K. and Rugg, M. (2005). Separating the brain regions involved in recollection and familiarity in recognition memory. *Journal of Neuroscience, 25.* 3002-3008.