Remembering the Past: Multimodal Imaging of Cortical Contributions to Episodic Retrieval

by

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Abstract

What is the nature of the neural processes that allow humans to remember past events? The theoretical framework adopted in this thesis builds upon cognitive models that suggest that episodic retrieval can be decomposed into two classes of computations: (1) *recovery processes* that serve to reactivate stored memories, making information from a past episode readily available, and *(2) control processes* that serve to guide the retrieval attempt and monitor/evaluate information arising from the recovery processes. A multi-modal imaging approach that combined fMRI and MEG was adopted to gain insight into the spatial and temporal brain mechanisms supporting episodic retrieval. Chapter 1 reviews major findings and theories in the episodic retrieval literature grounding the open questions and controversies within the suggested framework. Chapter 2 describes an fMRI and MEG experiment that identified medial temporal cortical structures that signal item memory strength, thus supporting the perception of item familiarity. Chapter 3 describes an fMRI experiment that demonstrated that retrieval of contextual details involves reactivation of neural patterns engaged at encoding. Further, leveraging this pattern of reactivation, it was demonstrated that false recognition may be accompanied by recollection. The fMRI experiment reported in Chapter 3, when combined with an MEG experiment reported in Chapter 4, directly addressed questions regarding the control processes engaged during episodic retrieval. In particular, Chapter 3 showed that parietal and prefrontal cortices contribute to controlling the act of arriving at a retrieval decision. Chapter 4 then illuminates the temporal characteristics of parietal activation during episodic retrieval, providing novel evidence about the nature of parietal responses and thus constraints on theories of parietal involvement in episodic retrieval. The conducted research targeted distinct aspects of the multi-faceted act of remembering the past. The obtained data contribute to the building of an anatomical and temporal "blueprint" documenting the cascade of neural events that unfold during attempts to remember, as well as when such attempts are met with success or lead to memory errors. In the course of framing this research within the context of cognitive models of retrieval, the obtained neural data reflect back on and constrain these theories of remembering.

Thesis Advisor: Anthony D. Wagner
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Dedicated to

Anna, my soul mate and partner to this journey

and

Dina and Eytan, my parents, for the support and love

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Chapter 1

Introduction

Declarative memory supports the ability to retain and retrieve facts (semantic memory) and events (episodic memory), enabling us to act in the present while taking advantage of the past (Cohen & Eichenbaum, 1993; Cohen & Squire, 1980; Squire, 1992; Tulving & Schacter, 1990). A core function of declarative memory is episodic retrieval, which can take the form of recognizing a stimulus as having been previously encountered or retrieving contextual details surrounding a stimulus's prior encounter.

Consider the following dialog taking place at a theater manager's window (as described in *The Twelve Chairs*[1]):

> "'Hurry up and give me the note!' he shouted to Ostap.
>
> 'Two seats,' said Ostap quietly, 'in the stalls.'
>
> 'Who for?'
>
> 'Me.'
>
> 'And who might you be to ask for seats from me?'
>
> 'Now surely you *know* me?'
>
> 'No, I don't'
>
> But the stranger's gaze was so innocent and open that the manager's hand by itself gave Ostap two seats in the eleventh row.

---

[1] *The Twelve Chairs / Ilf & Petrov* (1928), translated from Russian by John H. C. Richardson, pp. 283-284. Italics added.

> ‘All kinds come here,’ said the manager, shrugging his shoulders. ‘Who knows who they are? They may be from the Ministry of Education. I seem to *have seen him* at the Ministry of Education. *Where* could it have been?
>
> And mechanically issuing passes to the lucky film and theater critics, the manager went on quietly trying to *remember where he had seen* those clear eyes before.
>
> When all the passes had been issued and the light had gone down in the foyer, he *remembered he had seen them* in the Taganka prison in 1922, while he was doing time for some trivial matter.”

This dialogue illustrates the manager’s attempt to *recognize* whether a *retrieval cue* (the person standing at the window) has been previously encountered. As described, a *recognition memory* decision (I know I have seen that person before) can be based on a sense of item *familiarity* that is not accompanied by recollection of the context in which the stimulus was encountered (I have seen him but I don’t know where). Often this sense of *familiarity* will motivate an attempt to *recollect* additional contextual details (where and when have I seen him?). While such recollection attempts can be met with failure, when successful the additional recollected details can serve to further inform the recognition decision. For this to be the case, memory decisions require an assessment or evaluation of the relevance of the recollected details. That is, episodic retrieval requires processes that assess whether the recovered details should be rejected (I *may* have seen him at the Ministry of Education but I’m not sure) or endorsed (I saw him in the Taganka prison and I can recollect additional details), as well as whether sufficient details have been recovered to warrant a recognition judgment. Given the complexity of these components of retrieval, it perhaps is no surprise that theorists have argued that episodic retrieval also depends on other control operations, such as holding information in mind (maintenance in working memory) or directing attention to retrieval cues.

Central to understanding declarative memory is specification of the neural mechanisms that accomplish these different aspects of episodic retrieval. Accordingly, considerable effort has been devoted to addressing fundamental questions about retrieval: What neural processes produce a sense of stimulus familiarity? What neural processes mediate retrieval of the contextual details surrounding a prior stimulus encounter? More generally, what neural processes regulate attempts to remember, irrespective of the outcome of these attempts?

Monitoring the ongoing activity of the brain as a function of memory behavior can illuminate the neural mechanisms underlying specific aspects of episodic retrieval. For example, some neural processes may be related to successful item recognition and others may relate to context recollection, reflecting neural processes that signal familiarity or that guide the recovery of contextual details. Other mechanisms may not be correlated with the successful outcome of a retrieval attempt, but rather may reflect processes that support other aspects of attempts to retrieve, such as control processes that set the stage for retrieval (e.g., holding cues in working memory) or that work with any products of retrieval to arrive at a decision (e.g., monitoring item familiarity in relation to one's decision criterion or evaluating whether recollected details are relevant to the decision). Understanding how the brain supports the component processes of episodic retrieval is the topic of this thesis.

Over the past two decades, functional neuroimaging methods, such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and event related potentials (ERP), have advanced understanding of the workings of the human brain, as they enable delineation of the neural responses underlying specific cognitive processes (e.g., Bunge & Kahn, 2004; Frith & Friston, 1997; Kutas & Dale, 1998; Raichle, 1998). More recently, magnetoencephalography (MEG) has emerged as an additional method for measuring brain activity (Cohen & Halgren, 2003), providing higher temporal resolution than fMRI and superior spatial resolution relative to electroencephalography (Dale et al., 2000; Dale & Sereno, 1993; Hämäläinen, Hari, Ilmoniemi, Knuutila, & Lounasmaa, 1993). In the studies described in this thesis, we adopted a multi-modal imaging approach that leverages the high spatial resolution of fMRI and the high temporal resolution of MEG to gain insight into the nature, timing, and localization of the neural processes underlying the ability to remember past experiences.

Component Processes of Episodic Retrieval

Episodic retrieval is a complex act that involves a multifaceted set of cognitive (Burgess & Shallice, 1996; Norman & Bobrow, 1979; Tulving, 1983) and neural processes (e.g., Brown & Aggleton, 2001; Buckner & Wheeler, 2001; Eichenbaum, 2000; Eichenbaum & Cohen, 2001; Schacter & Tulving, 1994; Squire & Zola-Morgan, 1991; Wagner, 2002). Given this complexity, understanding the neural mechanisms subserving retrieval is a challenging endeavor. Constraints on generating neural models of remembering can be derived from cognitive models of retrieval, which have sought to decompose the act of retrieval to multiple subprocesses. Obtained neural data can then reflect back on cognitive models, resulting in theory modifications.

Cognitive theories of episodic retrieval suggest that for episodic retrieval to succeed, multiple subprocesses are necessary. In their influential theory of episodic retrieval, Norman and Bobrow (1979) proposed that retrieval involves three component processes working in concert to enable retrieval: (1) retrieval specification – generating a description of the target mnemonic information and verification criteria, (2) target matching to memory – accessing candidate memory traces and selecting those that are appropriate for the target description, and (3) evaluation of the suitability of emerging memory traces relative to the verification criteria (see also models by Anderson, 1976; Hintzman, 1988; Raaijmakers & Shiffrin, 1981; Ratcliff & Murdock, 1976). According to the theory, this sequence of retrieval processes can repeat using a revised retrieval specification based on information that becomes available during the retrieval cycle. Norman and Bobrow note that the three component processes can run in parallel or sequentially, arguing that in both cases the three aspects of retrieval remain essentially the same.

As a heuristic, the Norman and Bobrow theory provides a useful tool when considering the processes supporting retrieval, and thus subsequent work has sought to extend this general framework. For example, Burgess and Shallice (1996) built on the theory, with the goal of further specifying the nature of the processes during episodic retrieval. In their analysis, Burgess and Shallice suggested that the three component processes of retrieval proposed by Norman and Bobrow are regulated by processes of monitoring and control (also referred to as *strategic processes*) that run in parallel to the proposed component processes, rather than being restricted to any specific process. In particular, in addition to the control processes that support the specification of a retrieval plan and that monitor or evaluate the products of the target matching process, Burgess and Shallice identify an additional set of mechanisms that act to support episodic retrieval. These processes are assumed to operate continuously to modulate strategic and problem-solving operations concerning the plausibility of retrieved memory elements. For example, these processes include reasoning about whether the match or recovery process is following a course that is likely to lead to a conclusion that fits the initial specification. Notably, Burgess and Shallice used their model not only to account for accurate remembering, but also to explain situations of erroneous retrieval, as in the phenomenon of confabulation (the production of veridical memories in the wrong temporal context or of illusory memories in response to goal directed retrieval). As will be argued in this thesis, consideration of even simple memory errors (e.g., falsely endorsing new items as being previously encountered [false alarms] during recognition) provides critical evidence that can constrain models of retrieval (Schacter, 2001; Schacter, Norman, & Koutstaal, 1998).

An important aspect of these and other cognitive theories of remembering is the notion that retrieval depends on processes that might generally be characterized as mediating "cognitive control". Cognitive control refers to the ability to actively maintain and manipulate patterns of activity that represent goals and the means to achieve them (Miller & Cohen, 2001). In particular, across these theories of retrieval, three candidate control processes have been posited to be involved in a retrieval attempt (e.g., Burgess & Shallice, 1996; Moscovitch & Melo, 1997; Norman & Bobrow, 1979; Schacter, Norman,

& Koutstaal, 1998). The first is *cue specification*, which refers to the systematic analysis of the possible semantic relations between the cue and the known characteristics of the retrieved episode. That is, effective retrieval attempts depend on the ability to systematically choose the most pertinent characteristics of the retrieval cue with regard to the target episodes. For instance, when the theatre manager considers where he had seen Ostap, he considers the Ministry of Education because Ostap behaves and looks like an important person and often he had seen important people at the Ministry of Education. The second is *cue maintenance*, which entails holding relevant information in mind, such as holding the retrieval cue and the retrieval products in working memory. The third operation is *post-retrieval monitoring*, which involves evaluation of the products of the retrieval attempt with respect to their relevance to the retrieval task or decision criteria. Endorsing products as relevant to the target episode requires determining whether the retrieved information is consistent with the sought informationm or determining whether the strength of the recovered information is above one's response criterion. Importantly, at least some of these control processes are likely to be engaged irrespective of whether the attempt to remember results in successful recovery of mnemonic information or in failure.

By decomposing the act of episodic retrieval into multiple processing components, these models lay the ground for (and motivate) cognitive neuroscience approaches that seek to identify and characterize the neural mechanisms subserving these component processes. Notably, despite important differences, implicit in these models (Anderson, 1976; Hintzman, 1988; Norman & Bobrow, 1979; Raaijmakers & Shiffrin, 1981; Ratcliff & Murdock, 1976) is the notion that the processes underlying episodic retrieval can be broadly classified into two complementary classes: (1) *recovery processes* and *(2) control processes*. Recovery processes serve to reactivate stored memories, making information from a past episode readily available. As such, recovery processes support the retrieval of information regarding the mnemonic status of an item. One such process is pattern matching, which is thought to signal the degree of match between a retrieval cue and stored memories, with the strength of this signal then serving as a basis for determining whether the cue is sufficiently familiar to be classified as previously encountered or is less familiar and thus is classified as novel. Another form of recovery is pattern completion, wherein a retrieval cue triggers reactivation of associated contextual details present at the time of item encoding.

Recovery processes, by definition, are correlated with *successful* episodic retrieval. In contrast, control processes are computations that guide the act of retrieval. As discussed, when presented with a retrieval cue, control processes may support the ability to direct attention to the cue, hold it in mind, and elaborate upon it (e.g., Burgess & Shallice, 1996; Moscovitch & Winocur, 2002). Control processes also serve to monitor or evaluate any information arising from the pattern matching (familiarity) and pattern completion (recollection) recovery processes. Accordingly, engagement of these control processes is likely correlated with *attempts* to retrieve, and need not directly correlate with the success of these retrieval attempts.

Memory Recovery Processes

Understanding episodic retrieval requires specification of the neural processes that gain access to a memory trace, as these processes elicit retrieval of information regarding the mnemonic status of an item (i.e., signaling item *memory strength* or item familiarity) and/or serve to retrieve representations of associated contextual details present at the time of item encoding. Such *recovery processes* are central to the act of remembering, as they enable access to stored knowledge. Three central features of recovery processing are investigated here. First, the present research seeks to identify neural processes that act to retrieve information regarding the mnemonic status of a retrieval probe, resulting in the conscious perception of whether or not the stimulus was encountered in the past. A second objective is to characterize the neural processes engaged when the rememberer successfully retrieves the contextual details present at the time of an item's past encounter. The third aspect of recovery processes addressed here is to explore the nature of memory errors (e.g., false alarms) so as to determine whether such errors emerge due to the false perception of above-criterion item familiarity and due to guesses (as suggested by some cognitive theories of recognition) or whether such errors can also stem from erroneous retrieval of contextual details.

Recollection and Familiarity: Two Forms of Memory Recovery

As illustrated in the dialogue between Ostap and the theater manager, and more formally proposed by Mandler (1980) and Atkinson and Juola (1973), dual-process models of episodic retrieval suggest that recognition memory decisions can be based on two forms of memory: Familiarity (the sense that an item was encountered previously) and/or recollection (the recovery of contextual information surrounding the prior encounter with an item).

Behaviorally, two experimental paradigms have been extensively used to operationalize when recognition is thought to be based on recollection or familiarity. In the *Remember–Know* paradigm (e.g., Gardiner, 1988; Gardiner & Parkin, 1990; Tulving, 1985), participants respond *Remember* if they are able to retrieve contextual information from the study episode with an item, whereas they respond *Know* when they recognize the retrieval cue as having been presented, but are unable to recover any details about its past encounter. Thus, the Remember–Know paradigm defines recollection and familiarity in terms of subjective experience. In the *source recollection* paradigm, participants are asked to report whether they recognize a test probe, and when they can, they are further asked to recollect a particular contextual detail surrounding the encoding episode. Memory for the contextual (source) detail is taken as evidence of being able to use the retrieval probe to recollect additional information that occurred during encoding, such as being able to recollect which of two orienting tasks might have been performed with the stimulus at encoding (also referred to as "criterial recollection", Johnson, Hashtroudi, & Lindsay, 1993; Yonelinas & Jacoby, 1996). Recognition in the absence of source recollection is often interpreted as being based on item familiarity, though it could also be based on familiarity together with recollection of non-criterial event details (Dodson & Johnson, 1996).

Evidence that recognition memory decisions can be based on two distinct forms of information comes from behavioral studies aimed at dissociating familiarity and recollection. These studies have established that recollection and familiarity differ along a number of dimensions. First, familiarity information emerges earlier than does recollective information. Using speeded retrieval paradigms, where participants need to respond within a particular deadline, participants perform at above chance levels on item recognition tasks (i.e., did you encounter this item?) earlier than they do on context recollection tasks (e.g., which list was this item encountered in?) (Gronlund, Edwards, & Ohrt, 1997; Hintzman & Caulton, 1997; Hintzman, Caulton, & Levin, 1998). Second, the two processes are dissociable. For example, Jacoby, Woloshyn, and Kelley (1989) found that divided attention at encoding affects participants' ability to subsequently recollect the context in which a name had been learned, but did not influence subsequent familiarity. In addition to differential sensitivity to divided attention, an extensive literature has documented numerous other behavioral contexts in which recollection and familiarity can be shown to dissociate (for review, see Yonelinas, 2002).

Although it is widely accepted that recognition memory decisions are based on two distinct processes (but see, Donaldson, 1996; Dunn, 2004), there remains controversy regarding how to model familiarity and recollection in the context of a recognition memory decision. In particular, while it is accepted that familiarity can vary in a continuous manner and thus influences recognition as a signal detection process (Wixted & Stretch, 2004; Yonelinas, 2002), perspectives differ on the nature of recollection. Some theorists hypothesize that recollection is an all-or-none process, such that whenever any contextual detail is retrieved participants will subjectively experience recollection of the past and will make a positive memory decision (Yonelinas, 2002). By contrast, others argue that recollection also is associated with a continuous distribution, such that recognition based on recollection also operates as a signal detection process (Cary & Reder, 2003; Sherman, Atri, Hasselmo, Stern, & Howard, 2003). From this latter perspective, recognition decisions are thought to be based on an integration of the information from the familiarity distribution and from the recollection distribution, with gradations along this continuum mapping to gradations in perceived memory strength and recognition confidence (Wixted & Stretch, 2004).

Paralleling the debate in the cognitive literature regarding the nature and relationship between familiarity and recollection, the neural mechanisms supporting recognition judgments remain a matter of controversy. In particular, considerable debate surrounds the role of medial temporal lobe (MTL) structures in item recognition (Baxter & Murray, 2001; Brown & Aggleton, 2001; Rugg & Yonelinas, 2003; Squire, Stark, & Clark, 2004). This controversy emerged mainly from conflicting findings regarding whether non-human primates, rats, and human patients with damage restricted to the hippocampus show item recognition deficits (Baxter & Murray, 2001; Manns, Hopkins, Reed, Kitchener, & Squire, 2003; Stark, Bayley, & Squire, 2002; Stark & Squire, 2003; Yonelinas et al., 2002). We now turn to this controversy regarding how MTL subserves the recovery processes that underlie item familiarity and contextual recollection.

Memory Strength and the Medial Temporal Lobe

One key function of declarative memory is to support recognition of stimuli that were previously encountered, and to discriminate such stimuli from those that are novel. Behavioral studies of recognition suggest that discrimination between novel and encountered stimuli depends at least partially on an assessment of memory strength, which can vary in a continuous manner and which may underlie the subjective perception of stimulus familiarity (Wixted & Stretch, 2004; Yonelinas, 2002). A central question is what are the neural processes that signal memory strength such that graded differences in strength may be perceived?

The neural mechanisms supporting recognition judgments are a matter of debate, as considerable controversy surrounds the putative role of MTL structures—hippocampus and adjacent parahippocampal and perirhinal cortices—in item recognition (Baxter & Murray, 2001; Brown & Aggleton, 2001; Rugg & Yonelinas, 2003; Squire, Stark, & Clark, 2004). While investigators agree that the hippocampus is particularly important for remembering the relations between items and between items and context, they disagree about how MTL structures support recognition based on item memory strength. Much of the debate arises from inconsistent patterns of recognition memory deficits in infrahuman primates, rats, and human patients with damage thought to be restricted to the hippocampus. Some studies report that selective lesions of hippocampus impair recognition decisions (Zola et al., 2000), with patient data revealing similar deficits in recognition of both items and relations (Manns, Hopkins, Reed, Kitchener, & Squire, 2003; Stark, Bayley, & Squire, 2002; Stark & Squire, 2003). By contrast, other studies document spared recognition following hippocampal-specific lesions (Baxter & Murray, 2001), with such lesions resulting in a differential impairment of relational memory and relative preservation of item recognition (Baddeley, Vargha-Khadem, & Mishkin, 2001; Fortin, Wright, & Eichenbaum, 2004; Holdstock et al., 2002; Yonelinas et al., 2002). These latter data raise the possibility that item recognition is relatively preserved following hippocampal damage because it depends on mechanisms in medial temporal cortical regions adjacent to hippocampus (Brown & Aggleton, 2001; Yonelinas, Kroll, Dobbins, Lazzara, & Knight, 1998).

Support for a role of medial temporal cortex in item recognition comes from observations that in rats and monkeys with lesions of perirhinal cortex show consistent and often severe recognition memory deficits (Baxter & Murray, 2001; Brown & Aggleton, 2001). Further, single-cell recordings show experience-based changes in perirhinal neuronal firing patterns broadly consistent with item recognition, wherein firing rates decrease in response to previously encountered relative to novel stimuli (Xiang & Brown, 1998). Such firing rate decreases, termed "repetition suppression" (Desimone, 1996), can emerge as early as 75 ms after stimulus onset, occur after a single encounter with an item, and can be long-lasting (over 24 hrs), consistent with the hypothesis that they might support recognition discrimination based on item memory strength (Brown & Aggleton, 2001). Arguments based on computational principles have also been advanced to support the hypothesis that a medial temporal cortical system contributes to item recognition (Bogacz & Brown, 2003; Norman & O'Reilly, 2003).

Initial fMRI studies in humans also suggest a role for medial temporal cortex in item recognition. At encoding, anterior medial temporal cortex (at or near perirhinal cortex) is more active while processing items that are subsequently recognized compared to those subsequently forgotten, with perirhinal encoding activation not predicting later recollection (Davachi, Mitchell, & Wagner, 2003; Kensinger, Clark, & Corkin, 2003; Ranganath et al., 2004). At retrieval, activation levels in anterior medial temporal cortex (at or near perirhinal cortex) *decrease* during the processing of previously encountered ("old") items compared to novel ("new") items (Henson, Cansino, Herron, Robb, & Rugg, 2003), and during correct recognition of old items relative to old items incorrectly classified as new (Weis, Klaver, Reul, Elger, & Fernandez, 2004; Weis et al., 2004).

While the magnitude of this activation reduction does not appear to track conscious recollection (Henson, Cansino, Herron, Robb, & Rugg, 2003), at present it is unclear whether gradations in activation suppression relate to perceived differences in item memory strength or to non-conscious forms of memory (e.g., priming). Indeed, although it is possible that fMRI signal reductions in medial temporal cortex are a human analogue of the repetition suppression seen in single-unit recordings from animals, compelling evidence of their relation to memory strength requires evidence that fMRI activation suppression varies in a continuous manner according to gradations in *perceived* item strength.

Scalp-recorded ERPs have suggested two candidate correlates of memory strength, the FN400 and an earlier onsetting (100-300 ms) frontopolar component. The FN400 is a negative-going waveform that appears around 300-500 ms after stimulus onset, tends to be larger for new compared to old items, and can be unaffected by manipulations that impact recollection, such as levels-of-processing (Curran, 2000; Rugg et al., 1998). Intracranial ERP recordings indicate that the anterior medial temporal lobes may contribute to the FN400: Initial evidence suggests that this region is a source of the N400 (McCarthy, Nobre, Bentin, & Spencer, 1995), which differentially responds when participants encounter old compared to new items during recognition (Smith, Stapleton, & Halgren, 1986). As with fMRI activation reductions, however, the relation between the FN400 and item memory strength is unclear. First, the FN400 effect is not always seen in ERP studies of recognition (Yovel & Paller, 2004). Second, results are mixed regarding whether the FN400 is modulated by manipulations that have clear effects on familiarity, such as levels-of-processing (Rugg, Allan, & Birch, 2000; Rugg et al., 1998;

Wagner, Gabrieli, & Verfaellie, 1997). Third, gradations in the magnitude of the FN400 that track gradations in perceived item strength have not been established, although one study reported frontopolar signal differences from 300-450 ms post-stimulus onset across “remembered”, “known”, and “miss” recognition trials (Duarte, Ranganath, Winward, Hayward, & Knight, 2004).

The second candidate ERP correlate of memory strength is an earlier onsetting positive deflection (100-300 ms that can extend into the 300-450 ms window) maximal at frontopolar sites (Duarte, Ranganath, Winward, Hayward, & Knight, 2004; Tsivilis, Otten, & Rugg, 2001). This component differs in amplitude when comparing pairs of new stimuli (New-New) to pairs with at least one old/familiar stimulus (Old-Old and New-Old) (Tsivilis, Otten, & Rugg, 2001), and when comparing “remembered” and “known” test probes relative to “misses” (Duarte, Ranganath, Winward, Hayward, & Knight, 2004). While its early onset is temporally consistent with a rapidly available signal that can be used to compute item memory strength, ambiguities about the relation between this effect and item memory strength remain. First, the effect is “ungraded” in that pairs that clearly differ in item familiarity (Old-Old vs. New-Old pairs) nevertheless result in comparable ERP deflections relative to New-New pairs (Tsivilis, Otten, & Rugg, 2001). Second, as with the FN400, no extant data demonstrate a graded response during 100-300 ms post-stimulus onset that tracks graded item memory strength (Duarte, Ranganath, Winward, Hayward, & Knight, 2004), and some have argued that the effect could reflect visual perceptual priming (Curran & Dien, 2003). Although it has been hypothesized that this component may have an anterior medial temporal cortical generator, initial fMRI data did not reveal effects in medial temporal cortex comparable to this ERP component (Tsivilis, Otten, & Rugg, 2003).

The preceding review indicates that while there are candidate fMRI and ERP responses that may relate to item memory strength, results to date fail to establish a neural correlate of item memory strength in humans that shares the features of the effects seen in animal studies and in human behavior—namely a neural repetition suppression in medial temporal cortex that is continuous in nature and that onsets with an early latency. A critical step toward resolving the controversy regarding how MTL structures support recognition memory is to identify a neural signal of item memory strength in human MTL. Accordingly, as detailed in Chapter 2 of this thesis, we used a combined fMRI and MEG imaging approach to characterize medial temporal cortical responses and their relation to perceived memory strength.

Recapitulation of Neural Operations at Encoding

Hippocampal anatomy and functional dissociations between hippocampus and the surrounding MTL cortex suggest a complementary but computationally distinct role for the hippocampus in episodic retrieval (Amaral & Witter, 1989; Nakazawa, McHugh, Wilson, & Tonegawa, 2004). It was first suggested by Marr (1971) that a process of "pattern completion" takes place in the hippocampus (see also, McClelland, McNaughton, & O'Reilly, 1995; Norman & O'Reilly, 2003). *Pattern completion* refers to a unique computation that allows completing the whole-from-a-part to enable the recovery of information not present in the retrieval cue (e.g., recollecting contextual details). The CA3 subfield of the hippocampus has been shown to play a critical role in pattern completion (Nakazawa et al., 2002) because the ablation of the *N*-methyl-D-asparate (NMDA) receptor gene in CA3 pyramidal cells results in an inability to retrieve spatial reference memory when presented with partial cues (see also, Nakazawa et al., 2003; Norman & O'Reilly, 2003; Steele & Morris, 1999).

As suggested by Squire and Zola-Morgan (1991), neocortical connections with MTL are part of a network wherein distributed activity across several regions develops into a stable-long-term memory. Specifically, activity in lateral cortical regions propagates along projections to the parahippocampal cortex, perhirhinal cortex, and entorhinal cortex, and then to the hippocampus, exiting through the subiculum and through efferent projections back to the cortex. During encoding, the hippocampus is particularly important for binding together the representations arriving from neocortex, so that subsequently, memory for the details of an event can be reactivated from a partial cue (pattern completion). Pattern completion is thought to be the central MTL mechanism supporting recollection of contextual details (McClelland, McNaughton, & O'Reilly, 1995; Norman & O'Reilly, 2003).

While the role of hippocampus in pattern completion is well documented, the mechanisms through which pattern completion serves to elicit recollection of event details remains poorly specified. From one perspective, recollection is associated with the reactivation (or recapitulation) of patterns of neocortical activation that were present during stimulus encoding. Accordingly, during retrieval accompanied by recollection, it is thought that MTL pattern completion processes serve to trigger the recovery of event details (e.g., sensory information or information about the cognitive operations engaged at encoding) stored in neocortical processing modules.

Initial evidence for reactivation of sensory-specific cortex during retrieval comes from neuroimaging studies that observed re-engagement of domain-specific perceptual cortices when recollection of domain-specific information was required at retrieval (Nyberg, Habib, McIntosh, & Tulving, 2000; Vaidya, Zhao, Desmond, & Gabrieli, 2002; Wheeler, Petersen, & Buckner, 2000). For instance, Wheeler et al. (2000) asked participants to learn a set of pictures and a set of sounds over a period of several days, and then asked them to vividly recall the items and indicate whether they had seen or heard them. During encoding of pictures, activation was observed in ventral temporal regions implicated in object recognition (Grill-Spector, Knouf, & Kanwisher, 2004; Grill-Spector, Kourtzi, & Kanwisher, 2001), whereas during sound encoding, activation was observed in superior temporal regions implicated in auditory perception (Rauschecker, 1998; Wessinger, Buonocore, Kussmaul, & Mangun, 1997). Importantly, activity in these brain regions during recall demonstrated a domain-sensitive response. That is, a subset of the ventral temporal regions activated during perception of pictures was also activated during later recall of the pictures, whereas a subset of the superior temporal regions active during sound encoding were reactivated during recall of sounds.

Conceptually similar findings have been observed during semantic retrieval, as documented through activation in high level visual cortical regions. For example, in a study by O’Craven and Kanwisher (2000), activation was observed in fusiform gyrus during the recall of famous faces (cued by their names), whereas recalling familiar buildings activated the parahippocampal gyrus. Notably, on a trial-by-trial basis, activity within these regions predicted whether the participant was recalling a face or a building. Presumably, the fusiform and parahippocampal regions were differentially engaged during the numerous encoding encounters with each face and each place, respectively (Epstein, Harris, Stanley, & Kanwisher, 1999; Kanwisher, McDermott, & Chun, 1997), such that these retrieval effects may have marked reactivation of cortical patterns that were present during encoding.

Single-unit data provide compelling evidence that reactivation processes cascade backwards from MTL structures to neocortical sensory processing regions, consistent with the pattern completion hypothesis. Specifically, Naya et al. (2001) measured activity in single neurons in area TE and prehirhinal cortex while monkeys were performing a visual paired associate task. By identifying preferred and non-preferred stimuli for each neuron, these authors were able to document the response to individual stimuli during encoding. Using this knowledge, they then asked whether evidence of pattern completion emerges first in the MTL or in lateral neocortex. The neural marker of pattern completion was taken to be the reactivation of neurons that show a preferred response to stimulus A when presented with a non-preferred stimulus B that had be repeatedly associated with stimulus A during encoding. Strikingly, comparison of the temporal onset of these reactivation effects revealed that they appeared earlier in perhirhinal cortex, followed by the emergence of such effects in TE neurons. Naya et al. interpreted this finding to suggest that backward projections from MTL reactivate the TE representation of a visual object retrieved from long-term memory. While compelling, these reactivation effects occurred within the context of a semantic retrieval task (i.e., each stimulus-stimulus association had been studied repeatedly prior to test).

While these initial neuroimaging and single-unit data suggest that reactivation is a central component of recollecting event details, a number of issues remain. Most pressingly, all of these initial studies used multiple encoding trials per item, ensuring that items were strongly associated with domain-specific (visual or auditory) information or that strong item-item associations were formed. While this approach ensures a high probability of recollecting event details, a consequence of such designs is that retrieved knowledge about the general context associated with the item may be abstracted across the multiple sessions (e.g., abstracting the categorical knowledge that one saw a visual image of a stimulus). Consequently, a memory decision is based on this knowledge in the absence of any episode-specific information (e.g., categorizing the stimulus as having been seen as a picture without recollecting details about a particular encounter with the picture). Thus, an alternative interpretation of these initial "reactivation" effects is that they may reflect the top-down modulation of domain-specific regions based on retrieving such categorical (semantic) knowledge, even in the absence of episodic recollection. Chapter 3 of this thesis directly explores this important issue, using a paradigm wherein items were studied once at encoding and then were probed for contextual details (source information) at retrieval. Chapter 3 also considers whether reactivation (or recapitulation) effects can be seen in non-sensory regions when people recollect the cognitive operations performed on a stimulus at encoding (e.g., reactivating prefrontal cortices engaged during phonological encoding of a stimulus).

Recapitulation and False Recollection

In addition to illuminating the nature of recollection, neural recapitulation can provide a critical test for models of recognition. The causes of false recognition (i.e., endorsing a new item as old) and false recollection (i.e., claiming to remember details surrounding a new item) have generated some controversy among dual-process theorists. According to Yonelinas and colleagues (Jacoby, 1991; Yonelinas, 2002; Yonelinas, Dobbins, Szymanski, Dhaliwal, & King, 1996; Yonelinas, Kroll, Dobbins, Lazzara, & Knight, 1998), “remember” responses to lures (remember-false-alarms) are argued to entirely reflect guesses (i.e., they are not based on the recovery of mnemonic information), whereas “know” responses to lures (know-false-alarms) arise when lures are familiar enough to exceed one’s item strength decision criteria. This interpretation of false alarms suggests that false alarms do not result from erroneous retrieval of contextual details, but strictly reflect guesses for the remember-false-alarms and above-criterion familiarity for know-false-alarms.

Recently, this perspective was challenged by Wixted and Stretch (2004). These theorists argue that remember-false-alarms are not the result of false recollection nor of guessing, but rather reflect high-confidence familiarity that exceeds a second criterion beyond which participants claim to be “remembering” (see also, Donaldson, 1996). On the one hand, Wixted and Stretch note that remember-false-alarms are made more quickly than know-hits, and that they are correlated with the rate of know-false-alarms and guess-false-alarms and thus are unlikely to reflect false recollection. In addition, they argue that remember-false alarms are unlikely to reflect guesses because they are made with higher confidence relative to know-hits. Given these behavioral patterns, Wixted and Stretch concluded that remember-false-alarms are likely to reflect high confidence recognition based on high levels of item familiarity not accompanied by illusory or misbound recollection.

Strikingly at odds with these two competing perspectives, however, is a body of behavioral and neuroimaging evidence that suggests that, at least on some occasions, false recognition can be accompanied by illusory recollection. Extensive behavioral data indicate that false recognition can be accompanied by illusory recollection when new items are conceptually related to studied items (Roediger & McDermott, 1995; Schacter, Norman, & Koutstaal, 1998). Neuroimaging studies suggest that false recognition of related new items can be accompanied by MTL activation that resembles that seen during veridical recognition, whereas regions that represent domain-specific details may be differentially engaged during veridical, but not false, recognition (Cabeza, Rao, Wagner, Mayer, & Schacter, 2001; Schacter et al., 1996). Thus, from this literature, one might conclude that false recognition can be based on illusory recollection, though initial data suggest that such recollection may not be associated with the same reactivation effects in lateral neocortices as seen for veridical recollection.

Given these three perspectives on the nature of false recognition, a critical question is whether we can use neural recapitulation effects to provide a diagnostic test of these alternative models of erroneous recognition. In Chapter 3 of this thesis, we reasoned that to the extent that (a) false alarms reflect either guesses or high-confidence familiarity responses, and (b) neural recapitulation responses reflect recollection, then one would predict that false alarms should not be accompanied by neural recapitulation. By contrast, to the extent that false alarms can be accompanied by illusory recollection, it remains possible that recapitulation effects will be present in lateral neocortical processing modules during these memory errors (Slotnick & Schacter, 2004).

Control Processes in the Service of Episodic Retrieval

As discussed at the outset, in addition to recovery processes, the other class of operations engaged during episodic retrieval is generally characterized as control processes. At the neural level, initial evidence for the importance of cognitive control for episodic retrieval has come from patients with focal frontal lobe lesions (e.g., Milner, 1982; Moscovitch & Winocur, 1995; Schacter, 1987; Shimamura, 1995). While the deficits in episodic memory demonstrated by patient with frontal lobe lesions are not profound and global (as compared to those that follow medial temporal lobe lesions), nevertheless modest memory difficulties occur following frontal lesions on specific types of episodic retrieval tasks, including source memory, memory for temporal order, and meta-memory tasks (e.g., Janowsky, Shimamura, Kritchevsky, & Squire, 1989; Janowsky, Shimamura, & Squire, 1989; Milner, Corsi, & Leonard, 1991; Schacter, Harbluk, & McLachlan, 1984). Investigators have suggested that these deficits are likely related to deficient prefrontal-mediated cognitive control processes that influence processing in other cortical regions (e.g., top-down biasing mechanisms that facilitate the processing and maintenance of goal-relevant representations; Fuster, 1997; Goldman-Rakic, 1987; Miller & Cohen, 2001; Stuss & Benson, 1984). In relation to the cognitive theories of episodic retrieval introduced at the outset (Norman and Bobrow, 1979; Burgess and Shallice, 1996; Raiijmakeers and Shiffrin, 1981), the memory impairments that result from frontal lobe insult position prefrontal cortex (PFC) as a candidate for supporting the hypothesized pre-recovery operations of cue specification and analysis and the post-recovery operations of monitoring.

As reviewed below, initial neuroimaging evidence has begun to suggest candidate PFC mechanisms subserving these control functions during retrieval. Early studies of episodic retrieval used PET and fMRI to compare brain activity during extended epochs (blocks) of retrieval with brain activity during non-retrieval control conditions. These block-design studies consistently revealed activation in PFC, parietal cortex, and medial temporal structures during recognition of words, sentences, and pictures (e.g., Haxby et al., 1996; Rugg, Fletcher, Frith, Frackowiak, & Dolan, 1997; Tulving et al., 1994) and during cued-recall for words and pictures (e.g., Andreasen et al., 1995; Buckner et al., 1995; Buckner, Raichle, Miezin, & Petersen, 1996; Shallice et al., 1994). Other early block-design studies attempted to isolate more specifically correlates of successful episodic retrieval (as opposed to more generalized processes associated with attempts to retrieve), either by manipulating the percentage of old and new items in retrieval blocks (for review, see Lepage, Ghaffar, Nyberg, & Tulving, 2000) or eliciting differential levels of retrieval success by manipulating encoding conditions (e.g., levels-of-processing manipulations, Buckner, Koutstaal, Schacter, Wagner, & Rosen, 1998; Rugg, Fletcher, Frith, Frackowiak, & Dolan, 1997; Schacter, Alpert, Savage, Rauch, & Albert, 1996). Collectively, these studies identified structures in PFC, as well as in the parietal lobe, that were consistently correlated (a) with attempts to recognize that an item was previously encountered, (b) with attempts to recollect contextual details, and (c) to a limited extent, with successful recognition and/or successful recollection. As will become apparent below, open questions remain regarding the circumstances in which these PFC responses are engaged, as well as the neural mechanisms that initiate or abort their engagement.

Strikingly, while neuropsychological data have implicated PFC in supporting strategic or control aspects of the act of remembering, extant neuroimaging studies have also consistently observed memory-related responses in the parietal cortex, including activation in medial (retrosplenial, precuneus, and posterior cingulate) and lateral (intraparietal sulcus and inferior parietal lobule) regions (e.g., Buckner & Wheeler, 2001; Wagner, Shannon, Kahn, & Buckner, 2005). For example, a number of event-related fMRI studies have observed parietal responses that vary depending on whether recognition memory is accompanied by recollection or familiarity (e.g., Eldridge, Knowlton, Furmanski, Bookheimer, & Engel, 2000; Henson, Shallice, Gorno-Tempini, & Dolan, 2002; Konishi, Wheeler, Donaldson, & Buckner, 2000; Leube, Erb, Grodd, Bartels, & Kircher, 2003; McDermott, Jones, Petersen, Lageman, & Roediger, 2000; Wheeler & Buckner, 2003). Other studies have observed that parietal activation can be modulated depending on whether the retrieval attempt is oriented towards recovering recollective information or towards detecting novelty/familiarity (Dobbins, Foley, Schacter, & Wagner, 2002; Dobbins, Rice, Wagner, & Schacter, 2003; Dobbins & Wagner, in press), with these strategy-dependent modulations occurring independent of whether retrieval is successful or unsuccessful (Dobbins, Rice, Wagner, & Schacter, 2003).

At present, the nature of parietal contributions to retrieval remains unclear, and multiple speculative hypotheses have been proposed (Wagner, Shannon, Kahn, & Buckner, 2005). As reviewed below, one such hypothesis is that subregions within posterior parietal cortex contribute to the decision process supporting recognition judgments. Importantly, further evidence is required regarding the basic nature of parietal responses during retrieval, as such evidence will be a first step towards testing this and the alternative accounts of parietal involvement in episodic retrieval.

In the following section, I review evidence suggesting that: (1) control processes are necessary for episodic retrieval, (2) specific control processes, such as cue specification/analysis and retrieval monitoring, are subserved by different subregions of PFC, and (3) parietal cortex may play a role in recognition memory decisions.

Prefrontal Contributions to Episodic Retrieval

Neuropsychological evidence of memory dysfunction in patients with frontal lobe lesions (Schacter, 1987; Shimamura, 1995; Stuss & Benson, 1986; Wagner, 2002), together with neuroimaging observations, have motivated attempts to identify the nature and anatomical segregation of PFC processes that contribute to retrieval. Recently, Alexander et al (2003) studied a large group of patients with discrete frontal lobe lesions, thus allowing these researchers to cluster patients according to the PFC site of their lesions. The patients were divided into those with anterior and those with posterior frontal lobe lesions, and were further distinguished by whether their lesions were medial (typically bilateral frontal), left lateralized, or right lateralized. Memory was probed using a word-list learning task, with immediate recall, recognition, and delayed recall tests. Alexander et al. demonstrated that only the left posterior lateral and posterior medial groups had impairments in recall, with the left posterior group also showing higher false recognition rates (but see, Curran, Schacter, Norman, & Galluccio, 1997; Schacter, Curran, Galluccio, Milberg, & Bates, 1996). In addition, both anterior and posterior left lateral and right posterior groups showed modest perseveration (recalling a word a second time after it had already been presented as recalled), suggesting deficits in monitoring processes.

While such large-sample lesion studies provide a means of testing both the localization and necessity of frontal lobe function, the ability to access such large samples is relatively rare, and even when possible, the resolution of the lesions likely still encompasses multiple functional subregions. Accordingly, complementary evidence from neuroimaging studies provides a means of testing the functional role of PFC subregions in the controlled aspects of retrieval. As mentioned, across a large number of PET and fMRI studies of episodic retrieval, including studies using cued-recall, free-recall, and simple recognition, PFC activation has been consistently observed (e.g., Andreasen et al., 1995; Fletcher et al., 1995; Haxby et al., 1996; Henson, Rugg, Shallice, Josephs, & Dolan, 1999; Petrides, Alivisatos, & Evans, 1995; Tulving et al., 1994). Many of these neuroimaging studies have revealed retrieval-related activity in left frontal polar cortex (FPC), ventrolateral PFC (VLPFC) and posterior dorsolateral PFC (pDLPFC). Some experiments demonstrated that activation within these regions was sensitive to retrieval success, hypothesizing that these regions may support processes that signal or reflect recovery of information (Donaldson, Petersen, Ollinger, & Buckner, 2001; Habib & Lepage; Henson, Rugg, Shallice, Josephs, & Dolan, 1999; Konishi, Wheeler, Donaldson, & Buckner, 2000). By contrast, other experiments failed to show left PFC sensitivity to retrieval outcome, suggesting that left frontal regions reflect control processes that guide retrieval but do not determine or depend on the success of the recovery process(es) (Dobbins, Foley, Schacter, & Wagner, 2002; Dobbins, Rice, Wagner, & Schacter, 2003; Ranganath, Johnson, & D'Esposito, 2000).

Recently, use of source recollection paradigms has led to progress in understanding the specific cognitive operations subserved by specific PFC subregions in the service of episodic retrieval. For example, by varying the retrieval task instructions, Dobbins et al. (2002) manipulated the mnemonic information upon which participants could base a two-alternative forced-choice memory decision. In one condition, performance could be based on assessing differential item familiarity (*recency decision*; i.e., which item did you see most recently), whereas in the other, performance required recollection of contextual details (*source decision*; i.e., which item did you perform task X with). By comparing the two retrieval conditions (as well as a semantic encoding condition), it was possible to isolate PFC correlates of phonological access or maintenance operations (posterior VLPFC), semantic analysis/cue specification (anterior VLPFC), and post-recovery monitoring of recollection outcome (DLPFC and FPC). Based on a more recent study, it has been suggested that left PFC may differentially contribute to the use of contextual information when making a memory decision, whereas right PFC may be differentially important for recognition decisions based on familiarity (Dobbins, Simons, & Schacter, 2004).

Strikingly, these recent fMRI data would appear to converge with the observation that patients with left posterior frontal lesions, corresponding to VLPFC and pDLPFC, show deficits in recall and high FA rates. The data are also consistent with the observation that patients with left lateral anterior frontal lesions, corresponding to FPC, show monitoring deficits. Collectively, these findings suggest that regions in left PFC make important and apparently necessary contributions to episodic retrieval.

Prefrontal Correlates of Successful Episodic Retrieval

While the imaging literature just reviewed has documented PFC correlates of distinct aspects of episodic retrieval that are independent of recollection outcome, other data suggest that PFC activation may correlate with retrieval success. In particular, multiple fMRI studies have revealed left lateralized old–new effects (greater activation during hits vs. correct rejections), including in DLPFC, VLPFC, and FPC (Konishi, Wheeler, Donaldson, & Buckner, 2000; Maril, Simons, Mitchell, Schwartz, & Schacter, 2003; McDermott, Jones, Petersen, Lageman, & Roediger, 2000; Nolde, Johnson, & D'Esposito, 1998). These observations of PFC sensitivity to some form of retrieval success have led to the competing hypothesis that PFC may signal some aspect of or be modulated by successful retrieval (Donaldson, Petersen, Ollinger, & Buckner, 2001; Henson, Rugg, Shallice, Josephs, & Dolan, 1999; Konishi, Wheeler, Donaldson, & Buckner, 2000; Wheeler & Buckner, 2003).

Adjudicating between these competing hypotheses has been complicated because “success” accounts of PFC function have primarily emerged from studies of yes/no recognition (Henson, Rugg, Shallice, Josephs, & Dolan, 1999; Konishi, Wheeler, Donaldson, & Buckner, 2000; McDermott, Jones, Petersen, Lageman, & Roediger, 2000; Nolde, Johnson, & D'Esposito, 1998), whereas “attempt” accounts have primarily emerged using forced-choice recognition (Dobbins, Foley, Schacter, & Wagner, 2002; Dobbins, Rice, Wagner, & Schacter, 2003; cf., Ranganath, Johnson, & D'Esposito, 2000). One possible resolution of this apparent discrepancy suggests that perceived familiarity (the sense that an item was previously encountered) may act to gate activity in PFC, such that additional PFC processes will be engaged only for items perceived to be old, with these processes supporting pre- and post-recovery mechanisms associated with attempts to recollect contextual details. In Chapter 3 of this thesis, we used fMRI to characterize prefrontal cortical responses during a source recollection paradigm, examining whether regions showing old–new effects support processes sensitive to recollection success or recollection attempt. Further, we tested whether recollection-correlated processes might be sensitive to the perception that information is old, regardless of the true mnemonic status of the item.

Parietal Contributions to Episodic Retrieval

Event-related fMRI has revealed consistent activation in left parietal cortices during episodic retrieval tasks (for review see, Buckner & Wheeler, 2001; Wagner, Shannon, Kahn, & Buckner, 2005). These observations are particularly surprising, given that the function of parietal cortex has been traditionally associated with space-based attention and motor intention (Andersen & Buneo, 2002; Colby & Goldberg, 1999). Moreover, lesions of parietal cortex do not result in noticeable episodic memory deficits, with the exception of retrosplenial amnesia (Kobayashi & Amaral, 2003; Valenstein et al., 1987). Nevertheless, the consistent presence of parietal activation during episodic retrieval tasks—including greater activation during hits vs. correct rejections (i.e., old–new effects)—begs for an understanding of the relation between memory and parietal activation.

Across multiple event-related fMRI studies, parietal old–new effects generalize across verbal and visual-object targets, yes–no recognition, Remember–Know, recognition confidence, and source recollection paradigms (e.g., Eldridge, Knowlton, Furmanski, Bookheimer, & Engel, 2000; Henson, Shallice, Gorno-Tempini, & Dolan, 2002; Konishi, Wheeler, Donaldson, & Buckner, 2000; Leube, Erb, Grodd, Bartels, & Kircher, 2003; McDermott, Jones, Petersen, Lageman, & Roediger, 2000; Wheeler & Buckner, 2003). Recent reports suggest that parietal activation may be modulated by (a) the subjective perception that items are old (Wheeler & Buckner, 2003), (b) recollective- as compared to famililarity-based recognition (Cansino, Maquet, Dolan, & Rugg, 2002; Dobbins, Rice, Wagner, & Schacter, 2003; Eldridge, Knowlton, Furmanski, Bookheimer, & Engel, 2000; Henson, Rugg, Shallice, Josephs, & Dolan, 1999; Wheeler & Buckner, 2004), and (c) retrieval oriented towards the recollection of episodic details versus towards detecting familiarity (e.g., Dobbins, Foley, Schacter, & Wagner, 2002; Dobbins, Rice, Wagner, & Schacter, 2003; Herron, Henson, & Rugg, 2004; Herron & Rugg, 2003; Morcom & Rugg, 2004; Rugg & Wilding, 2000). Moreover, Wheeler and Buckner (2004) observed that some lateral and medial parietal regions show responses that are correlated with recollection, whereas the intraparietal sulcus shows an insensitivity to recollection, arguing that subregions within parietal cortex may serve different functions.

ERP studies targeting recognition memory have also observed old–new effects that emerge approximately 400 msec post-stimulus onset and extend for approximately 400-600 msec, with the largest amplitude over left parietal scalp electrodes. Multiple ERP studies have demonstrated that responses at left parietal electrodes are sensitive to tasks that require source memory decisions (Wilding, 2000; Wilding, Doyle, & Rugg, 1995; Wilding & Rugg, 1996), subjective reports of Remember–Know (Duzel, Yonelinas, Mangun, Heinze, & Tulving, 1997; Smith, 1993; Trott, Friedman, Ritter, Fabiani, & Snodgrass, 1999), and other manipulations that promote recollection (Paller &

Kutas, 1992; Rugg et al., 1998; Ullsperger, Mecklinger, & Muller, 2000). Moreover, tasks that require the recognition of items along with recollection of contextual information also tend to elicit a late posterior negative slow wave (Cycowicz, Friedman, Snodgrass, & Duff, 2001; Johansson, Stenberg, Lindgren, & Rosen, 2002; Wilding, 1999). Considering these ERP parietal patterns in relation to the findings from fMRI reveals an important gap between the two literatures, raising questions about relation between these various parietal indices. That is, the fMRI literature has documented multiple parietal memory-related patterns, some recollection-sensitive and others tracking perceived familiarity, whereas the ERP literature has revealed primarily old–new effects that track recollection.

Relevant Parietal Anatomy and Functional Hypotheses

Although lateral parietal lesions do not appear to yield episodic memory deficits, the potential importance of some parietal regions to memory is suggested from the consequences of medial parietal lesions as well as from the anatomy. With respect to necessity, lesions to parietal midline structures can produce memory impairments (‘retrosplenial amnesia’; Valenstein et al., 1987), though no published data support a critical role for lateral parietal structures in episodic memory. At the anatomical level, in the monkey, the MTL is directly or indirectly connected to lateral parietal, retrosplenial, and posterior cingulate cortices (Insausti, Amaral, & Cowan, 1987; Kobayashi & Amaral, 2003; Suzuki & Amaral, 1994). Indeed, based on the fact that the retrosplenial cortex predominantly receives afferent projections from the MTL, investigators have argued that this region acts as an interface zone between working memory functions supported by the

PFC (similar to what I have termed ‘cognitive control’ herein) and declarative memory functions subserved by the MTL (Kobayashi & Amaral, 2003; Valenstein et al., 1987). Moreover, although lateral parietal lesions have not been observed to result in memory impairments, it remains possible that these regions play an important, though subtle, role in supporting episodic retrieval performance.

As we have recently argued (Wagner, Shannon, Kahn, & Buckner, 2005), one possible role of parietal cortex in episodic retrieval may be to accumulate “evidence” in the service of making a decision about the mnemonic status of the retrieval cue (*mnemonic accumulator hypothesis*). Motivated by results from non-human primates suggesting that LIP neurons integrate sensory signals in preparation for action (e.g., Shadlen & Newsome, 2001; Sugrue, Corrado, & Newsome, 2004), we have speculated that the role of the intraparietal sulcus in humans may extend to performing a similar function on mnemonic signals. Such a role would be compatible with models of episodic retrieval (Ratcliff, 1978) that posit that evidence is accumulated in the service of a signal-detection memory decision. Further, to the extent that functional dissociations exist across parietal regions engaged during retrieval, it is possible that other parietal subregions support processes that direct attention to internal mnemonic representations, in line with theories that implicate parietal cortex in spatial attention (Colby & Goldberg, 1999).

Acquiring evidence that bears on these competing accounts of parietal lobe function would appear critical for advancing understanding of parietal contributions to retrieval. In Chapters 3 and 4 of this thesis, we used fMRI and MEG, respectively, to characterize the spatio-temporal pattern of parietal responses during a source recollection task. We specifically sought to examine whether parietal regions show old–new effects, whether these regions are further sensitive to recollection success or track perceived familiarity, and whether these regions are sensitive to the perception that an item is old regardless of its true mnemonic status. In the course of addressing these outstanding questions, the resultant data provide informative evidence for understanding how distinct parietal regions contribute to the act of arriving at a recognition memory decision.

Summary and Outline of Thesis

Extensive neuroimaging, neuropsychological, and electrophysiological data suggest that multiple brain regions (including MTL, parietal, and PFC) support distinct aspects of episodic retrieval. Many open questions remain regarding the nature of the neural mechanisms underlying specific aspects of episodic retrieval. In particular, what are the candidate neural processes that produce a sense of stimulus familiarity? What is the nature of the neural processes mediating retrieval of contextual details surrounding a prior stimulus encounter? Which neural processes are involved in regulating attempts to remember, irrespective of the outcome of these attempts?

To address these questions, this thesis adopts a theoretical framework that builds on cognitive models suggesting that episodic retrieval can be decomposed into two broad classes of subprocesses: (1) *recovery processes* that serve to reactivate stored memories, making information from a past episode readily available, and *(2) control processes* that serve to guide the retrieval attempt and monitor/evaluate information arising from the recovery processes. Beginning with this framework, we adopted a multi-modal imaging approach that combined data from fMRI and MEG to gain insight into the spatial and temporal properties of the neural mechanisms supporting episodic retrieval.

In Chapter 2 of this thesis, we combined fMRI and MEG to characterize one form of recovery process. Specifically, we identified medial temporal cortical structures that signal item memory strength, thus supporting the perception of item familiarity. In Chapter 3, we used fMRI to examine the neural signature of recollection. In particular, we asked whether retrieval of contextual details entails reactivation of neural patterns engaged at encoding, targeting sensory and non-sensory processing regions of the brain. Further, leveraging this pattern of reactivation, we also tested whether false recognition may be accompanied by recollection. The fMRI experiment reported in Chapter 3, when combined with an MEG experiment reported in Chapter 4, also directly addressed outstanding questions regarding the control processes engaged during episodic retrieval. In particular, Chapter 3 examined whether retrieval-related activity in parietal and prefrontal cortices is sensitive to recollection success, and thus correlated with recovery processes, or whether such activity is insensitive to recollection success, potentially implicating these regions in controlling the act of arriving at a retrieval decision. Chapter 4 then describes the MEG experiment that illuminates the temporal characteristics of parietal activation during episodic retrieval, providing novel evidence about the nature of parietal responses and thus constraints on possible theories of parietal involvement in episodic retrieval.

In conclusion, the research described here targeted distinct aspects of the multi-faceted act of remembering the past. Our results contribute to the building of an anatomical and temporal "blueprint" documenting the cascade of neural events that unfold during attempts to remember, as well as when such attempts are met with success or lead to memory errors. In the course of framing this research within the context of cognitive models of retrieval, the obtained neural data serve to reflect back on and constrain these cognitive theories of remembering.

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Chapter 2

Memory Strength and Repetition Suppression: Multimodal Imaging of Medial Temporal Cortical Contributions to Recognition[1]

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Introduction

Most individuals have had the experience of seeing a person and knowing that the person was previously encountered, but being unable to consciously remember the details of the prior encounter, such as putting a name to the familiar face. Such feelings of familiarity in the absence of detailed remembering suggest that there are two ways that we can recognize a previously encountered stimulus (Mandler, 1980). *Recollection* is recognition accompanied by retrieval of detailed information about the context or source of the recognized item, whereas *familiarity* is recognition of the item in the absence of retrieval of event details. Behavioral studies of human recognition memory indicate that these two processes make dissociable contributions to recognition decisions (Jacoby, 1991; Yonelinas, 1994), with some suggesting that perceived familiarity is best modeled as a continuous measure of memory trace strength (Yonelinas, 2002).

The neural mechanisms that support recognition are a matter of debate (Aggleton & Brown, 1999; Baxter & Murray, 2001; Rugg & Yonelinas, 2003; Ryan & Cohen, 2004; Squire, Stark, & Clark, 2004), with considerable controversy focusing on the role of medial temporal lobe structures—hippocampus and the surrounding parahippocampal and perirhinal cortices—in familiarity-based recognition. While there is general agreement that recollection is particularly dependent on the hippocampus, there is less agreement about the neural substrates of familiarity. Much of the debate arises from inconsistent patterns of recognition memory deficits in infrahuman primates, rats, and human patients with damage thought to be restricted to the hippocampus. Some studies report that selective lesions of hippocampus impair recognition decisions (Zola et al., 2000), with patient data revealing similar deficits in recognition based on recollection and on familiarity (Manns, Hopkins, Reed, Kitchener, & Squire, 2003; Stark, Bayley, & Squire, 2002; Stark & Squire, 2003). By contrast, other studies document spared recognition following hippocampal-specific lesions (Baxter & Murray, 2001), with such lesions resulting in a differential impairment of recollection and relative preservation of familiarity (Baddeley, Vargha-Khadem, & Mishkin, 2001; Fortin, Wright, & Eichenbaum, 2004; Holdstock et al., 2002; Yonelinas et al., 2002). These latter data raise the possibility that familiarity is relatively preserved following hippocampal damage because familiarity differentially depends on mechanisms in medial temporal cortical regions adjacent to hippocampus, including perirhinal cortex (Brown & Aggleton, 2001; Yonelinas, Kroll, Dobbins, Lazzara, & Knight, 1998).

Support for a role of medial temporal cortex in familiarity-based recognition comes from observations that in rats and monkeys lesions of perirhinal cortex result in consistent and often severe recognition memory deficits (Aggleton & Brown, 1999; Baxter & Murray, 2001). Further, single-cell recordings show experience-based changes in perirhinal firing patterns broadly consistent with familiarity, wherein firing rates decrease in response to previously encountered relative to novel stimuli (Xiang & Brown, 1998). Such firing rate decreases, termed “repetition suppression,” can emerge as early as 75 ms after stimulus onset, occur after a single encounter with an item, and be long-lasting (over 24 hrs), consistent with the hypothesis that they might support recognition discrimination between the familiar and unfamiliar (Brown & Aggleton, 2001). Arguments based on computational principles have also been advanced to support the hypothesis that familiarity depends on a medial temporal cortical system (Bogacz & Brown, 2003; Norman & O'Reilly, 2003). Functional magnetic resonance imaging (fMRI) studies in humans also suggest a role for medial temporal cortex in familiarity. At encoding, perirhinal cortex is more active while processing items that are subsequently recognized on the basis of familiarity compared to those subsequently forgotten, but perirhinal encoding activation does not predict later recollection (Davachi, Mitchell, & Wagner, 2003; Kirwan & Stark, 2004; Ranganath et al., 2004). At retrieval, several experiments comparing the processing of previously encountered ("old") and unstudied ("new") items showed an activation decrease in anterior medial temporal cortex (at or near perirhinal cortex) for old compared to new items (Henson, Cansino, Herron, Robb, & Rugg, 2003), and activation in anterior medial temporal cortex is also reduced for correctly recognized old items relative to old items incorrectly classified as new (Weis, Klaver, Reul, Elger, & Fernandez, 2004; Weis et al., 2004). Although these studies did not document a continuous change in the magnitude of activation reductions according to graded levels of perceived familiarity, the magnitude of the reduction for old items did not track recollection. One possibility is that this effect is a human analogue of the repetition suppression seen in single-unit recordings from animals, though compelling evidence of its relation to familiarity requires evidence that such fMRI activation suppression varies in a continuous manner according to *perceived* stimulus familiarity.

The present study used a multimodal imaging approach that combined fMRI and *anatomically constrained* magneto-encephalography (*a*MEG) to obtain information about the location and timing of neural correlates of perceived gradations in item recognition in humans. We specifically sought to assess the role of medial temporal cortex in signaling item memory strength at recognition, testing whether the responses in this region converge with *a priori* predictions regarding the properties that should be evidenced by a neural correlate of memory strength. Reasoning from prior behavioral and electrophysiological observations, retrieval-based activity in a region supporting item recognition should show three features. First, the magnitude of activity should decline for recognized relative to novel items. Second, these repetition reductions should be continuous, showing a graded pattern that tracks parametric levels of perceived memory strength. Third, a strength-dependent graded pattern should emerge relatively early, given the rapid onset of repetition suppression in single unit data, as well as human behavioral data showing that discriminations based on item memory can be made relatively rapidly (Hintzman & Curran, 1994).

Participants studied a series of faces, memory for which was then tested via recognition. During the critical recognition test, participants viewed old faces together with novel (unstudied) faces (see Methods). For each test face, participants made recognition decisions, indicating memory strength using a one-step "Remember"/"Know" procedure (Tulving, 1985). One group of participants performed recognition while undergoing fMRI scanning and a second, independent group performed while undergoing MEG scanning. A third group participated in a behavioral version of the experiment, wherein Remember (R), Know (K), and New responses were either preceded or followed by confidence ratings. This behavioral experiment validated that "remembered" faces, while entailing recollective information that is distinct from familiarity, also likely tend to correspond to highly familiar items, that "known" faces correspond to moderately familiar items, and that "new" responses correspond to the least familiar items (Donaldson, 1996; Wixted & Stretch, 2004). That is, perceived memory strength—as indexed by confidence (Yonelinas, 2002)—differs across R-hits, K-hits, Misses, and

Correct Rejections (CRs), thus permitting a test of whether strength-dependent gradations in fMRI signal reductions are present in medial temporal cortex, and whether similar gradations in *a*MEG signal are observed to onset early after test probe presentation.

Methods

Participants

A total of 51 participants participated, 16 in the fMRI experiment (6 males; mean age of 22.1 yrs), 11 in the MEG experiment (4 males; 21.5 yrs), and 24 in the behavioral experiment (10 males; 20.7 yrs). All participants gave informed consent and were remunerated for their participation in accord with human participants procedures approved by the institutional review boards at Stanford University, M.I.T., and Massachusetts General Hospital. fMRI data from an additional six participants were not analyzed (three due to false alarm rates > .50; three due to having fewer than 10 trials for a given condition); MEG data from three additional participants were not analyzed (two due to extensive eye blink artifacts; one due to having only two R-hit trials).

Stimuli

The stimuli were artificially generated faces created using the Faces 3.0 program (IQ Biometrix, Fremont, CA). The stimuli consisted of a set of 180 face “families,” with hairstyle and head shape held constant within a family. Each family had two “Parent” faces (A and B), and these Parent faces were morphed to create a third face, the “Morph”, that was perceptually highly similar to the Parent faces (see **Figure 1**). Parent A faces appeared during encoding, and Parent A and Morph faces appeared during the recognition test (Parent B faces were only used to create the Morphs).

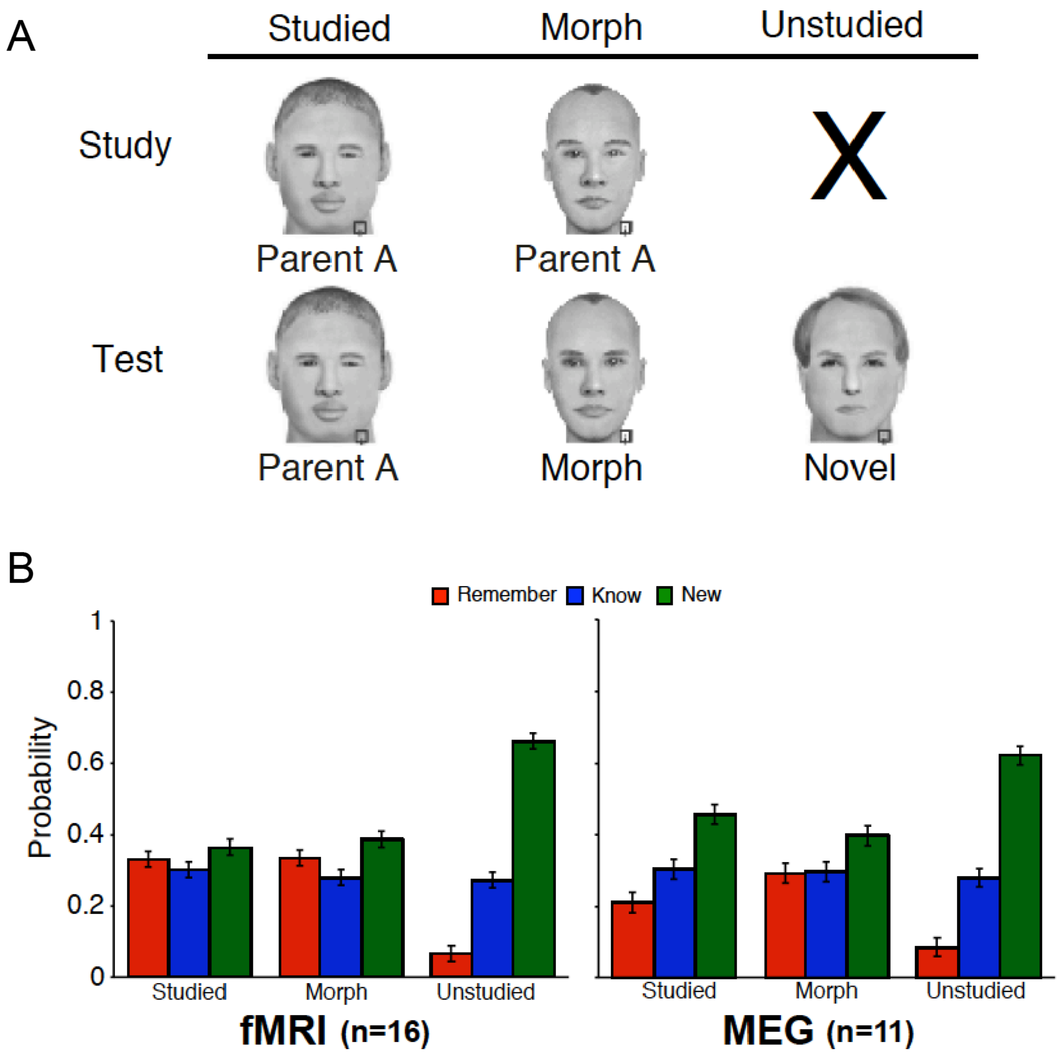

Figure 1. Stimuli and behavioral performance. *A.* Stimuli and experimental conditions. Participants studied Parent faces, and then were tested on Parent faces (Studied), perceptually highly similar morphed versions of studied faces (Morph), and faces not seen during the study phase (Unstudied). B. Behavioral performance. Graphs show proportions of “Remember”, “Know”, and “New” probabilities to Studied, Morph, and Unstudied faces in the fMRI and MEG experiments. Response patterns were similar for Studied and Morph faces in both experiments.

Generation and use of Morphs at test was designed to examine the sensitivity of item memory strength to study-test perceptual similarity. However, as detailed in the Results, participants were insensitive to this subtle perceptual manipulation, treating Morphs in a comparable manner to that of studied faces (see **Figure 1**). Accordingly, the behavioral and neuroimaging data analyses collapsed Parent faces and Morphs into a single "studied" condition.

fMRI Behavioral Procedure

Participants performed three study–test runs. For each, 40 Parent faces were initially encountered within the context of a target detection task, and after a short delay, recognition memory decisions were made for 20 test probes that were perceptually identical to studied faces (i.e., Parents), 20 probes that were perceptually nearly identical to studied faces (i.e., Morphs), and 20 unstudied face probes that were perceptually dissimilar to studied faces (i.e., Novel) (**Figure 1**).

Each study scan consisted of 45 face trials—40 critical nontarget faces and 5 presentations of a target face. On each trial, participants intentionally encoded the face while simultaneously performing a target detection task that ensured attention to the stimulus. Specifically, participants had to detect whether the present face was or was not that of a target, pressing one button for targets and another for nontargets. The target face had been shown to participants prior to scanning, and was the same throughout the experiment. Each study trial consisted of a face presented for 1500 ms, followed by 500 ms of fixation. Following the study scan, there was a 60-s break during which participants maintained fixation. Subsequently, the recognition test scan was initiated.

Each test scan consisted of 60 face trials—20 Parents, 20 Morphs, and 20 Novel—about which participants made one-step "remember"/"know"/"new" recognition decisions by pressing one of three keys under their left hand. When indexed in this one-step manner, it has been argued that "remember" and "know" responses may map to differing levels of item memory strength or confidence (Eldridge et al., 2002; Hicks and Marsh, 1999), though it remains probable that "remember" responses also partially depend on qualitatively distinct (recollective) information. The familiar stimuli (Parents and Morphs) were derived from the 40 studied faces—20 reappeared as Parents at test and 20 as Morphs. Assignment of faces to conditions was counterbalanced across participants. On each test trial, the face was presented for 2000 ms, followed by 2000 ms of fixation; participants had the entire 4000 ms to make a response.

The order of trial types within each scan was determined using an optimal sequencing program designed to maximize the efficiency of recovery of the BOLD response (Dale, 1999). This design optimization included interspersing a total of 60 s of null fixation events in each study scan, and 160 s of null fixation events in each test scan (in 2-s increments). Although scanning was performed at encoding and retrieval, the present manuscript focuses on the data collected at retrieval.

fMRI Data Acquisition and Analysis

Scanning was performed on a 1.5T Siemens Sonata system using a standard whole-head coil. Functional data were acquired using a gradient-echo echo-planar pulse sequence (TR=2 sec, TE=40 ms, 21 axial slices, 3.125 x 3.125 x 5 mm voxels, 1 mm inter-slice gap, 319 volumes per run). Prior to each scan, four volumes were discarded to allow for T1-equilibration effects. High-resolution T1-weighted (MP-RAGE) anatomical images were collected. Head motion was restricted using a pillow and foam inserts that surrounded the head. Visual stimuli were back projected onto a screen and viewed through a mirror mounted on the head coil.

Data were preprocessed using SPM99 (Wellcome Dept. of Cognitive Neurology, London). Images were corrected for differences in timing of slice acquisition, followed by rigid body motion correction (using sinc interpolation). Structural and functional volumes were spatially normalized and resampled to 3-mm cubic voxels, based on the MNI templates. Functional volumes were spatially smoothed with an 8-mm FWHM isotropic Gaussian kernel.

Statistical analyses were performed using the general linear model in SPM99. The fMRI data from the recognition scans were modeled by a series of events convolved with a canonical hemodynamic response function and its first-order temporal derivative. Trials in the test scans were coded based on participants' responses and item status. The resulting functions were used as covariates in a general linear model, along with nuisance regressors for the linear trend across individual runs, for session effects, and for participant motion. The least squares parameter estimates of height of the best fitting synthetic HRF for each condition were used in pairwise contrasts, and the resulting contrast images computed on a participant-by-participant basis were submitted to group analyses. At the group level, contrasts between conditions were computed by performing one-tailed t-tests on these images, treating participants as a random effect. Responses in *a priori* predicted medial temporal cortical regions were considered significant if they consisted of at least 5 contiguous voxels that exceeded an uncorrected threshold of $\underline{p} < .001$. Left medial temporal cortical regions observed in the baseline > recognition contrast (see **Results**) were reliable at a corrected threshold ($\underline{p} < .05$, small volume corrected). An additional contrast was performed to identify regions that showed a monotonic change according to perceived levels of memory strength (**Figure 3C**). For this more subtle contrast, medial temporal lobe responses were considered significant if they consisted of at least 5 contiguous voxels that exceeded an uncorrected threshold of $p < .0025$.

Region-of-interest (ROI) analyses were performed to characterize—in an unbiased manner—regions that were modulated by performance of recognition memory decisions. Unless otherwise noted, each ROI included all significant voxels ($p < .001$) within an 8-mm radius of each maximum defined from the contrast of all recognition trials compared to fixation. Signal within an ROI was calculated for each participant by selectively averaging the data with respect to peristimulus time for trials in each condition. Statistics were performed on the integrated peak amplitude response for each condition from 2-10 s post-stimulus onset. All ROI and behavioral analyses included the Hunyh-Feldt correction for non-sphericity where appropriate (denoted by p_{H-F}).

MEG Behavioral Procedure and Data Acquisition

The behavioral procedure was the same as in the fMRI experiment, except that the extra null fixation events were removed, as they were unnecessary for MEG data analysis. MEG data were acquired at a sampling rate of 600 Hz using a 306-channel NeuroMag Vectorview system. Prior to recording, participants were fitted with five electrodes, four for monitoring eye movements and one ground electrode. Four head-position coils (HPI) were also attached to the scalp for use in MEG-MRI alignment. The locations of the HPI coils relative to the participant’s scalp were measured using several landmark locations on the head with a Polhemus FastTrack 3-D digitizer (Polhemus Inc., Colchester, VT). Participants were then placed in a magnetically shielded room and were seated upright in a chair with their heads placed inside the instrument. Stimuli were back-projected onto a screen placed in front of the participant. High-resolution T1-weighted (MP-RAGE) anatomical MRI images were acquired for each participant in the MEG experiment for use in *anatomically constrained* MEG (*a*MEG) source localization.

MEG Data Analysis

The basic MEG analysis procedure used here is described in detail elsewhere (Dale, Fischl, & Sereno, 1999; Dale & Halgren, 2001; Dale et al., 2000; Liu, Belliveau, & Dale, 1998). In brief, raw MEG data were first downsampled to 200 Hz. Downsampled MEG waveforms were then averaged as a function of recognition memory status: R-hits, K-hits, Misses, and CRs. The averaging procedure included artifact rejection, wherein trials with blinks or eye movements were excluded from averaging. Cortical surfaces were created for each participant by segmenting the T1-weighted anatomical MRI volume into gray and white matter, and defining the border between gray and white matter as the cortical surface. The resulting anatomical surfaces were used to constrain the location of dipoles used in the MEG source analysis. To compute the inverse solution, the cortical surface was subsampled into approximately 3000 dipole locations per hemisphere. Each of these dipole locations was then used to calculate the forward solution for three components per dipole (in the x, y, and z directions). These forward solutions were computed using a boundary element model, with the conductivity boundaries derived from the segmented MR images for each participant. The activation at each of these dipole locations was then estimated every 5 ms using a noise-sensitivity normalized, *anatomically constrained* linear estimation approach to the inverse solution (Dale et al., 2000). To be explicit, fMRI data were not used to bias the inverse solution; only anatomical data informed the solution. The noise covariance was defined as the MEG activity in the 150 ms prior to the presentation of the stimuli, averaged across all conditions. The noise normalization procedure reduces the variability in the point-spread function between dipole locations (Liu, Dale, & Belliveau, 2002), thereby increasing the consistency of spatial resolution of the inverse solution across brain regions. For ROI analyses of the MEG data, minimum-norm estimates of the current contributions of all dipoles falling within an ROI were averaged for each participant. Waveforms for all participants were then entered into repeated measures ANOVAs to assess patterns in the data that were consistent across participants.

Supplemental linear regression analyses were conducted to further qualitatively characterize the distribution of sources that showed a monotonic change in signal across the four memory conditions—R-hits, K-hits, Misses, and CRs—during the 150-450 ms post-onset time window. Specifically, the mean minimum-norm current estimate during this time window was computed for each condition at each dipole surface location for each participant, and a linear regression was conducted on the four points. The r value at each location was then averaged across participants by using a spherical morphing procedure to transform each participant's cortical surface to a standard spherical template (Fischl, Sereno, Tootell, & Dale, 1999). The group averaged r values were then transformed to an inflated cortical surface for display purposes, with the r values at each dipole being displayed on the cortical surface using an arbitrary threshold and spatial smoothing to show those regions that showed the strongest linear trend according to item memory strength (i.e., the highest average r values; **Figure 4D**).

Companion Behavioral Experiment Procedures

An additional behavioral experiment that included confidence ratings as well as R/K responses was conducted to test an assumption important for interpreting the observed fMRI and MEG graded response patterns—that the memory strength associated with R-hits was stronger than that of K-hits, and that Misses were associated with a modestly higher strength than were CRs. The stimuli and general procedures were the same as in the fMRI and MEG experiments, with the exception that the recognition test now required two responses. Specifically, half of the participants (n=12) first made a recognition decision by indicating their memory confidence on a six-point scale: 1 = absolutely sure the face is new, 2 = somewhat sure it is new, 3 = guessing it is new, 4 = guessing it is old, 5 = somewhat sure it is old, and 6 = absolutely sure it is old. After making this confidence rating, these participants were given 3 s to respond "remember" or "know" for faces that they had classified as "old" (i.e., a 4, 5 or 6 rating). The other half of the participants (n=12) performed recognition with the order of memory responses reversed. These participants first made a remember/know/new response, and subsequently made a confidence rating using the same 6-point scale. Test order was varied across these two groups of behavioral participants to rule out the possibility that the order of the R/K and confidence responses impacted behavior. Critically, the results from these two groups were nearly identical, with there being no significant interactions between test order and mean confidence ratings by condition, nor between test order and mean R/K probabilities by condition (Fs < 1). Importantly, if our assumptions are correct about the relative strength associated with R-hits, K-hits, Misses, and CRs, then K-hits and Misses should be associated with confidence ratings closer to the middle of the scale, whereas R-hits and CRs should be associated with more extreme confidence values, which is the pattern that was obtained (**Figure 3B**).

Results

Recognition Performance

Recognition responses from the fMRI, MEG, and behavioral experiments were analyzed for studied and unstudied faces (see **Methods**). In these analyses, we first considered the observed (raw) K probabilities, and subsequently considered estimates of recollection and familiarity under the assumption that recollection and familiarity are independent (i.e., estimated familiarity = K responses/(1-R responses)). This familiarity computation corrects for the fact that faces given an R response may also be highly familiar, but participants do not have the opportunity to express this familiarity because of the mutual exclusivity of the R and K response options (Yonelinas, 2002).

Both raw recognition responses and process estimates of recollection and familiarity revealed similar performance across the fMRI and MEG groups (Group × Performance, $\underline{F}$s < 1). R response rates were higher for studied than for unstudied faces ($\underline{F}(1,20) = 55.05$, $\underline{p} < .0001$), whereas raw K rates did not differ ($\underline{F} < 1.0$). Estimates of recollection and familiarity were both higher for studied than for unstudied faces [$\underline{F}$s > 6.32, $\underline{p}$s < .025]. Collectively, these data demonstrate successful discrimination between studied and novel items (**Figure 2A**). Similar raw R and K probabilities and recollection and familiarity estimates were observed in the behavioral experiment (Group ×

Performance, Fs(2,48) < 1.13, ps > .33), suggesting that all three groups treated the R/K distinction in a comparable manner.

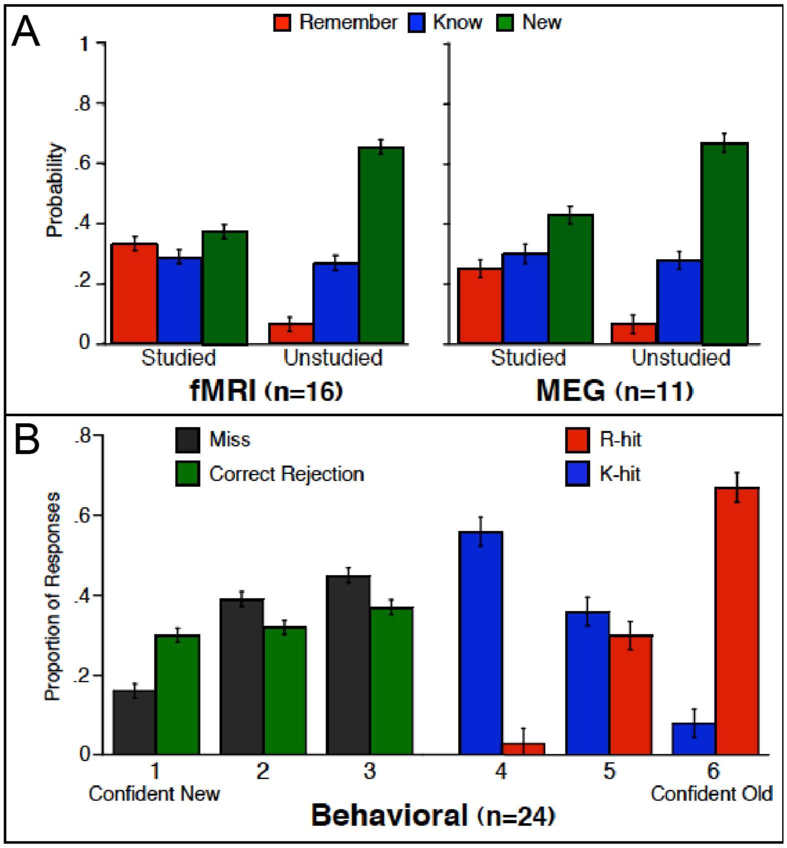

Figure 2. Behavioral performance. *A*. Probability of "Remember", "Know", and "New" responses to Studied and Unstudied faces in the fMRI and MEG experiments. *B*. Confidence ratings from the companion behavioral experiment. Graphs show the mean proportion of responses within each condition that were given a particular confidence rating.

In the behavioral study, R-hits were associated with higher confidence "old" responses than were K-hits [F(1,23) = 346.8, p < .0001], indicating greater memory strength for R-hits (**Figure 2B**). This pattern is consistent with arguments that highest confidence recognition may reflect the presence of recollection (Yonelinas, 2002), as well as with the perspective that R-hits can be accompanied by strong item familiarity (Donaldson, 1996; Dunn, 2004; Wixted and Stretch, 2004). Similarly, CRs were associated with modestly, but reliably higher confidence "new" responses than were

Misses [F(1,23) = 34.0, p < .0001]. Thus, although participants responded "new" to both Misses and CRs, subjective reports of recognition confidence revealed that Misses were perceived to be modestly more familiar than CRs. Collectively, these data indicate that perceived memory strength declined across R-hits, K-hits, Misses, and CRs.

Average median response times were computed for the fMRI group for the four conditions. The fastest responses were for R-hits (1290 ms), followed by CRs (1403 ms), Misses (1417 ms), and K-hits (1535 ms). That is, the conditions that were closer to the participants' response criterion (i.e., K-hits and Misses) showed the slowest response times. A similar pattern of response times was observed in the MEG experiment (R-hits = 1226 ms, CRs = 1272 ms, Misses = 1268 ms, K-hits = 1461 ms).

Recognition responses from the fMRI and MEG experiments were initially analyzed for studied faces, morph faces that were perceptually highly similar to studied faces, and unstudied faces. Across the fMRI and MEG experiments, the patterns of R and K response rates were highly similar for studied and morph faces (**Figure 2**), with R and K rates for both classes of old items (studied and morphs) being reliably greater than R and K rates to unstudied foils [Fs > 5.32; ps < .05]. Given this similarity in the behavioral responses and the fMRI responses (see below) to studied and morph faces, the behavioral and neuroimaging analyses reported in the manuscript collapse across this dimension.

fMRI Results

Voxel-based fMRI analyses, targeting MTL regions that were modulated by memory task performance, revealed a response along the left medial temporal cortex, wherein activation during recognition was reliably lower than that during the arbitrary fixation baseline. This response extended from the posterior portion of the collateral sulcus to its anterior extent (**Figure 3A**). To assess the consistency of MTL normalization across participants, which permits determination of the anatomical localization of this group-averaged MTL response projected to the individual participant level, the group-averaged left medial temporal cortical response was projected onto each participant's normalized anatomy. This procedure revealed that the posterior portion of this recognition-related response fell in the medial bank of posterior collateral sulcus (corresponding to left parahippocampal cortex) in 16 of the 16 participants. Anteriorly, this response included the medial bank of the collateral sulcus in 14 of the 16 participants, and appeared to correspond to perirhinal and entorhinal cortices in these individuals. For the remaining two participants, the anterior response was situated in subiculum/entorhinal cortex. Accordingly, data from these participants were not included when assessing strength-dependent responses in the left anterior medial temporal cortex (though as noted below, the obtained pattern did not change when including these participants in the analysis).

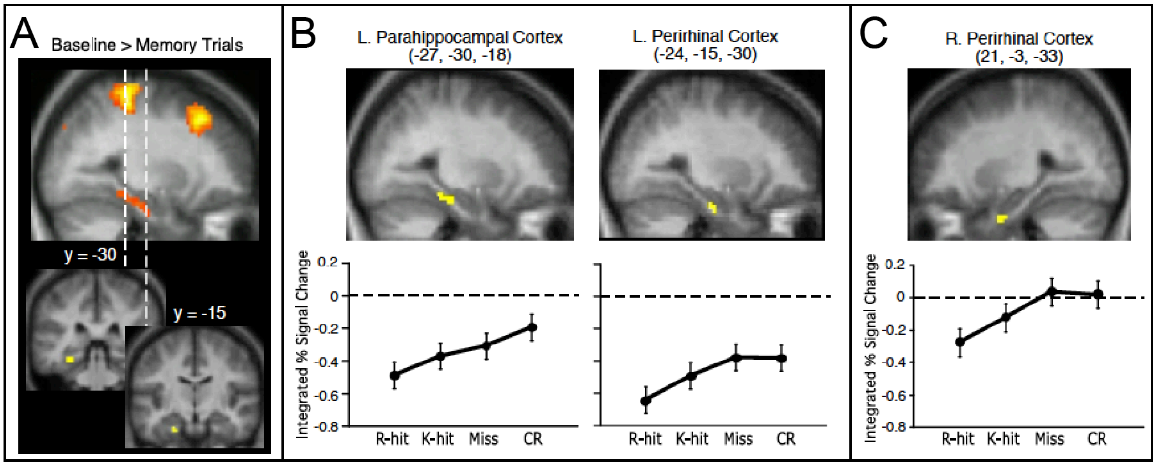

Figure 3. fMRI results. *A.* Activation along the collateral sulcus from the contrast of baseline > memory trials ($p < .001$; 5 voxel extent). The coronal slices depict medial temporal regions of interest rendered on the group average anatomical image, with the anterior region (y=-15) corresponding to left perirhinal cortex and the posterior (y=-30) to left parahippocampal cortex. *B.* Activation in left medial temporal ROIs in parahippocampal and perirhinal cortices (coordinates in MNI stereotaxic space); ROIs were defined from the unbiased baseline > memory contrast. The magnitude of activation significantly declined as perceived memory strength increased across the four conditions. *C.* A right perirhinal ROI identified from the voxel-based monotonic contrast of memory strength ($p < .0025$, uncorrected) showed a similar strength-dependent activation pattern.

To examine the effect of perceived memory strength on activation levels in medial temporal cortex, the hemodynamic response (% signal change) associated with each memory condition was extracted from regions-of-interest (ROIs) in left perirhinal and left parahippocampal cortices. These ROIs corresponded to peak medial temporal cortical maxima defined from the unbiased contrast of baseline vs. recognition. Importantly, the left perirhinal and parahippocampal ROIs showed graded repetition suppression effects that tracked perceived memory strength — as memory strength increased, activation in these regions decreased from Misses to K-hits to R-hits, with CRs yielding either comparable or greater activation than Misses (**Figure 3B**). Analyses of this perceived memory strength effect revealed a significant linear decline in left perirhinal cortex (MNI coordinates of -24, -15, -30: $F(1,13) = 4.57$, $p_{H-F} < .05$). This effect was also obtained when including data from all 16 participants ($F(1,15) = 5.66$, p_{H-F}

$< .05$), and when restricting the linear trend analysis to the R-hit, K-hit, and Miss conditions ($F(1,13) = 3.80$, $p_{H\text{-}F} < .07$; $F(1,15) = 5.31$, $p_{H\text{-}F} < .05$). Thus, in left perirhinal cortex, a graded decline was apparent across these levels of perceived memory strength. Similarly, a significant linear decline was observed in multiple foci within left parahippocampal cortex (-24, -21, -21: $F(1,15) = 4.57$, $p_{H\text{-}F} < .05$; -27, -30, -18: $F = 8.25$, $p_{H\text{-}F} = .01$; and -24, -39, -12: $F = 3.71$, $p_{H\text{-}F} = .06$). This linear decline also tended to be reliable in parahippocampal cortex (-27, -30, -18: $p_{H\text{-}F} = .09$) when the analysis was restricted to K-hits, Misses, and CRs, and activation during K-hits was reliably lower than CRs ($p_{H\text{-}F} = .05$, one-tailed). These outcomes suggest that the observed strength-dependent declines were not entirely driven by R-hits.

Further supporting this interpretation, in the subsample of the fMRI participants (n=10 for parahippocampal cortex; 9 for perirhinal cortex) with sufficient numbers of false alarms, consideration of the signal intensity to false alarms revealed reduced activation relative to misses and CRs (Weis et al., 2004b). Analyses revealed that K-based false alarms tended to be associated with decreased activation in parahippocampal cortex relative to CRs (-24, -21, -21: $p_{H\text{-}F} = .06$; -27, -30, -18: $p_{H\text{-}F} = .08$, one-tailed).

An additional voxel-based contrast targeting regions showing a monotonic decrease with increasing memory strength revealed a similar monotonic decline in an anterior region of right medial temporal cortex (21, -3, -33; **Figure 3C**). Further analysis of the responses in this ROI revealed (a) that the monotonic decline was also observed when restricting the analysis to R-hits, K-hits, and Misses ($p_{H\text{-}F} < .05$), (b) a trend for lower activation to K-hits relative to Misses ($p_{H\text{-}F} < .08$, one-tailed), and (c) reliably lower activation to K-based false alarms relative to Misses and CRs ($p_{H\text{-}F} < .05$, one-tailed).

These findings, together with the effects in left MTL, indicate that fMRI signal in bilateral perirhinal/entorhinal and left parahippocampal cortices showed a pattern of decreasing activation as perceived memory strength increased, with these effects not be solely driven by R-hits.

In contrast to the observed strength-dependent activation decreases, exploratory voxel-based analyses revealed that no medial temporal region showed greater activation during R-hits vs. K-hits or a graded *increase* in activation with increasing perceived memory strength (this was the case even at a lenient threshold, $p < .01$). Moreover, neither voxel-based nor ROI analyses revealed a strength-dependent response reduction in hippocampus. Thus, hippocampus did not demonstrate a recollection effect (see Eldridge et al., 2000), as R-hits did not differ from K-hits, nor a graded effect that tracked perceived item memory strength, suggesting interpretative caution when considering the implications of the present findings for understanding hippocampal contributions to recognition.

Beyond MTL, the voxel-based monotonic contrast identified an additional temporal lobe region—right fusiform cortex—that showed decreasing activation with increasing perceived memory strength (**Figure 5A**). As we describe next, this result in right fusiform and the findings in left medial temporal cortex have parallels in the MEG correlates of recognition.

Voxel-based contrasts between studied and morph faces revealed that fMRI responses to these two types of stimuli were very similar. In particular, there were no differences in the responses to studied and morph faces in medial temporal regions at standard thresholds. Further, response patterns across conditions (R, K, and Miss) did not significantly interact with stimulus type (studied, morph) in any of the medial temporal lobe ROIs that showed a linear effect of memory strength [Fs < 3, ps > .05].

MEG Results

MEG data were analyzed using each participant's cortical anatomy, obtained from MRI, to constrain the localization of electromagnetic sources recorded at the scalp (Dale, Fischl, & Sereno, 1999; Dale et al., 2000). To be explicit, fMRI did not contribute to the source solution. However, motivated by the fMRI results, initial analyses adopted an ROI approach to assess whether the *anatomically constrained* MEG (*a*MEG) activity source-localized to medial temporal cortex varied according to perceived memory strength. ROIs corresponding to right and left parahippocampal and perirhinal cortices were defined on each participant's MRI structural volume according to anatomical landmarks (**Figure 4A**) (Amaral & Insausti, 1990; Insausti et al., 1998). The contribution of the dipoles within each ROI to the recorded MEG signals were computed, and the extracted MEG current estimates, averaged across dipoles within each ROI, were submitted to ANOVA (see **Methods**).

Current estimates in the left perirhinal ROI differed as a function of perceived memory strength—R-hits, K-hits, Misses, and CRs—as revealed by a Time epoch × Condition interaction, using four 150-ms time epochs from 0-to-600 ms post-stimulus onset [$\underline{F}(9,90) = 2.04$; $\underline{p}_{H-F} < .05$; **Figure 4B**]. Unpacking this interaction, analyses of mean amplitudes from 150-450 ms revealed a significant linear effect of perceived memory strength [$\underline{F}(1,10) = 4.27$, $\underline{p}_{H-F} < .05$] wherein MEG signal declined across the four conditions, from CRs to R-hits (**Figure 4C**). A similar linear effect during the 150-

450 ms time window was observed in the left parahippocampal ROI [$F(1,10) = 5.81$; $p_{H\text{-}F} < .05$; **Figure 4B-C**], whereas no such linear effects were observed during this time window in the right medial temporal ROIs [Fs < 1.6, ps $> .2$].

Consideration of the waveforms from the left medial temporal ROIs suggested further distinctions within the 150-450 ms window. Thus, we assessed the early (150-300 ms) and late (300-450 ms) epochs of this window. For each, we tested for (a) differences between the memory extremes (R-hits vs. CRs) and (b) linear effects across the four memory conditions. Results revealed that, in the early epoch, the left perirhinal ROI showed a reliable signal decline between CRs and R-hits ($p < .05$) and a significant linear effect across the four conditions [$F(1,10) = 4.57$; $p_{H\text{-}F} < .05$]. In the late epoch, this region did not show a reliably different response to CRs relative to R-hits ($p > .10$) and the linear effect did not reach significance [$F(1,10) = 2.90$; $p_{H\text{-}F} = .10$; **Figure 4C**]. Turning to the left parahippocampal ROI, in the early epoch the response was greater for CRs relative to R-hits ($p < .05$) and there was a marginal linear effect across conditions [$F(1,10) = 3.58$; $p_{H\text{-}F} = .07$]. In the later epoch, CRs differed from R-hits ($p < .05$) and there was a significant linear effect [$F(1,10) = 6.44$; $p_{H\text{-}F} < .05$; **Figure 4C**]. While these patterns suggest distinctions across the two epochs, the memory condition × epoch interaction did not reach significance in either ROI (Fs$(3,30)<1.17$, ps $> .16$). Thus, strength-dependent signal differences were present in the left perirhinal and parahippocampal ROIs as early as the 150-300 ms window.

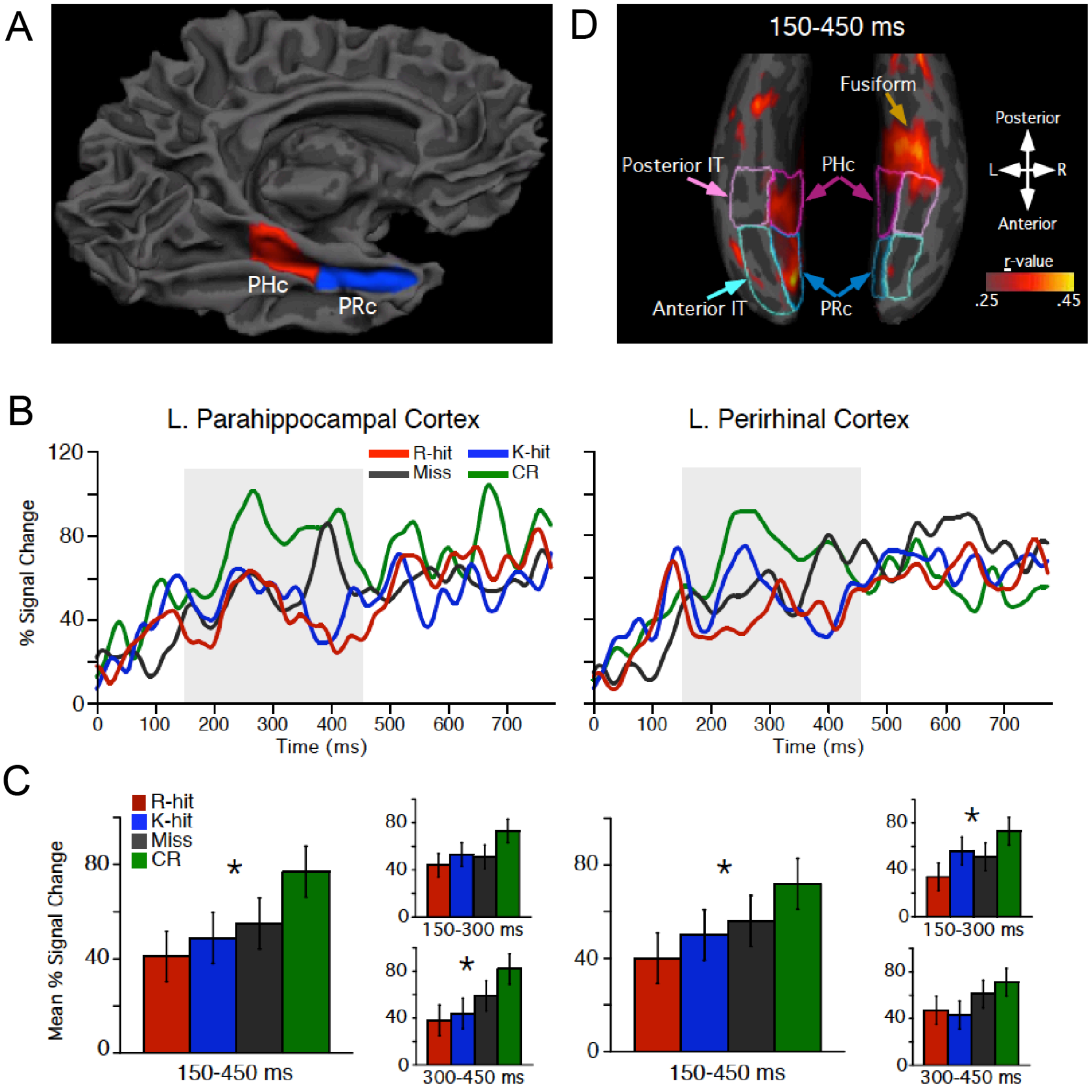

Figure 4. MEG Results. *A.* Medial view of the folded reconstructed left hemisphere of an individual participant, showing anatomically-defined perirhinal (PRc) and parahippocampal (PHc) cortical ROIs along the collateral sulcus. *B.* *Anatomically constrained* MEG (*a*MEG) current estimates derived from the left parahippocampal and perirhinal ROIs. Data are shown as percent change from the average of the pre-stimulus baseline as a function of time, in 5 ms increments (smoothed with a Gaussian kernal–25 ms FWHM–for presentation purposes). Shaded area corresponds to the 150-450 ms time window. *C.* Mean *a*MEG current estimates from PHc and PRc in the 150-450 ms time window revealed a graded pattern across conditions, similar to that observed in the fMRI data. At right, mean amplitudes from 150-300 ms and 300-450 ms epochs are shown. (*denotes significant linear effect, $p < .05$). *D.* Linear regression map showing average strength-dependent effect across participants. Images show the ventral surface of the inflated temporal lobes, with outlines of the anatomically defined ROIs used for the MEG analyses. The map represents the average r values from linear regression analyses performed on each dipole location for each participant, spatially smoothed and projected onto the ventral surface of the temporal lobes. Consistent with the ROI analyses, this arbitrarily thresholded map revealed that left medial temporal and right fusiform sources showed the strongest decline with increasing perceived memory strength.

Finally, to further characterize the spatial specificity of these MEG patterns and to validate our ROI approach, we performed a dipole-based linear regression on each participant's average current estimates as a function of condition from 150-450 ms, and mapped the group average of the r statistic from this regression to identify regions that showed the strongest linear trend across conditions. The resulting group maps showed relatively focal sources of the linear trend in left medial temporal cortex, including sources that fell within our anatomically-defined perirhinal and parahippocampal ROIs, as well as an effect in right fusiform (**Figure 4D**). We emphasize that the spatial resolution of these MEG source analyses do not permit definitive conclusions about the sources of the observed MEG activity, as they partially depend on precise co-registration of MRI and MEG sensor locations, and we make no claims that perirhinal and parahippocampal regions can be functionally distinguished with MEG. Nevertheless, the outcomes of this regression analysis are consistent with the conclusion that left medial temporal cortices show a similar pattern of activity in the MEG current estimates as was observed in the fMRI data—namely a monotonic response decrease that tracked perceived memory strength.

In addition to generating the dipole-based regression maps, to further test the spatial specificity of the observed monotonic effects, we anatomically defined additional ROIs adjacent and lateral to the four medial temporal cortical regions, and tested for a linear trend in the mean amplitudes from 150-450 ms from these bilateral anterior and posterior inferior temporal regions (**Figure 4D**). Whereas there were no significant effects in the right hemisphere ROIs [Fs < 2, ps > .1], the left anterior inferior temporal ROI showed a marginal linear effect [F(1,10) = 4.00; pH-F = .055] as did the left posterior inferior temporal ROI [F(1,10) = 3.97, pH-F = .056]. The regression analysis (**Figure 4D**) suggests that these trends may reflect extension of the medial temporal responses into these lateral regions, though caution is warranted when drawing conclusions about the anatomical sources of the observed monotonic signal decline, given the known limitations of the spatial resolution of MEG source localization.

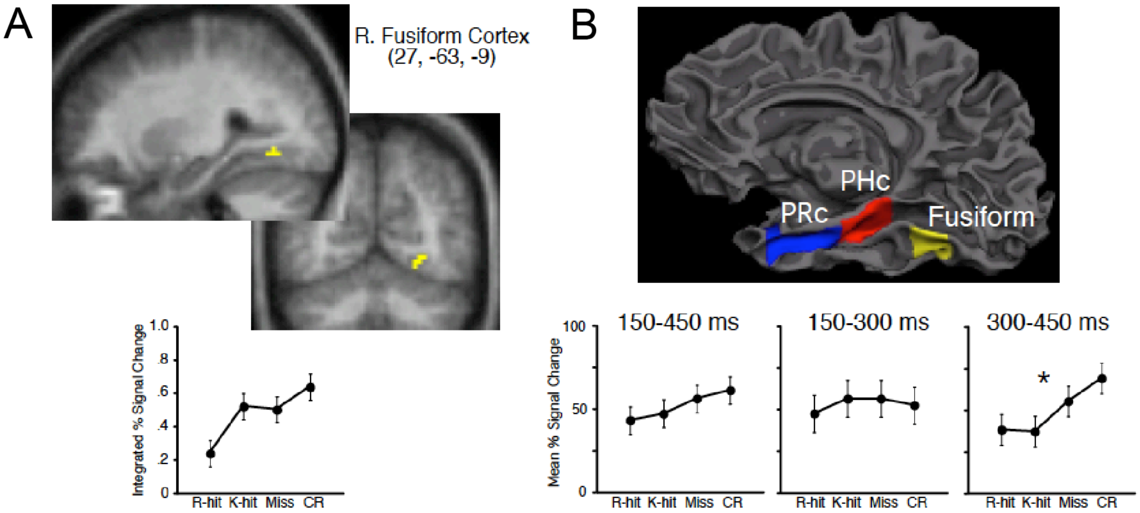

Figure 5. Responses in right fusiform cortex. *A.* The right fusiform ROI, defined from the voxel-wise monotonic contrast in the fMRI data, revealed an activation pattern that tracked perceived memory strength (*p < .0025). *B.* Right fusiform ROI and mean amplitudes of *a*MEG current estimates. There was a significant effect of perceived memory strength during the 300-450 ms epoch (*p < .01).

To additionally validate the source-constrained estimates of MEG data to medial temporal cortex, we generated (a) sensor-based maps depicting the topography of old/new recognition differences during the two critical early time windows (150-300 and 300-450 ms), and (b) forward solution predictions of the sensor sites estimated to be sensitive to signal arising in the left perirhinal and parahippocampal ROIs depicted in **Figure 4**. As can be seen in **Figure 6**, the topography of early old/new effects suggests that item recognition is associated with rapidly emerging responses at temporal and parietal sensor sites. Lending support to the source-constrained MEG estimates, the forward solution predicts that similar temporal and parietal sensor sites are sensitive to effects in perirhinal and parahippocampal cortices (**Figure 7**). Though, again, we note that definitive conclusions about source localization based on *a*MEG are not possible, these additional supplemental analyses are consistent with the interpretation that medial temporal cortex revealed graded signals according to perceived item memory strength.

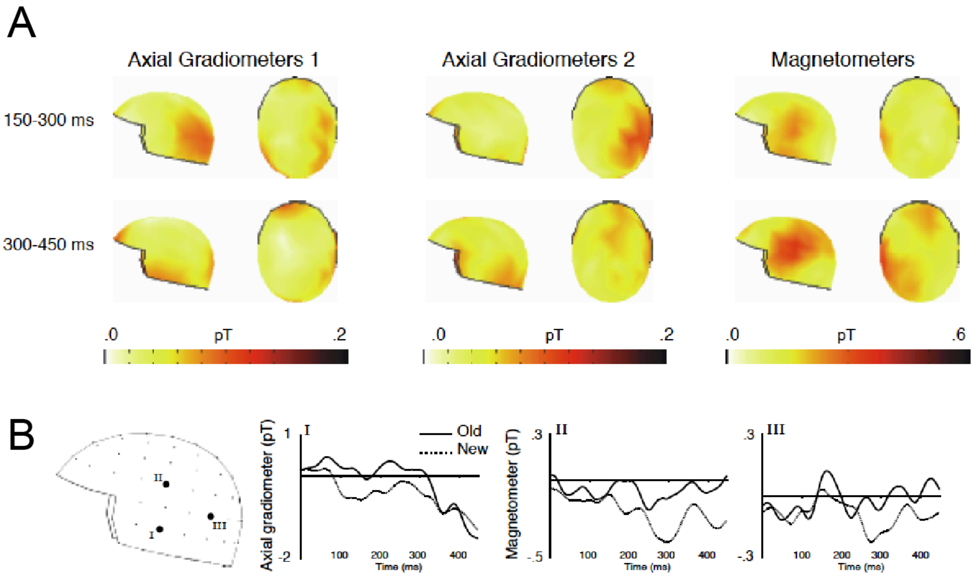

Figure 6. Topographical maps and event-related fields (ERFs) of early MEG "old"/"new" effects. *A.* Topographical maps depicting differences between "old" recognition responses (collapsed across R-hits and K-hits) and "new" responses (collapsed across Misses and CRs) during the 150-300 and 300-450 ms window, displayed for the three sensor types. Early effects (in pico-Tesla; pT) were observed at temporal/parietal sensors, with magnetometers appearing to be particularly sensitive consistent with the putatively deep sources of these item recognition effects. *B.* Sensor-based ERFs revealed early "old"/"new" differences.

Finally, we note that there were insufficient numbers of false alarms for meaningful analysis in the MEG data (due to low false alarm rates, as was also seen in the fMRI study, combined with exclusion of trials accompanied by eye blinks).

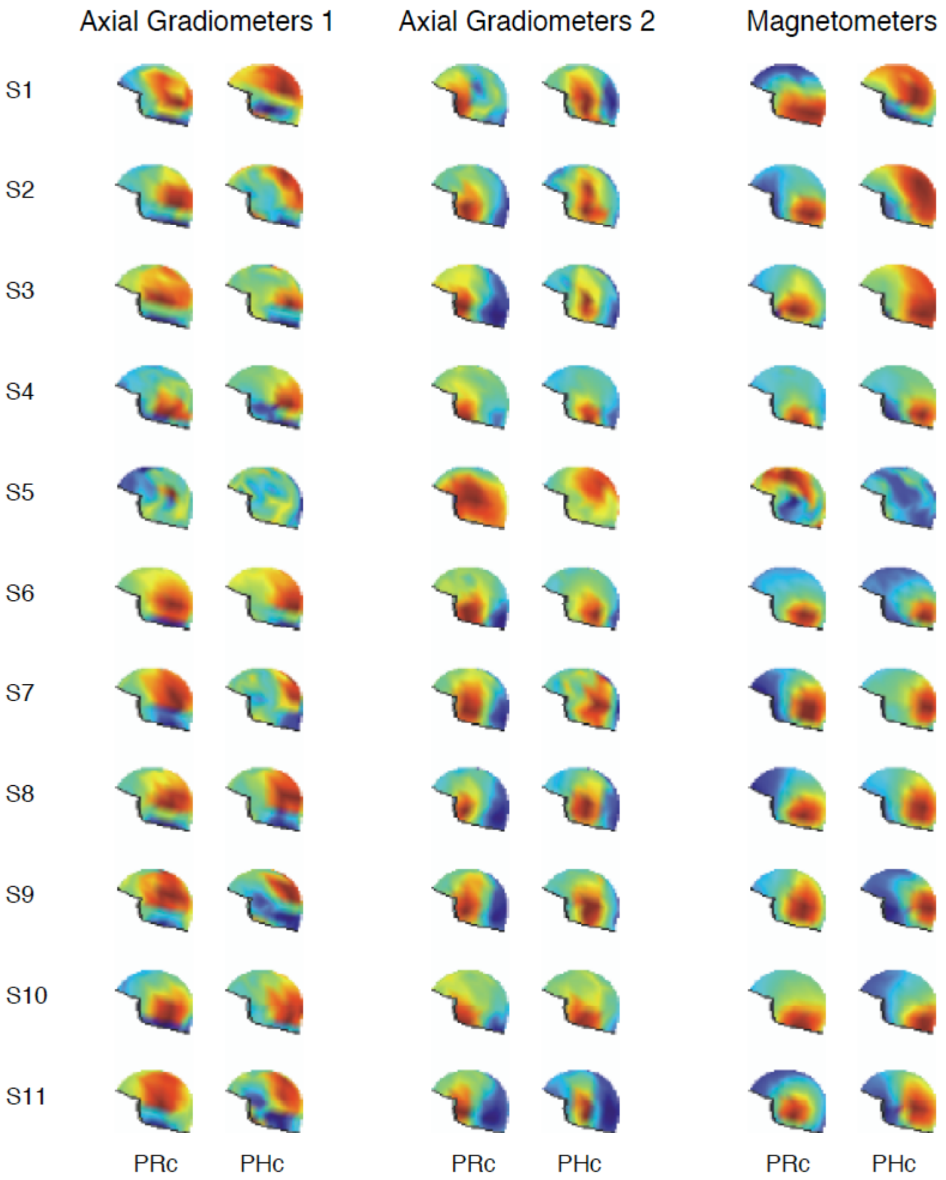

Figure 7. Forward-solution estimates of MTL sensitive sensors. For each participant (S1-S11), forward solutions of the sensor sites estimated to be sensitive to responses in left perirhinal cortex (PRc) and parahippocampal cortex (PHc) are depicted for each sensor type (gradiometers and magnetometers). Consistent with the temporal/parietal localization of early old/new effects (**Figure 6**), sensors estimated to be sensitive to left PRc and PHc appear to fall over temporal and parietal regions, with sensors sensitive to PRc falling slightly anterior to those sensitive to PHc.

Discussion

The present fMRI and MEG data reveal patterns of activity in human medial temporal cortex that are consistent with a continuously varying mnemonic signal that is perceived as varying degrees of item memory strength. In non-human animals, medial temporal cortex is thought to signal item recognition by reducing neural firing rates in response to previously encountered stimuli (Brown & Aggleton, 2001). Our fMRI data reveal experience-dependent response reductions in medial temporal cortices when humans recognize faces that were previously encountered relative to faces that are novel (Henson, Cansino, Herron, Robb, & Rugg, 2003; Weis, Klaver, Reul, Elger, & Fernandez, 2004; Weis et al., 2004). Moreover, the present fMRI findings provide new evidence that the magnitude of this repetition reduction in human medial temporal cortex can vary in a continuous manner and that these gradations correlate with different mnemonic perceptions — that is, greater reductions are associated with the perception of stronger item recognition. Anatomically constrained MEG measures further indicate that these strength-dependent response reductions can be seen as early as 150-300 ms post-stimulus onset, consistent with behavioral data indicating that humans have rapid access to mnemonic information about item strength (Hintzman & Curran, 1994) and with single unit data in animals revealing an early onset of repetition suppression (Brown & Aggleton, 2001).

To this point, we have characterized the observed strength-dependent functional gradients as markers of item memory strength. Yet this characterization leaves open the question as to what type of memory process(es) or representation(s) might underlie these subjective perceptions of strength. Dual-process theories of recognition decisions posit that recognition can be based on two distinct processes or types of representations — recollection and familiarity (Jacoby, 1991; Mandler, 1980; Yonelinas, 2002). Within this framework, recent evidence suggests that, in contrast to common assumptions, R/K decisions are not necessarily process pure. Rather R decisions can be based on high levels of recollection and also can be associated with high levels of familiarity, such that R/K responses bear a systematic relation with gradations in recognition confidence (Wixted & Stretch, 2004). This may be especially the case when using a one-step R/K procedure, as implemented here (Eldridge et al., 2002; Hicks and Marsh, 1999). Other theorists have argued that R/K distinctions entirely reflect graded differences along a unitary strength dimension (Donaldson, 1996; Dunn, 2004). Consistent with the interpretation that R decisions may reflect high-levels of familiarity (*most likely* together with recollection), the present one-step behavioral expressions of remembering and knowing mapped to different points in the recognition confidence continuum, with R responses being predominantly associated with the upper two recognition confidence levels and K responses being predominantly associated with less confident old responses (**Figure 2B**).

Given these outcomes and current dual-process theories of recognition, how might the present graded repetition suppression effects relate to recollection and familiarity? One possibility is that graded repetition suppression forms the basis for the subjective perception of stimulus familiarity; gradations in repetition suppression may arise from differences in pattern matching (Norman & O'Reilly, 2003). Another possibility is that graded repetition suppression reflects a difference in the amount of recollected information; such gradations may arise from differences in pattern completion processes (Norman & O'Reilly, 2003). Alternatively, graded repetition suppression may reflect an integrated response that blends information supporting both familiarity and recollection (Wixted & Stretch, 2004).

Three characteristics of the present data—when considered in relation to findings from animal studies of item recognition, fMRI studies of recollection, and behavioral studies of recognition—suggest that the observed strength-dependent gradient reflects processes supporting the perception of item familiarity. First, as noted, perirhinal repetition suppression effects in single unit studies suggest that perirhinal neurons signal item familiarity (Brown & Aggleton, 2001), though additional single unit data are required to definitively relate perirhinal repetition suppression to the perception of item familiarity in non-human animals (as opposed to recollection, priming, or some combination). The present localization of graded memory strength effects to human medial temporal cortex converges with this localization in non-human animals, and provides a critical link to mnemonic perception.

Second, extant fMRI data suggestion that repetition reductions do not appear to track recollection. For example, quantitative differences in recollection are present when comparing recognized items accompanied by correct source recollection to recognized items associated with source recollection failure. As noted by Henson et al (Henson, Cansino, Herron, Robb, & Rugg, 2003), the magnitude of fMRI signal suppression to hits compared to CRs in anterior medial temporal cortex does not differ when sorting hits into those accompanied by correct source recollection and those accompanied by source recollection failure. As such, these prior data suggest that anterior medial temporal repetition suppression does not track recollection outcome per se. The present data constitute an important new observation within this vein, wherein the magnitude of activation decreases in anterior and posterior medial temporal cortices track gradations in perceived memory strength, providing even stronger evidence of a relation between these activation reductions and mnemonic perception.

It should be noted that other fMRI observations suggest that more complex patterns of medial temporal cortical activation also can be observed during retrieval. Using a two-step Remember/Know paradigm, Eldridge et al. (2005) observed increased perirhinal activation during R-hits relative to K-hits, though R-hits did not reliably differ from CRs or Misses, raising difficulties in interpreting this pattern in relation to recollection or familiarity. In an earlier two-step Remember/Know study, Eldridge et al. (2000) observed increased parahippocampal cortical activation during R-hits relative to K-hits, whereas in their more recent study (Eldridge et al., 2005) comparable decreases in activation were observed when comparing R-hits and K-hits to Misses. Using an associative recognition test, Kirwan and Stark (2004) observed greater entorhinal and parahippocampal cortical activation during correct relative to incorrect associative recognition. Trials on which the studied items were forgotten also yielded greater activation compared to incorrect associative recognition trials (where the items were recognized but the item-item association was forgotten). It is unclear whether this pattern reflects a blend of retrieval and encoding operations during associative recognition performance. Using a source recollection paradigm, Cansino et al. (2002) observed increased parahippocampal activation during correct relative to incorrect source trials; this effect appears to have fallen posterior to the parahippocampal foci observed in the present experiment. In addition to differences in localization, in contrast to these other retrieval studies, it is possible that the present one-step Remember/Know method served to induce participants to predominantly rely on graded differences in item familiarity as the bases for their memory decisions. Indeed, a fundamental qualitative distinction exists between the present data (graded activation decreases) and these prior reports of complex activation patterns that are marked by a consistent activation increase during conditions associated with recollection. As such, the present monotonic *decrease* in medial temporal cortex would appear to qualitatively differ from such recollection-sensitive activation increases.

A third characteristic of the present data further motivates a familiarity interpretation. Specifically, although we emphasize that definitive claims cannot be made about the source localization of the obtained strength-dependent gradient in MEG signal, the early onset of this response is in accord with a rapidly accessible index of item familiarity. As noted, behavioral data indicate that information about item familiarity is available earlier than recollective information, and thus permits above chance recognition even under speeded-response deadline conditions (Hintzman et al., 1998; Hintzman and Curran, 1994; McElree et al., 1999). Accordingly, the present fMRI and MEG response reductions provide a possible human analogue to the rapidly emerging repetition suppression effects seen in animal studies, being expressed as item familiarity in human recognition behavior. That is, the magnitude of repetition suppression in human medial temporal cortex appears to not only support discrimination between novel and familiar stimuli, but also relates to gradations in the subjective perception of item familiarity — thus driving differences in mnemonic perception that translate into differences in memory confidence.

Beyond the medial temporal lobe, our fMRI and MEG data also reveal experience-dependent response reductions in lateral temporal regions thought to represent stimulus form. In particular, the fMRI data demonstrate a strength-dependent effect in right fusiform cortex (**Figure 5**), putatively near the fusiform face area (Kanwisher, McDermott, & Chun, 1997). Strikingly, consideration of the MEG linear regression map indicates that a strength-dependent response was present in a similarly localized right fusiform region (**Figure 4D**). From a memory theory perspective, observation of memory strength effects in lateral temporal structures raises the possibility that experience-dependent tuning of representational cortices may contribute to recognition decisions, or alternatively that mnemonic responses in medial temporal cortex may feed back to earlier representational regions. At present it remains unclear whether experience-dependent lateral cortical changes, and their interactions with such changes in medial temporal cortex, are necessary for the perception of familiarity. The present observation of memory strength effects in fusiform cortex motivates future research aimed at resolving this question.

In summary, medial temporal structures, in the service of declarative memory, support recognition of stimuli that were previously encountered, allowing organisms to discriminate between novel and familiar items. The marked convergence between the present fMRI and MEG correlates of perceived memory strength suggest that graded reductions in medial temporal cortical responses support graded perceptions of item familiarity, providing a basis for such discriminations. As such, medial temporal mechanisms rapidly signal knowledge about an item's relation to one's past.

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Chapter 3

Functional-Neuroanatomic Correlates of Recollection: Implications for Models of Recognition Memory[1]

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Introduction

Recognition memory can be based on *familiarity* — the sense that an item was previously encountered — and/or *recollection* — the conscious recovery of contextual information surrounding a previous encounter with an item (Yonelinas, 2002). Recognition with recollection depends on multiple mechanisms, including prefrontal cortical (PFC) “control” processes that guide retrieval attempts, and recapitulation mechanisms that reactivate neocortical representations present at encoding (Buckner & Wheeler, 2001; Rugg & Wilding, 2000; Wagner, 2002).

In humans, leverage on the neural mechanisms supporting recognition comes partially from neuroimaging comparisons between correctly recognized *old* items (Hits) and correctly rejected *new* items (CRs). Event-related fMRI has revealed “old–new” effects in left PFC and parietal cortices (Konishi *et al*., 2000; Maril *et al*., 2003; McDermott *et al*., 2000; Nolde *et al*., 1998), suggesting that these regions are sensitive to or signal successful retrieval (Donaldson *et al*., 2001; Henson *et al*., 1999; Konishi et al., 2000; Wheeler & Buckner, 2003), and event-related potentials have revealed a parietal-situated old–new effect that tracks recollection (Duzel *et al*., 1997; Smith, 1993; Wilding *et al*., 1995). Other evidence, however, suggests that PFC and parietal old–new effects reflect differential engagement of control processes brought to bear in attempts to recollect, irrespective of recollection success (Dobbins *et al*., 2002; Ranganath *et al*., 2000). Resolving this apparent conflict between “retrieval success” and “recollection attempt” hypotheses will be a key step towards understanding PFC and parietal contributions to recognition.

Recollection is hypothesized to entail the reactivation of representations that were present at encoding (Naya *et al*., 2001). Consistent with this hypothesis, neuroimaging studies have demonstrated that domain-specific (e.g., visual vs. auditory) perceptual cortices that were engaged during encoding are re-engaged during the retrieval of domain-specific event details (Nyberg *et al*., 2000; Vaidya *et al*., 2002; Wheeler *et al*., 2000). However, these prior studies used multiple study events per item, raising the possibility that such effects do not reflect episodic recapitulation. Rather, such effects may reflect a top-down attentional modulation of domain-specific representational layers during attempts to recollect caused by having acquired semantic knowledge about the encoding context of an item. A key question is whether recapitulation effects emerge during recollection of single episodes.

Neural recapitulation can also provide a critical test of models of recognition. A central assumption of leading dual-process models is that false recognition (i.e., False alarms; FAs) reflects above-criterion familiarity in the absence of recollection (Jacoby, 1991; Yonelinas *et al*., 1996): Hits are based on recollection and/or above-criterion familiarity, whereas FAs are thought to be recollection free. To the extent that this assumption is valid and that neural recapitulation responses reflect recollection, FAs should not be accompanied by such responses. Alternatively, given behavioral evidence of false recollection (Roediger & McDermott, 1995), it remains possible that FAs are accompanied by illusory recapitulation responses.

The present fMRI experiment examined whether regions showing old–new effects support processes sensitive to recollection success or attempt, whether neural correlates of recapitulation emerge during veridical recollection of single episodes, and whether such responses are selective to veridical recognition or generalize to false recognition.

Methods

Participants

Eight female and nine male right-handed, native-English speakers (aged 18-33 yrs) were paid $65 for their participation. Data were acquired but discarded from three additional participants, two because they failed to respond to 15% or more of the trials and one because of performance levels that resulted in multiple conditions with fewer than 15 events (thus resulting in unstable measurements). Informed consent was obtained in a manner approved by the institutional review boards at MIT and Massachusetts General Hospital.

Behavioral Procedures.

Participants performed two intermixed incidental encoding tasks identical to those previously explored by Davachi et al. (2003), and were subsequently scanned while making item recognition decisions combined with a source recollection judgment.

Across eight (non-scanned) study lists, 200 visually presented adjectives were encoded via an orienting task requiring mental imagery (‘Image’ task) and 200 via an orienting task requiring orthographic-to-phonological transformation (‘Read’ task) (**Figure 1A**). On each trial, a 500-ms cue (*place*/*read*) signaled the encoding task to be performed on an adjective that was then presented for 500 ms. During Image trials, participants generated a mental image of a spatial scene (i.e., a "place") described by the adjective (e.g., for *DIRTY*, the participant might imagine a garbage dump). During Read trials, participants covertly pronounced the word backwards (e.g., *HAPPY* might be pronounced /ip-pæ/). After a 4000-ms fixation period, during which participants performed the indicated task, the fixation cross changed color signaling participants to indicate their level of task success by pressing one of four buttons: 1=unsuccessful, 2=partially successful, 3=succeeded with effort, 4=succeeded with ease. To ensure that the fMRI retrieval effects do not reflect differential task success at encoding, analyses were restricted to trials on which the encoding task was performed successfully (i.e., received a response of 3 or 4, see also Davachi et al., 2003). Across participants, the assignment of items to conditions was counterbalanced.

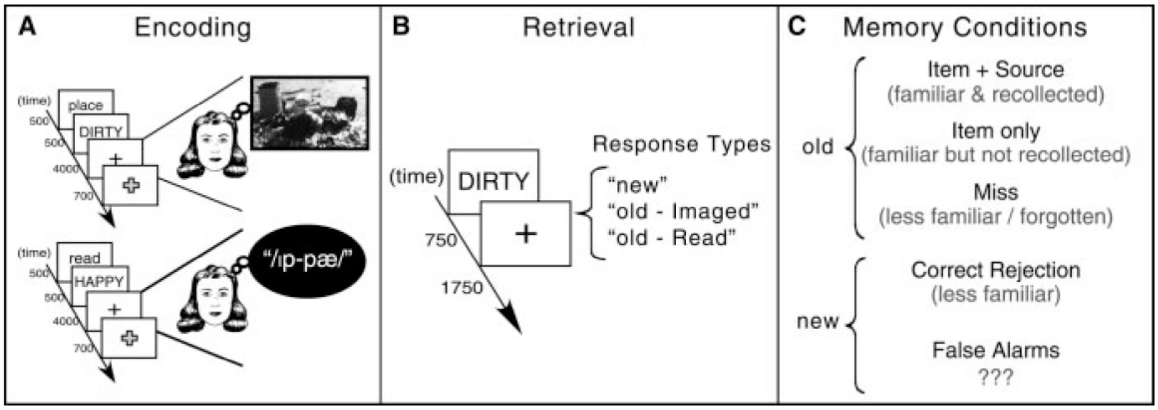

Figure 1. A schematic of the Encoding and Retrieval trials, and the possible resulting Memory conditions. *A*, Encoding conditions performed prior to scanning. *B*, A one step old–new recognition and source memory test was administered during fMRI scanning. *C*, Possible memory outcomes for the studied (old) and unstudied (new) items, with putative memory processes contributing to the outcomes in grey.

Approximately 20 hr post-encoding, participants returned for an event-related fMRI scanning session. Participants were initially scanned while engaging in a "Parahippocampal Place Area" (PPA) localizer task designed to identify parahippocampal voxels that differentially respond to perception of visual scenes (for details, see Epstein & Kanwisher, 1998). Subsequently, eight critical memory retrieval scans were conducted, during which memory for the encoded words was tested (**Figure 1B**). Specifically, recognition of studied items and recollection of the source (Imaged or Read) associated with each item were indexed by a one-step memory test. During this test, participants were presented all 400 studied words (Old items) as well as 400 unstudied lures (New items). On each trial, a test word was presented for 750 ms followed by a fixation cross for 1750 ms. During this combined 2500-ms window, participants indicated whether they recognized the word as having been studied and which encoding task was performed with the item when studied. Specifically, the participant made one of three responses: (1) “Old–Imaged” or (2) “Old–Read” indicated that the participant recognized the item as having been studied and recollected which encoding task was performed with the item, whereas (3) “New” indicated that the participant did not recognize the item as studied. Thus, measures of item recognition (recognized vs. forgotten) and source recollection (source correct vs. source incorrect) were obtained for each Old word, and measures of correct rejections (CRs) and false recognition (FA-“Imaged” and FA-“Read”) were obtained for New words (**Figure 1C**).

The order of conditions at test (Imaged, Read, and New) was determined using a sequencing program designed to maximize the efficiency of the event-related design (Dale, 1999). Conditions were “jittered” using variable duration (2 – 18 s) fixation null events.

FMRI Procedures

Functional data were acquired using a gradient-echo echo-planar sequence (1.5T Siemens Sonata, TR=2 s, TE= 40 ms, 21 axial slices, 3.125 x 3.125 x 5 mm, 1-mm skip, 210 volumes/run). High-resolution T1-weighted (MP-RAGE) structural images were collected for anatomical visualization. A bite-bar minimized head motion. Visual stimuli were projected onto a screen viewed through a mirror; responses were collected using a magnet-compatible response pad.

Data were analyzed using SPM99 (Wellcome Dept. of Cognitive Neurology, London), with standard preprocessing procedures that included slice-timing and motion correction (for details, see Davachi & Wagner, 2002). Structural and functional images were normalized to templates based on the MNI stereotaxic space. Images were re-sampled into 3-mm cubic voxels and spatially smoothed with an 8-mm FWHM isotropic Gaussian kernel.

Statistical analyses were performed using the general linear model. Trials were modeled using a canonical hemodynamic response function and its first-order temporal derivative. Effects were estimated using a participant-specific fixed-effects model, with session-specific effects and low-frequency signal components treated as confounds. Linear contrasts yielded participant-specific estimates that were entered into second-level random-effects analyses. As detailed below, targeted voxel-based contrasts permitted identification of neural signals associated with performance of the recognition memory task, as well as signals that differed across retrieval outcome (i.e., successful and unsuccessful trials). Regions consisting of at least 5 contiguous voxels that exceeded an uncorrected threshold of $p < .001$ were considered reliable.

Targeted region-of-interest (ROIs) analyses were performed to further characterize the nature of the retrieval patterns in PFC and parietal regions that, *a priori*, were expected to show old–new effects. Unless otherwise stated, the ROIs were defined based on the group-level voxel-wise contrast of all retrieval trials > fixation; note that this approach ensures that the ROIs were unbiased with respect to the retrieval conditions, thus permitting analyses of variance (ANOVA) tests of the activation patterns across conditions. For ROI definition, each ROI included all significant voxels within 6-mm of each maximum. For each participant, signal from the ROI was calculated by selectively averaging data with respect to peri-stimulus time per condition. The timepoint corresponding to peak activation in the ROI was identified by averaging across conditions and participants; the timepoint associated with the maximum value was identified as the peak. Subsequently, peak activation values in the ROI were then determined for each condition for each participant. The memory conditions consisted of (a) Old items that were recognized and accompanied by correct source recollection (*Item+Source*), (b) Old items that were recognized without correct source recollection (*Item Only*), (c) Old items that were forgotten (*Miss*), (d) New items that were correctly rejected as novel lures (*Correct Rejections; CRs*), and (e) New items that were falsely embraced as studied (*False alarms; FAs*) (**Figure 1C**). Moreover, all Hits (Item+Source and Item Only) and FAs were further subdivided based on the nature of the source response (“Imaged” or ”Read”) indicated by the participant. The resulting ROI data were subjected to mixed-effect ANOVAs, treating Encoding task (Imaged and Read) and Memory condition as repeated measures and participants as a random effect. Interaction analyses further assessed between-region differences in the patterns of activation across conditions.

Prior imaging data have revealed parahippocampal cortical activation during scene imagery (Davachi et al., 2003; O'Craven & Kanwisher, 2000), and left posterior ventrolateral prefrontal/premotor cortical activation during tasks requiring the generation of a novel phonological representation based on orthographic inputs (Clark & Wagner, 2003). Imaging investigations of episodic retrieval suggest that regions engaged during encoding are likely to be re-engaged when participants successfully recollect specific details from the study episode (Nyberg et al., 2000; Wheeler et al., 2000). Thus, we *a priori* expected that parahippocampal and left posterior ventrolateral PFC/premotor regions would show task-sensitive recollection success effects for the Imaged and Read items, respectively. To complement the voxel-based analyses of the effects of recollection success (i.e., Item+Source > Item Only, per task), additional targeted ROI analyses were performed. For these analyses, ROIs in parahippocampal and ventrolateral/premotor cortices were identified from the task-specific recollection contrasts, and the nature of the activation patterns in these ROIs across the retrieval conditions was subsequently explored with ANOVA.

Results

Recognition Performance

Behavioral effects were considered reliable at an alpha-level of .05. Recognition response probabilities differed across Memory condition (Item+Source, Item Only, and

FAs) for Imaged (F(2,32) = 33.65) and Read trials (F(2,32) = 10.56; **Figure 2A**). Item recognition with source recollection (Item+Source) was greater than (a) recognition without recollection (Item Only) and (b) the corresponding FA rate (Imaged: Fs(1,16) > 34.14; Read: Fs(1,16) > 12.96). Item Only recognition levels for Imaged (.50) and Read trials (.41) were higher than the corresponding FA rate (Fs(1,16) > 20.10), when correcting for the opportunity to make such a response (Davachi et al., 2003; Yonelinas & Jacoby, 1995). Finally, corrected recognition (collapsed across Item+Source and Item Only trials) was superior following Imaged (.55) than following Read encoding (.38) (F(1,16) = 17.21), and recognition with recollection (Item+Source) was higher following Imaged than following Read encoding (F(1,16) = 7.40; **Figure 2A**).

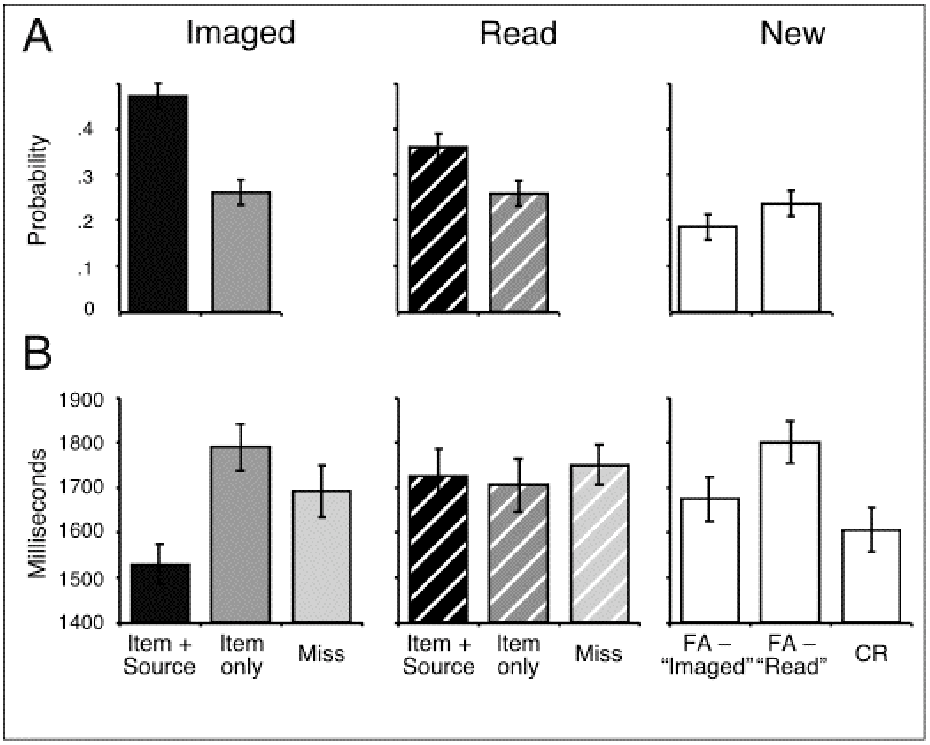

Figure 2. Item recognition and source memory performance and reaction times are plotted according to encoding condition. *A*, Probabilities of recognizing studied items (Item+Source and Item Only) or False Alarming to new items (FA-"Imaged", and FA-"Read") are shown. *B*, Reaction times are displayed for studied (Item+Source, Item Only, Miss) and new (FA-"Imaged", FA-"Read", and CR) items.

Reaction times (RTs; **Figure 2B**), analyzed using a two-way ANOVA of Encoding task (Imaged, Read, New) × Response type ("Imaged", "Read", "New"), revealed (a) an effect of Encoding task (F(2,32) = 3.29) such that RTs were faster for Imaged compared to Read items (F(1,16) = 6.50), (b) an effect of Response type (F(2,32) = 5.73) such that RTs were faster during "Imaged" and "New" compared to "Read" responses (Fs(1,16) > 4.75), and (c) an interaction (F(4,64) = 4.52). Post-hoc contrasts revealed a non-significant RT difference between CRs relative to Hits (1687 ms) (F(1,16) = 3.58, *p* = .068) and reliably faster RTs for CRs relative to FAs (1737 ms) (F(1,16) = 7.78). Per task, RTs differed across Memory condition (Item+Source, Item Only, Miss, and FA) for Imaged (F(3,48) = 6.48) but not for Read trials (F < 1). For Imaged words, RT was reliably faster for Item+Source compared to Item Only, Miss, and FA trials accompanied by the erroneous claim that the novel item had been imaged (FA-"Imaged"; Fs(1,16) > 5.92). RTs did not reliably differ across Item Only, Miss, and FA-"Imaged" trials (Fs(1,16) < 3.70, *p*s > .065). The fact that RTs were faster on Item+Source trials relative to all other trial types indicates that any observed fMRI retrieval responses associated with successful recollection cannot reflect a longer duty cycle/retrieval effort. Moreover, any similarities between the neural patterns of Item+Source and FA trials cannot reflect duty cycle effects, as RTs differed across these conditions during Imaged trials and were comparable during Read trials.

Neural Old–New Effects

Initial fMRI analyses identified neural responses that differed between studied items that were correctly recognized as "old" (i.e., Hits) and unstudied items correctly recognized as "new" (i.e., CRs). Contrasting Hits (collapsed across correct and incorrect source recollection) with CRs revealed greater activation in left inferior parietal, left precuneus, and posterior cingulate cortices, as well as in left frontopolar, ventrolateral, and posterior dorsolateral PFC (**Figure 3A** and **Table 1A**). These findings converge with prior demonstrations of left-lateralized old–new effects during episodic retrieval (Kensinger, Clarke, & Corkin, 2003; Konishi, Wheeler, Donaldson, & Buckner, 2000; Maril, Simons, Mitchell, Schwartz, & Schacter, 2003; McDermott, Jones, Petersen, Lageman, & Roediger, 2000; Nolde, Johnson, & D'Esposito, 1998; Wheeler & Buckner, 2003) and with observations of differential activation in similar structures during (a) source recollection versus temporal recency decisions (Dobbins *et al.*, 2003) and (b) source recollection versus novelty detection (e.g., Dobbins et al., 2002; Dobbins & Wagner, 2003). In the reverse contrast, greater activation during CRs relative to Hits was observed in a number of regions, including right inferior parietal, bilateral lateral temporal, and right dorsolateral and frontopolar PFC (**Table 1B**). Similar right PFC regions have been observed during comparisons of (a) familiarity-based vs. recollection-based recognition (Eldridge *et al.*, 2000; Henson et al., 1999), (b) temporal recency vs. source recollection decisions (Dobbins et al., 2003) (Dobbins et al., 2003), and (c) Hits vs. CRs when the target density of old to new test probes is less than 50:50, and CRs vs. Hits when the target density of old to new test probes is greater than 50:50 (Herron *et al.*, 2004).

Table 1A. Regions demonstrating differential activation during correctly recognized old items (Hits) relative to correctly rejected new items (CRs)

Region	Max-Z	MNI Coordinates x	y	z	~BA
Hits > CRs					
Left lateral parietal					
Post. superior parietal	5.72	-30	-75	48	7/19
	4.82	-30	-69	45	7
	3.66	-30	-78	33	19/7
Inferior parietal	5.08	-36	-60	42	40/7
	4.76	-42	-54	54	40/7
	4.56	-48	-48	51	40/7
Medial parietal/precuneus					
Precuneus	3.56	-9	-72	36	7
	3.27	-12	-66	27	7/31
Post. cingulate	3.69	-3	-36	33	31/23
Ant. calcarine	4.12	-6	-51	6	30
Left lateral PFC					
Frontopolar	4.88	-39	45	3	10/46
	4.79	-36	48	0	10
Ant. inferior frontal	5.30	-45	39	-3	10/47
	4.14	-45	33	15	45/46
	3.72	-54	27	6	45/47
	3.51	-45	21	3	47/45
Inferior frontal	3.31	-54	18	12	44/45
	3.25	-57	18	3	45/47
Post. inferior/middle frontal	5.06	-45	15	33	9/8/44
	4.84	-51	18	24	9/45/44
	4.78	-54	21	27	9/45
	4.36	-45	9	42	8
	4.28	-45	9	48	8
Orbital frontal	3.71	-30	27	-18	11
Ant. Insula/fronto-operculum	4.11	-30	15	6	45/47
	4.06	-30	24	-3	47
Superior frontal					
Medial superior frontal	4.61	-3	21	48	8
Left superior frontal	3.45	-24	15	45	6/8
Right ventrolateral PFC					
Fronto-operculum	3.65	33	27	-3	47
Fronto-operculum/inferior frontal	3.60	33	21	-12	47
Ant. Inferior frontal	3.18	42	33	-6	47
Basal Ganglia					
Right caudate/nucleus accumbens	4.95	12	9	-3	
Left caudate	4.92	-12	0	15	
Left caudate/nucleus accumbens	4.71	-12	9	3	

Note: Ant. = anterior; Max-Z = maximum Z-score; Post. = posterior

Importantly, in the presently observed regions showing old–new effects (i.e., Hits > CRs), subsequent voxel-based comparisons of item recognition with recollection (Item+Source) to recognition without recollection (Item Only) failed to reveal activation differences that tracked recollection outcome. This was the case even when lowering the threshold to a lenient level (*p* < .01), suggesting that these left lateralized regions are sensitive to "perceived oldness" (Wheeler & Buckner, 2003) or "perceived familiarity" (i.e., Hits > CRs) but are insensitive to recollection success (i.e., Item+Source vs. Item Only, cf., Cansino *et al*., 2002).

Table 1B. Regions demonstrating differential activation during correctly recognized old items (Hits) relative to correctly rejected new items (CRs)

		MNI Coordinates			
Region	**Max-Z**	**x**	**y**	**z**	**~BA**
CRs > Hits					
Occipital					
Left middle occipital	3.31	-27	-87	9	18
Left fusiform	3.59	-27	-66	-15	19
Right fusiform	4.01	27	-60	-15	19
	3.58	42	-66	-21	19
Right lateral inferior parietal	3.78	36	-48	27	40
	3.61	30	-42	48	40
	3.50	66	-30	30	40
Lateral temporal					
Left inferior temporal	3.65	-48	-78	-3	19
Left middle temporal	4.08	-54	3	-21	21
Left medial temporal	3.58	-57	-21	-3	21
Right superior temporal	3.75	51	-57	12	21/22
Right PFC					
Middle/superior frontal	3.61	24	15	51	6/8
Medial frontal	3.53	6	57	6	10
Frontopolar	4.79	27	54	15	10
Middle frontal	4.99	24	36	33	9

Note: Ant. = anterior; Max-Z = maximum Z-score; Post. = posterior

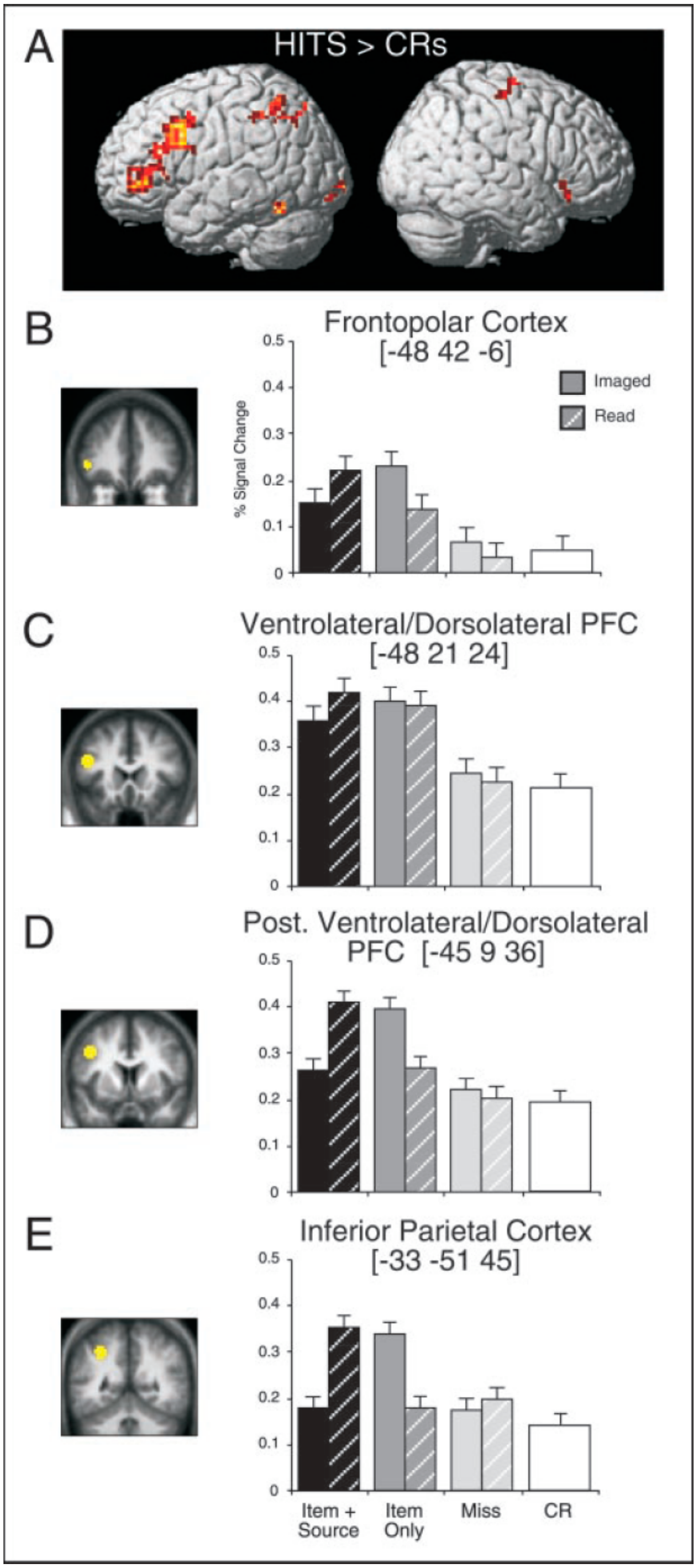

Figure 3. Left frontal and parietal cortices showing an old–new effect, and activation patterns in targeted regions of interest. *A*, Statistical parametric map of regions showing greater activation during correct recognition of old items (HITS) than during correct rejection of new items (CRs) displayed on a canonical 3D anatomy image. *B*, *C*, *D, E,* Percent signal change, relative to baseline fixation, is depicted for studied items (Item+Source, Item Only, Miss) and unstudied items (CR) from left frontopolar (~BA 10/47), ventrolateral/dorsolateral PFC (~BA 9/45), posterior (post.) ventrolateral/dorsolateral PFC (~BA 44/6/8), and inferior parietal (~BA 40/7) regions of interest (ROIs), defined from the contrast of all retrieval trials relative to baseline. ROIs are depicted on group-averaged coronal anatomy images, with activation for studied items subdivided according to encoding task (Imaged, *solid bars*; Read, *hatched bars*).

“Retrieval Success” vs. “Recollection Attempt”

To further explore the effect of Memory condition (Item+Source, Item Only, and CRs trials), ROI analyses were conducted to examine the responses of *a priori* predicted frontal and parietal structures previously observed to show old–new effects (**Figure 3B-E**). As described in the Methods, ROIs were defined from an unbiased contrast comparing all retrieval trials to the fixation baseline. For each ROI, (a) a one-way ANOVA of Memory condition (Item+Source, Item Only, and CR) was performed separately for Imaged and Read trials, and (b) a two-way ANOVA was performed with factors of Recollection success (Item+Source vs. Item Only) and Encoding task (Imaged vs. Read). Two classes of regions were revealed: those showing an old–new effect and (1) insensitivity to Recollection success for both Imaged and Read items, or (2) a Recollection success effect that depended on Encoding task.

Left frontopolar/anterior ventrolateral PFC (~Brodmann’s area [BA] 10/47; **Figure 3B**), left mid-ventrolateral/dorsolateral PFC (~BA 9/45; **Figure 3C**), and anterior cingulate cortices (ACC; ~BA 32; MNI-coordinates of -6, 21, 45) showed a reliable effect of Memory condition for both Imaged ($\underline{F}$s(2,32) > 5.02, *p*s < .02) and Read trials ($\underline{F}$s(2,30)[1] > 4.74, *p*s < .02). In each region, activation (a) was greater during Hits relative to CRs, (b) did not differ according to Encoding task ($\underline{F}$s(1,15) < 1.05), (c) did not differ according to Recollection success ($\underline{F}$s < 1), and, (d) with the exception of

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[1] The degrees of freedom are lower for the Read contrasts because one participant had to be excluded from this subset of the analyses due to having an insufficient number of trials in the Read–Item Only condition.

frontopolar cortex, did not demonstrate a Recollection success × Encoding task interaction (Fs(1,15) < 1.75, ps > .21) (**Figure 3B-C**). Although the interaction was reliable in frontopolar cortex ($F(1,15) = 4.68$, $p < .05$), post-hoc comparisons indicated that activation did not differ according to Recollection success for either the Imaged ($F(1,15) = 2.18$, $p > .15$) or Read trials ($F(1,15) = 2.51$, $p > .13$). Collectively, the ROI analyses (and the above described voxel-based contrasts) revealed that these regions showed old–new effects, but were insensitive to recollection outcome or encoding task. This pattern suggests that these regions are sensitive to "perceived familiarity", being engaged during recollection attempts only for items eliciting above-criterion familiarity.

As with the preceding regions, left posterior ventrolateral/dorsolateral PFC (~BA 44/6/8; **Figure 3D**), left inferior parietal cortex (~BA 40/7; **Figure 3E**), and precuneus (~BA 7; coordinates of -9, -69, 51) showed a reliable effect of Memory condition for both Imaged and Read trials (Fs > 7.66, ps < .005). However, each of these structures also showed greater activation for old items embraced as "Read" (Imaged–Item Only trials and Read–Item+Source trials) relative to old items embraced as "Imaged" or CRs (Fs > 8.12, ps < .01). Confirming this pattern, these regions demonstrated a reliable Recollection outcome × Encoding task interaction (Fs(1,15) > 23.31, ps < .0005), but no reliable effects of Recollection success (Fs(1,15) < 4.14, ps > .06) nor of Encoding task (Fs < 1). Thus, for Read encoded items, activation was greater during Item+Source trials relative to Item Only trials (Fs(1,15) > 12.33, ps < .005), whereas for Image encoded items, the opposite activation pattern was observed (Fs(1,15) > 6.31, ps < .05). Collectively, the ROI analyses complemented the voxel-wise analyses, indicating that these regions (a) showed old–new effects, and (b) were insensitive to recollection outcome across encoding tasks. Thus, these regions were sensitive to “perceived familiarity”, being engaged during recollection attempts only for items eliciting above-criterion familiarity. However, unlike left frontopolar and mid-ventrolateral/dorsolateral PFC, these structures demonstrated the additional characteristic that activation differed according to recollection outcome depending on the encoding task: when participants claimed to have previously “read” the item, activation during Hits was greater relative to when participants claimed to have previously “imaged” the item, irrespective of the actual task at encoding. We return to the effect of encoding task when we consider "recapitulation" responses below.

Responses to Misses and FAs in Regions Showing Old–New Effects

Prior fMRI investigations of neural old–new effects have tended to lack sufficient power to permit comparison of Hits and CRs to Misses and FAs (but see, Weis *et al.*, 2004; Wheeler & Buckner, 2003). Such comparisons are critical for determining whether old–new effects are restricted to accurately performed trials (i.e., Hits > CRs) or whether they generalize (a) to the contrast between “perceived familiar” items (i.e., Hits and FAs) relative to “perceived novel” items (i.e., Misses and CRs), irrespective of the true memory status of the test probes, or (b) to the contrast between studied items (i.e., Hits and Misses) relative to unstudied items (i.e., CRs and FAs), irrespective of memory accuracy.

The present recognition performance levels were sufficient to permit a test of this question. Voxel-based comparisons revealed greater activation for Hits relative to Misses in similar left-lateralized structures as detected by the Hits vs. CRs contrast, including inferior parietal, frontopolar, and posterior ventrolateral PFC, as well as left anterior insular and bilateral fronto-opercular cortex. ROI analyses confirmed these patterns, as activation during Misses was comparable to that during CRs (Fs < 2.43, *p*s $> .12$) (**Figure 3B-E**), indicating that the responses in regions showing old–new effects did not simply track the studied/unstudied dimension.

Intriguingly, given theoretical accounts of the mnemonic bases of FAs, the voxel-based contrast of Hits to FAs failed to reveal differential cortical responses between these two trial types in regions showing old–new effects. This outcome suggests that regions showing old–new effects demonstrate a generalized response to recognized relative to unrecognized items irrespective of the true study status of the test probe. Because the pattern of activation during FAs is a central question of interest, especially in regions thought to be associated with recollection (or the "recapitulation" of encoding-based representations), we expand on FA-related activations below.

Neural Recapitulation Effects

Item recognition accompanied by recollection is hypothesized to re-engage regions that were engaged during encoding of the subsequently recollected event/stimulus attributes. Accordingly, we predicted that in regions demonstrating "recapitulation", the effect of Recollection success at retrieval will differ depending on the task performed at encoding; encoding task presumably influences the nature of the episodic features bound to the item during learning and thus reinstated at retrieval (Cycowicz *et al.*, 2001; Gonsalves & Paller, 2000b; Johnson *et al.*, 1997; Nyberg et al., 2000; Senkfor & Van Petten, 1998; Wheeler et al., 2000). Consistent with this prediction, voxel-based comparisons, performed separately on Imaged trials and Read trials, revealed regions that were differentially engaged during recognition with (Item+Source) compared to without (Item Only) recollection (**Table 2**). These regions included left parahippocampal cortex (PHc; ~BA 36) in the Imaged condition, and left premotor/posterior ventrolateral PFC (~BA 6/44) in the Read condition (**Figure 4A**). Right PHc (~BA36; coordinates of 30, -36, -24) was also observed in the Imaged condition, at a slightly more lenient threshold ($p <$ .005).

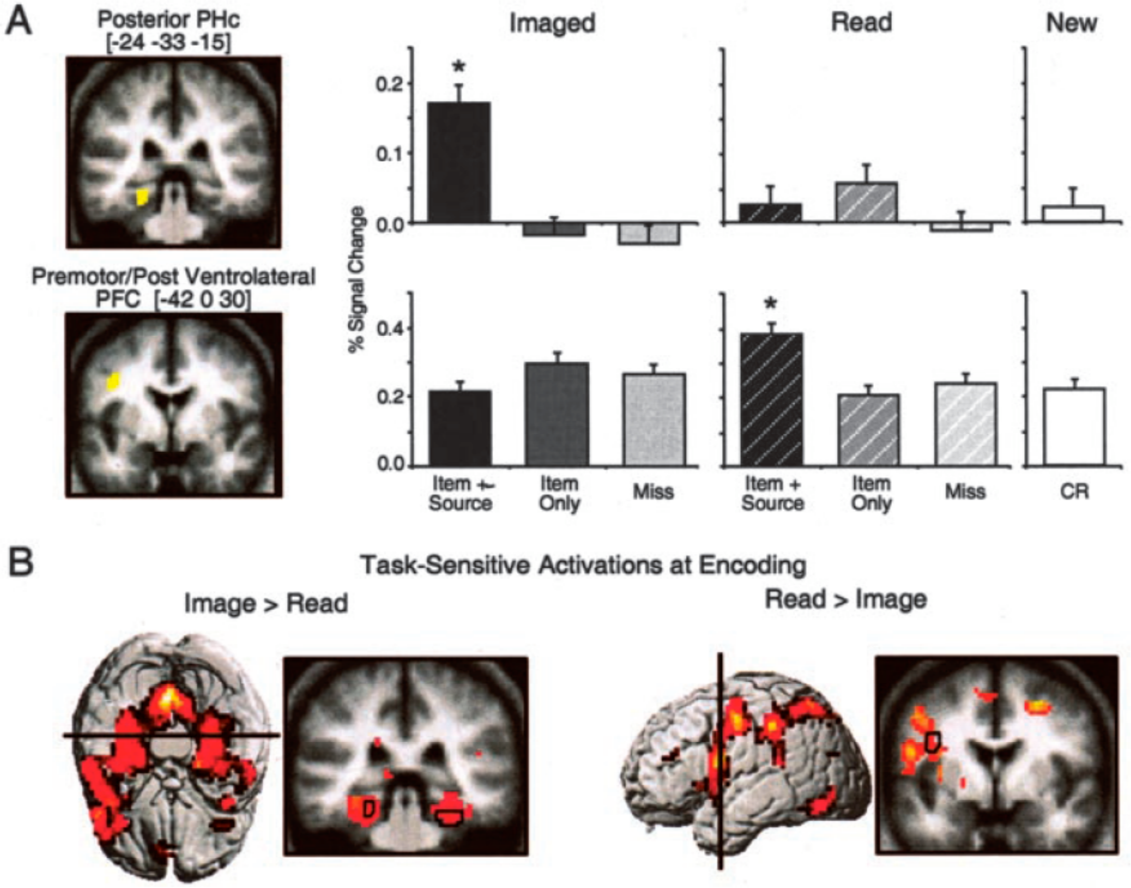

Figure 4. Regions showing task-sensitive recollection success effects, and the overlap between these effects at retrieval with task-sensitive encoding correlates. *A*, Per task, regions of interest emerged from voxel-based comparison of regions differentially engaged during recognition accompanied by recollection (Item+Source trials) compared to recognition without recollection (Item Only trials). Recollection-selective activation was revealed in left posterior parahippocampal cortex (PHc; ~BA 36) in the Imaged condition, and left premotor/posterior ventrolateral PFC (~BA 6/44) in the Read condition. *B*, Statistical parametric maps of task-sensitive activation at encoding (data from Davachi et al., 2003), superimposed with the recollection-selective ROIs identified at retrieval (*black outlines* in coronal images).

Targeted ROI analyses were subsequently performed on the PHc and left premotor/posterior ventrolateral PFC regions observed in the voxel-based recollection success contrasts. These analyses aimed to further assess the broader pattern of activation in these structures using (a) a two-way ANOVA with factors of Recollection success (Item+Source, Item Only, and Miss) and Encoding task (Imaged vs. Read), and (b) a one-way ANOVA, performed separately for Imaged and Read trials, with Memory condition (Item+Source, Item Only, Miss, and CR) as the factor.

Table 2. Regions demonstrating greater activation during recognition accompanied with recollection (Item+Source) vs. without recollection (Item Only)

		MNI Coordinates			
Region	**Max-Z**	**x**	**y**	**z**	**~BA**
Imaged Trials					
Medial frontal	4.30	-3	57	-9	10
Ant. cingulate	3.56	-18	42	6	32
Medial superior frontal	3.30	-6	39	45	8
Left ant. hippocampus/amygdala	3.74	-21	-3	-24	
Left parahippocamal	4.14	-24	-33	-15	36
Post. cingulate/precuneus	3.67	-6	-45	27	23/31
	3.65	-6	-42	39	31/7
	3.60	-6	-36	39	31
Left superior parietal	3.57	-27	-45	60	7
Ant. calcarine	4.41	-6	-45	9	30
Left cerebellum/lingual	3.44	-12	-54	-9	19
Left lingual	3.35	-6	-60	0	18/19
Right lingual/occipital	4.02	12	-90	-3	17
Lingual	3.97	15	-87	-15	18
Lingual	3.97	9	-84	-12	18
Occipital	3.71	30	-84	-15	18/19
Thalamus	3.54	-3	-18	-6	
	3.45	-3	-15	0	
	3.28	3	-15	0	
	3.33	15	-27	9	
Read Trials					
Left premotor/lateral PFC					
Post. inferior/middle frontal	3.98	-48	12	30	8/9
Post. premotor/Inferior frontal	3.63	-42	0	30	6/44
Right inferior parietal	3.30	36	-48	42	40/7

Note: Ant. = anterior; Max-Z = maximum Z-score; Post. = posterior

Left PHc showed an effect of Recollection success (F(2,30) = 8.51, *p* < .005) and a Recollection success × Encoding task interaction (F(2,30) = 6.65, *p* < .005) (**Figure**

4A). For Image-encoded items, left PHc demonstrated an effect of Memory condition (F(3,48) = 10.26, *p* < .0001), with post-hoc contrasts revealing greater activation during Item+Source compared to Item Only, Miss, and CR trials (Fs(1,16) > 13.67, *p*s < .001). These latter three conditions did not reliably differ (Fs(1,16) < 1.48, *p*s > .23), indicating that during Imaged trials this response was selective to recognition with recollection. Moreover, for Read-encoded items, activation did not differ according to Memory outcome (F(3,45) = 1.17, *p* > .32). A qualitatively similar pattern was observed in right PHc, which showed a Recollection success × Encoding task interaction (F(2,30) = 7.57, *p* < .005): activation was greatest during Item+Source trials for Image-encoded items (*p* < .05), but did not differ across the Memory conditions for Read-encoded items (*p* > .35). Thus, Recollection success effects in left and right PHc were restricted to Imaged trials.

Left premotor/posterior ventrolateral PFC also showed a Recollection success × Encoding task interaction (F(2,30) = 10.38, *p* < .0005), but, in contrast to PHc, the effect of Memory condition (F(3,45) = 7.07, *p* < .001) was observed for Read encoded items, with post-hoc contrasts revealing greater activation for Item+Source compared to Item Only, Miss, and CR trials (Fs(1,15) > 10.82, *p*s < .005) (**Figure 4A**). No other conditions differed reliably for Read items (Fs(1,15) < 1), indicating that during Read trials this response was selective to recognition with recollection. Moreover, for Image-encoded items, the effect of Memory condition was not reliable (F(3,48) = 2.45, *p* < 0.08); if anything, there was greater activation during Item Only vs. Item+Source trials and comparable activation between Item Only and Miss trials. Thus, the Recollection success effect in left premotor/ventrolateral PFC was restricted to Read trials.

A Region (left PHc vs. premotor/ventrolateral PFC) × Task (Imaged vs. Read) × Recollection success (Item+Source vs. Item Only) interaction ($\underline{F}(1,15) = 13.97$, $p < .005$) confirmed that the functional patterns in left PHc and premotor/ventrolateral PFC were distinct. This outcome indicates that the Recollection success effects in left PHc and premotor/ventrolateral PFC were tied to the task performed at encoding, as would be expected if these regions were engaged during the "recapitulation" of visuo-perceptual and phonological representations that were respectively present during encoding.

Finally, although multiple regions were observed in the voxel-based Recollection success contrasts (i.e., Item+Source > Item Only, per task; **Table 2**), the above analyses focus on PHc and left premotor/posterior ventrolateral PFC because of *a priori* expectations that these regions would show task-selective effects. Posterior PHc is known to be engaged during scene imagery (O'Craven & Kanwisher, 2000), and greater PHc encoding activation is predictive of subsequent recollection of having performed the Image task during study (Davachi et al., 2003). By contrast, left posterior ventrolateral PFC/premotor cortex is thought to subserve the assembly of novel phonological representations (Clark & Wagner, 2003), processes that are differentially required during the Read task. Confirming that the presently observed regions were differentially engaged by the two tasks *at encoding*, we took advantage of the fact that we previously collected fMRI measures of neural activation during performance of the Image and Read tasks in an independent sample of participants (Davachi et al., 2003). Importantly, the present Recollection success effects overlapped with (a) the bilateral PHc regions demonstrating an Image>Read pattern of encoding activation, and (b) the left premotor/PFC region demonstrating a Read>Image pattern of encoding activation

(**Figure 4B**). Moreover, Recollection success effects in bilateral PHc overlapped with the parahippocampal regions detected by the "PPA localizer" scan.

Neural Responses during FAs

A voxel-based contrast of FAs to CRs revealed differential activation during FAs in the same regions that were differentially engaged when comparing Hits with CRs. This finding suggests that many of the neural computations supporting veridical recognition are qualitatively similar to those supporting false recognition. That is, to the extent that a test probe elicits above-criterion familiarity, then the computations subserved by these structures appear to be recruited to guide recollection attempts.

Leading models of recognition memory assume that FAs are exclusively based on recognition without recollection (i.e., above-criterion familiarity), rather than on familiarity, recollection, or both (Jacoby, 1991; Yonelinas et al., 1996). We tested this assumption by comparing trials on which participants falsely embraced new items as having been studied in either the Image or the Read task. To the extent that FAs are recollection free, then regions showing task-selective "recapitulation" effects for studied items should fail to differentiate according to the false source ("Imaged" or "Read") being misattributed to new items. By contrast, to the extent that false recollection partially contributes to FAs, then the pattern of task-selectivity (Imaged vs. Read) seen for Item+Source trials in PHc and left premotor/ventrolateral PFC (**Figure 4A**) should also be seen for FAs mistakenly attributed to having been encountered in the Imaged vs. Read tasks, respectively. The sensitivity of these ROIs to false recollection was assessed using a two-way ANOVA, with factors of Encoding task (Imaged and Read) and Memory condition (Item+Source, Item Only, and FA).

Left PHc showed an effect of Encoding task ($F(1,15) = 6.61$, $p < .05$), of Memory condition ($F(2,30) = 5.76$, $p < .01$), and a reliable interaction ($F(2,30) = 9.41$, $p < .001$). Importantly, activation during FA-“Imaged” trials was reliably greater than that during Imaged–Item Only and FA-“Read” trials (Fs$(1,15) > 7.28$, ps $< .05$), suggesting that false recollection of imagery-based information accompanied FA-“Imaged” trials[1]. By contrast, FA-“Read” trials did not differ from Read–Item+Source, Read–Item Only, and Imaged–Item Only trials (Fs$(1,15) < 2.95$, ps $> .10$), suggesting that this false recollection effect was selective to FAs to which participants falsely indicated that they had imagined a spatial referent of the item. Interestingly, activation during FA-“Imaged” trials was weaker than that during Imaged–Item+Source trials ($F(1,15) = 4.46$, $p < .05$) (**Figure 5A**), suggesting that, although false recollection may have accompanied some FA-“Imaged” decisions, the probability of this occurring was lower than that during veridical recollection. A qualitatively similar pattern was observed in right PHc (Encoding task × Memory condition, $p < .01$), although the false recollection effect was less robust (FA-“Imaged” vs. Imaged–Item Only; FA-“Imaged” vs. FA-“Read”, ps $< .10$).

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[1] Note that the pattern of neural activation did not track the pattern of reaction times, arguing against the interpretation that differential neural activation was due to differential retrieval effort.

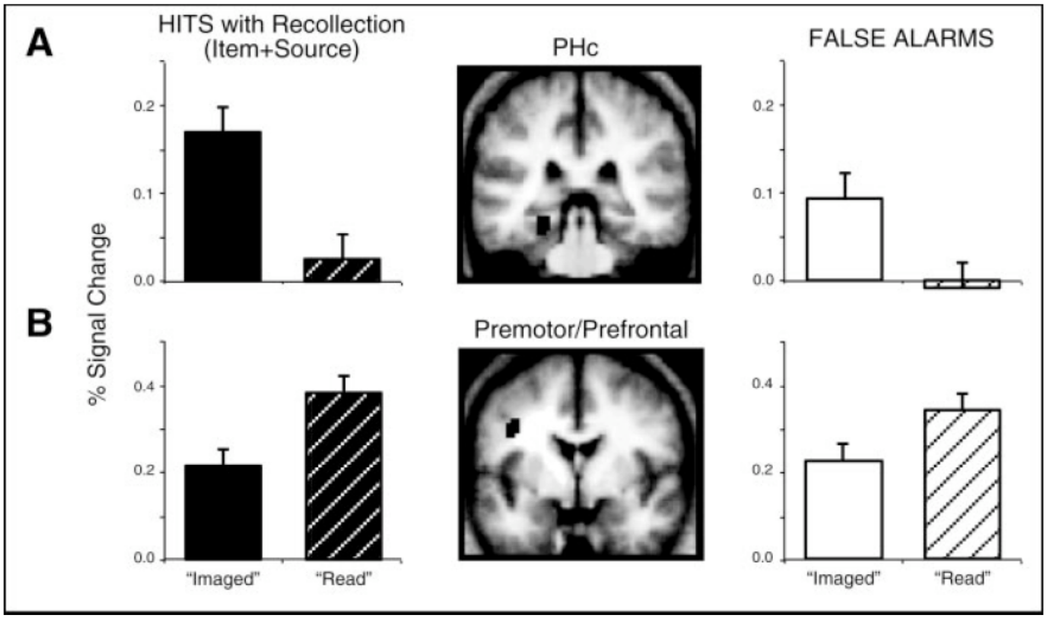

Figure 5. Map-wise and region-of-interest neural correlates of false recognition. *A*, Statistical parametric map comparing FAs to CRs. *B*, Percent signal change in the left posterior PHc and left premotor/posterior ventrolateral PFC regions showing Recollection success effects (from Figure 4A). Displayed is activation during veridical recollection (*left*) for Imaged (*solid bars*) and Read (*hatched bars*) items, and during false recognition (*right*) accompanied by an "Imaged" or "Read" response. The task-sensitivity of false recognition activation paralleled that of veridical recollection.

A complementary pattern was observed in left premotor/posterior ventrolateral PFC, which demonstrated an effect of Encoding task ($\underline{F}(1,15) = 5.31$, $p < .05$) and a Memory × Encoding task interaction ($\underline{F}(2,30)=11.85$, $p < .0005$). Activation during FA-"Read" trials was reliably greater than that during Read–Item Only and FA-"Imaged" trials ($\underline{F}$s(1,15) > 7.69, *p*s < .01), but did not differ from that during Read–Item+Source trials ($\underline{F}(1,15) = 1.09$, $p > .27$) (**Figure 5B**). Additionally, activation during FA-"Read" trials was reliably greater than that during Imaged–Item+Source ($\underline{F}(1,15) = 9.74$, $p < .01$), whereas activation during FA-"Imaged" trials did not reliably differ from that during Imaged–Item+Source, Imaged–Item Only, and Read–Item Only trials ($\underline{F}$s(1,15) < 3.11, *p*s > .10). Collectively, this pattern of activation is consistent with the conclusion that FA-"Read" trials were accompanied by false recollection.

Discussion

Recollecting the past depends on multiple mechanisms, including cognitive control processes that guide retrieval attempts and recovery processes that "recapitulate" episodic details (Buckner & Wheeler, 2001; Dobbins et al., 2002; Rugg & Wilding, 2000). The present results advance understanding of recollection in three important ways. First, the findings offer a resolution to the debate regarding whether left PFC regions—known to show old–new effects—are sensitive to "retrieval success" (Konishi et al., 2000) or "recollection attempt" (Dobbins et al., 2003; Ranganath et al., 2000). Our data indicate that both hypotheses have merit, as left PFC subregions were sensitive to *familiarity-based* retrieval success but were insensitive to *recollection-based* success. These structures appear to support control processes that guide recollection attempts when familiarity levels fall above an internal decision criterion. Second, successful recollection elicited representation-specific activation in premotor/posterior prefrontal and parahippocampal cortices that paralleled that seen at encoding. This outcome was observed for once encountered items, suggesting a "recapitulation" rather than "attentional modulation" interpretation. Finally, false recognition was accompanied by "recapitulation" responses, suggesting that FAs can be partially based on illusory recollection.

Familiarity-gated Recollection Attempt

Consistent with prior studies (Konishi et al., 2000; Maril et al., 2003; Nolde et al., 1998), our data revealed left-lateralized old–new effects in left frontopolar, ventrolateral, and posterior dorsolateral PFC, and inferior parietal cortex and precuneus (**Figure 3A**, **Table**

1). Such effects could reflect processes that are sensitive to successful retrieval (Donaldson et al., 2001; Habib & Lepage; Henson et al., 1999; Konishi et al., 2000), or processes that are brought to bear during attempts to recollect, irrespective of recollection outcome (Dobbins et al., 2002; Dobbins et al., 2003; Ranganath et al., 2000). Heretofore, adjudicating between these competing hypotheses has been complicated because "success" accounts primarily emerged from studies of yes/no recognition (Henson et al., 1999; Konishi et al., 2000; McDermott et al., 2000; Nolde et al., 1998), whereas "attempt" accounts primarily emerged using forced-choice recognition (Dobbins et al., 2002; Dobbins et al., 2003; cf., Ranganath et al., 2000).

The present data—from a one-step yes/no recognition, plus source recollection paradigm—offer a resolution that accommodates both hypotheses: specific left PFC and, to a lesser extent, parietal subregions mediate control processes that guide recollection attempt, with these processes being gated/disengaged when the recognition probe is perceived to be of low familiarity. Two observations motivate this conclusion. First, the left PFC and parietal regions showing old–new effects (a) also showed greater activation during FAs compared to CRs, but did not show differential activation during (b) Hits vs. FAs and (c) Misses vs. CRs. Thus, these regions were insensitive to the true memory status of the probe, as they were engaged to the extent that above-criterion familiarity ("perceived familiarity") was elicited. Recently, Wheeler and Buckner (2003) reported greater activation during FAs relative to CRs in left ventrolateral PFC and parietal cortices; the present findings extend such "perceived oldness/familiarity" effects to left frontopolar and dorsolateral PFC. Second, irrespective of encoding task, these regions were insensitive to recollection outcome (Item+Source vs. Item Only), though parietal cortex was modulated by response type ("Imaged" vs. "Read").

It is possible that this null effect of recollection outcome in left PFC and parietal regions emerged because the recognition test indexed source memory in a forced-choice manner. Accordingly, because participants could not respond "old" without designating a source, some source responses reflect guessing. The behavioral results, however, revealed Item+Source rates that were well above guessing, suggesting that recollection was present. Moreover, and more compellingly, recollection success effects were detected in other brain structures—bilateral PHc and left premotor/posterior ventrolateral PFC—indicating that the experimental design was sensitive to such effects when present. Finally, although it remains possible that other regions may have shown recollection success effects were guesses removed, a prior study that demonstrated recollection success effects in medial PFC and right parietal regions (Cansino et al., 2002) also failed to observe such effects in the presently noted left PFC and parietal regions showing "perceived familiarity" effects.

Collectively, our data indicate that left-lateralized PFC and, to a lesser extent, parietal cortices mediate processes that guide attempts to recollect, such as maintaining and elaborating on retrieval cues and monitoring the products of recollection attempts (Dobbins et al., 2002; Rugg & Wilding, 2000). Engagement of these processes depends on "perceived familiarity", suggesting that these regions have early access to familiarity signals and are gaited (in an automatic or controlled manner) depending on the expected utility of effortful recollection attempt.

Neural Recapitulation Supports Recollection

Separate analyses on Imaged and Read trials revealed regions that were differentially engaged during recognition with compared to without recollection. Bilateral PHc (**Figure 4A**) were differentially engaged during accurate recollection of having engaged in scene imagery at encoding, whereas left premotor/posterior ventrolateral PFC (**Figure 4A**) was differentially engaged during recollection of having performed the Read task. These structures were also differentially active during performance of the Image and Read tasks at encoding (**Figure 4B**), suggesting that task-sensitive recollection effects (**Figure 4A**) mark the "recapitulation" of neocortical representations that were present at encoding.

An alternative interpretation of such task-sensitive recollection effects is that they reflect a consequence of top-down attentional orienting to domain-specific representational layers (i.e., cortical structures that differentially represent particular kinds of features), rather than the "recapitulation" of episodic details. From this perspective, retrieved knowledge about the general context associated with an item (e.g., visuo-perceptual vs. verbal) permits recruitment of attentional mechanisms that bias specific representational layers in attempts to recollect experiential details (irrespective of the outcomes of such attempts). Attentional orienting may be particularly prevalent when items are encoded multiple times (Nyberg et al., 2000; Vaidya et al., 2002; Wheeler et al., 2000), as "semantic" knowledge about an item's context may be abstracted across the multiple encoding events, allowing for recovery of this general knowledge even in the absence of experience-specific recollection. To diminish this possibility, in the present experiment, items were encoded once, eliminating the possibility of acquiring semantic knowledge about an item's encoding context and demanding recollection of event-specific/trial-unique details. By definition, at retrieval, any knowledge of the task context must reflect episodic recollection as there was only a single episode in which the item appeared in the task context. Nevertheless, questions may still remain as to whether the neural effects reflect episodic recollection of the context *per se* or recollection of the representations (i.e., visuo-spatial imagery or phonological codes) elicited by this context.

False Recognition and Recollection

The "recapitulation" responses observed in PHc and left premotor/ventrolateral PFC during veridical recollection were also observed during false recognition accompanied by an erroneous "Imaged" or "Read" judgment, respectively. This parallel between the activation patterns during veridical recollection and false recognition (**Figure 5**) provides important new evidence that FAs may be partially based on false recollection. Moreover, weaker "recapitulation" responses were observed in bilateral PHc during false recognition (FA-"Imaged") relative to veridical recollection (Imaged–Item+Source), suggesting that false recognition is not always accompanied by recollection (or is accompanied by recollection of fewer details).

Behavioral data indicate that false recognition can be accompanied by illusory recollection when novel recognition probes are conceptually related to studied items (i.e., "related lures", Roediger & McDermott, 1995; Schacter *et al.*, 1998). Prior neuroimaging data indicate that false recognition of related lures can be accompanied by medial temporal lobe activation that resembles that seen during veridical recognition, whereas regions that represent domain-specific experiential details have been selectively or differentially engaged during veridical recognition (Cabeza *et al.*, 2001; Schacter, 1996). The present findings, however, suggest that the same neocortical "recapitulation" effects that occur during veridical recollection can also occur during false recognition, but to a lesser extent (Gonsalves & Paller, 2000a), lending support to the conclusion that false recognition is partially based on erroneously triggered recollection. Intriguingly, this false recollection effect emerged within the context of a paradigm that did not purposefully manipulate study/lure similarity, though the sheer number of experimental stimuli raises the possibility that this effect nevertheless stems from similarity between experienced and novel stimuli.

The present observation of false recollection during FAs, as indexed by illusory "recapitulation", has important implications for models of recognition. A critical assumption of leading dual-process models is that FAs are based on above-criterion familiarity in the absence of recollection (Jacoby, 1991; Yonelinas et al., 1996). To the extent that neural "recapitulation" effects mark recollection, then, at a minimum, the present findings indicate that there are instances in which this assumption is violated. One possibility is that such effects emerge when participants are forced to make source decisions during recognition, as in the present experiment. It remains an open question as to whether illusory recollection also emerges during performance of simple recognition tasks, where old and new items can be discriminated based solely on familiarity. A critical goal for future research is to determine the conditions in which FAs are partially based on recollection, as theoretically important estimates of recollection and familiarity in healthy and clinical populations rest on this assumption (Yonelinas, 1997; Yonelinas *et al.*, 2002).

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Chapter 4

Functional Neurobiology of Episodic Retrieval: Parietal Contributions to Recollection[1]

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Introduction

Episodic memory supports conscious remembering of everyday events, and has long been known to critically depend on the medial temporal lobe memory system and on modulatory functions of prefrontal cortex (Cohen & Eichenbaum, 1993; Shimamura, 1995; Squire, 1992; Stuss & Benson, 1984). Somewhat unexpectedly, positron emission tomography and functional MRI (fMRI) studies have demonstrated that episodic retrieval is also accompanied by activation in left lateral parietal cortex, including inferior parietal lobule and intraparietal sulcus, and in medial parietal structures, including precuneus, retrosplenial cortex, and the posterior cingulate (for review see, Buckner & Wheeler, 2001; Wagner, Shannon, Kahn, & Buckner, 2005). Such findings complement earlier event-related potential (ERP) data revealing differential responses at parietal electrodes when comparing *old* (hits) versus *new* (correct rejections) items during recognition (for review see, Rugg & Allan, 2000), motivating recent efforts to characterize the relation between memory and activation in human parietal cortex.

Initial event-related fMRI data documenting parietal sensitivity to episodic retrieval include observations of greater parietal activation when correctly identifying *old* items as compared to correctly rejecting *new* items. Parietal "old–new" effects have been observed using a variety of stimuli (verbal and visual-object targets) and a variety of paradigms (yes/no recognition, remember/know, recognition confidence, and source recollection) (e.g., Eldridge, Knowlton, Furmanski, Bookheimer, & Engel, 2000; Henson, Shallice, Gorno-Tempini, & Dolan, 2002; Konishi, Wheeler, Donaldson, & Buckner, 2000; Leube, Erb, Grodd, Bartels, & Kircher, 2003; McDermott, Jones, Petersen, Lageman, & Roediger, 2000; Wheeler & Buckner, 2003). Given the consistency of these effects, attention has rapidly focused on whether parietal activation co-varies with recognition decisions based on *recollection* (retrieving contextual details surrounding a stimulus's prior encounter) and/or with *familiarity* (the subjective sense of having encountered the item).

Recent fMRI data suggest that parietal activation can be modulated by a number of mnemonic factors, including (a) the subjective perception that items are old or familiar (Kahn, Davachi, & Wagner, 2004; Wheeler & Buckner, 2003), (b) whether recognition is recollective- as compared to familiarity-based (Cansino, Maquet, Dolan, & Rugg, 2002; Dobbins, Rice, Wagner, & Schacter, 2003; Eldridge, Knowlton, Furmanski, Bookheimer, & Engel, 2000; Henson, Rugg, Shallice, Josephs, & Dolan, 1999; Wheeler & Buckner, 2004), and (c) whether retrieval attempts are oriented towards recollecting episodic details or towards detecting novelty/familiarity (e.g., Dobbins, Foley, Schacter, & Wagner, 2002; Dobbins, Rice, Wagner, & Schacter, 2003; Herron, Henson, & Rugg, 2004). Critically, for present purposes, Wheeler and Buckner (2004) observed that activation in lateral inferior parietal lobule and in medial parietal regions correlates with recollection (see also, Yonelinas, Otten, Shaw, & Rugg, 2005), whereas activation in intraparietal sulcus is insensitive to recollection, suggesting that these parietal subregions serve different functions (for review, see Wagner, Shannon, Kahn, & Buckner, 2005).

A rich electrophysiological literature has documented ERP old–new effects that emerge approximately 400 msec post-stimulus onset, that extend 400-600 msec in duration, and that are largest in amplitude over left parietal scalp electrodes. ERP studies have demonstrated that the left parietal old–new effect is sensitive to source recollection

(Wilding, 2000; Wilding, Doyle, & Rugg, 1995; Wilding & Rugg, 1996), to "remembering" versus "knowing" (Duzel, Yonelinas, Mangun, Heinze, & Tulving, 1997; Smith, 1993; Trott, Friedman, Ritter, Fabiani, & Snodgrass, 1999), and to other manipulations that promote recollection (Herron & Rugg, 2003; Paller & Kutas, 1992; Rugg et al., 1998; Ullsperger, Mecklinger, & Muller, 2000). However, in contrast to the fMRI literature, ERP studies have not observed differential mnemonic responses across parietal electrodes—perhaps due to limited spatial resolution and constraints on source localization.

The present study sought to bridge the gap between the ERP and fMRI literatures. *Anatomically constrained* magneto-encephalography (*a*MEG) was used to provide higher temporal resolution than fMRI and superior spatial resolution relative to ERPs (Dale et al., 2000; Dale & Sereno, 1993; Hämäläinen, Hari, Ilmoniemi, Knuutila, & Lounasmaa, 1993), thus yielding information about the location and timing of parietal responses engaged during episodic retrieval. We specifically assessed whether aMEG reveals subregions within parietal cortex that are differentially sensitive to source recollection success and subregions that are sensitive to perceived familiarity.

Methods

Participants

Six female and six male right-handed, native-English speakers (18-35 yrs of age) participated. Data from two of these participants were discarded because performance levels and artifact rejection resulted in there being less than 20 events in at least one condition (see below). Informed consent was obtained in a manner approved by the institutional review boards at the Massachusetts Institute of Technology and Massachusetts General Hospital.

Behavioral Procedures

Participants performed a source recollection task identical to that previously investigated using fMRI (Kahn, Davachi, & Wagner, 2004). Initially, participants performed two intermixed incidental encoding tasks (non-scanned). Following a 20-hr retention interval, participants were scanned while making item recognition decisions combined with a source recollection judgment.

Across eight study lists, 200 visually presented adjectives were encoded via an orienting task requiring mental imagery (‘Image’ task) and 200 via an orienting task requiring orthographic-to-phonological transformation (‘Read’ task) (**Figure 1A**). On each trial, a 500-ms cue (*place*/*read*) signaled the encoding task to be performed on an adjective that was then presented for 500 ms. During Image trials, participants generated a mental image of a spatial scene (i.e., a “place”) described by the adjective (e.g., for *DIRTY*, the participant might imagine a garbage dump). During Read trials, participants covertly pronounced the word backwards (e.g., *HAPPY* might be pronounced /ip-pæ/). After a 4000-ms fixation period, during which participants performed the indicated task, the fixation cross changed color signaling participants to indicate their level of task success by pressing one of four buttons: 1=unsuccessful, 2=partially successful, 3=succeeded with effort, 4=succeeded with ease. To ensure that the MEG retrieval effects do not reflect differential task success at encoding, analyses were restricted to trials on which the encoding task was performed successfully (i.e., received a response of 3 or 4; see also Davachi, Mitchell, & Wagner, 2003; Kahn, Davachi, & Wagner, 2004). Across participants, the assignment of items to conditions was counterbalanced.

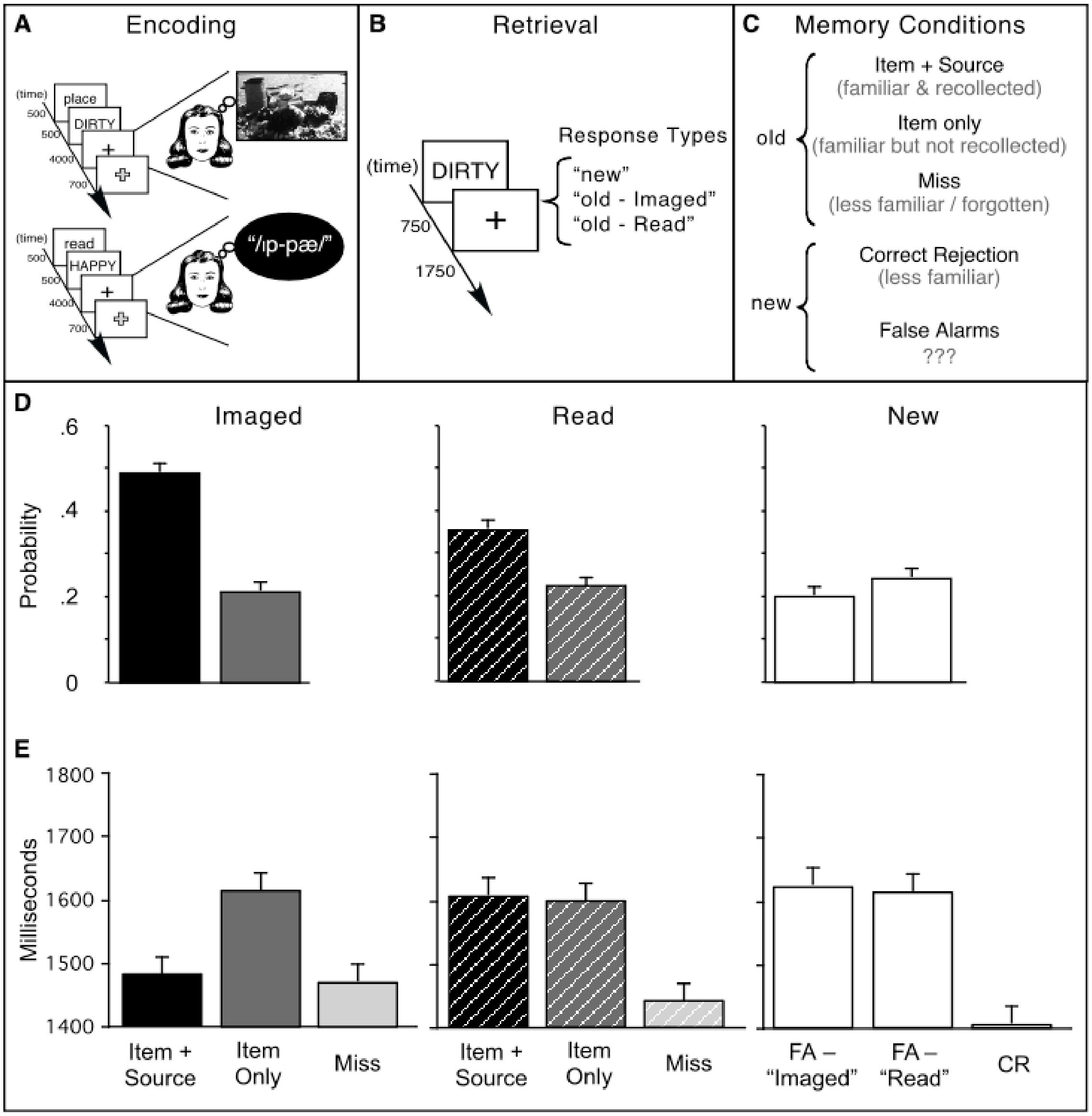

Figure 1. A schematic of the Encoding and Retrieval trials, the possible resulting Memory conditions, and behavioral performance. *A*. Encoding conditions performed before scanning. *B*. A one-step old–new recognition and source memory test was administered during MEG recording. *C*. Possible memory outcomes for the studied (old) and unstudied (new) items, with putative memory processes contributing to the outcomes in gray. *D*. Probabilities of recognizing studied items (Item+Source and Item only) or False Alarms to new items (FA–Imaged and FA–Read) are shown; Reaction times are displayed for studied (Item +Source, Item only, Miss) and new (FA–Imaged, FA–Read, and CR) items.

Approximately 20 hr post-encoding, participants returned for a MEG scanning session. Event-related fields were recorded while participants were engaged in eight memory retrieval scans during which memory for the encoded words was tested (**Figure 1B**). Specifically, recognition of studied items and recollection of the source (Imaged or Read) associated with each item were indexed by a one-step memory test. During this test, participants were presented all 400 studied words (Old items) as well as 400 unstudied lures (New items). On each trial, a test word was presented for 750 ms followed by a fixation cross for 1750 ms. During this combined 2500-ms window, participants indicated whether they recognized the word as having been studied and which encoding task was performed with the item when studied. Specifically, the participant made one of three responses: (1) “Old–Imaged” or (2) “Old–Read” indicated that the participant recognized the item as having been studied and recollected which encoding task was performed with the item, whereas (3) “New” indicated that the participant did not recognize the item as studied. Thus, measures of item recognition (recognized vs. forgotten) and source recollection (source correct vs. source incorrect) were obtained for each Old word, and measures of correct rejections (CRs) and false recognition (FA) were obtained for New words (**Figure 1C**).

MEG Data Acquisition

MEG data were acquired at a sampling rate of 600 Hz using a 306-channel NeuroMag Vectorview system. Prior to recording, participants were fitted with five electrodes, four for monitoring eye movements and one ground electrode. Four head-position coils (HPI) were also attached to the scalp for use in MEG–MRI alignment. The locations of the HPI coils relative to the participant's scalp were measured using several landmark locations on the head with a Polhemus FastTrack 3-D digitizer. Participants were then placed in a magnetically shielded room and were seated upright in a chair with their heads placed inside the magnetometer. Stimuli were back-projected onto a screen placed in front of the participant. Participants responded using a fiber optic button box. In addition to MEG data acquisition, high-resolution T1-weighted (MP-RAGE) anatomical MRI images were acquired for each participant for use in *anatomically constrained* MEG (*a*MEG) source localization.

MEG Data Analysis

The basic MEG analysis procedure used here is described in detail elsewhere (Dale, Fischl, & Sereno, 1999; Dale & Halgren, 2001; Dale et al., 2000; Liu, Belliveau, & Dale, 1998). In brief, raw MEG data were first downsampled to 200 Hz. Average downsampled MEG waveforms were extracted as a function of a trial's memory status. The average extraction procedure included artifact rejection, wherein trials with blinks or eye movements were excluded before computing the average. To allow for a stable signal, participants with less than 20 events in at least one condition were excluded from analysis. Moreover, due to the modest numbers of events per memory condition, analyses of the retrieval data were performed, collapsed across the two encoding tasks. In doing so, to ensure that the MEG retrieval effects were not confounded with encoding task (due to differences in retrieval performance for Imaged and Read items), a random subset of retrieval events were included in the analysis, thus ensuring an equal number of events from the two encoding tasks contributing to each memory condition (i.e., Item+Source trials consisted of an equal number of Imaged and Read items, etc).

Cortical surfaces were created for each participant by segmenting the T1-weighted anatomical MRI volume into gray and white matter, and defining the border between gray and white matter as the cortical surface. The resulting surfaces were used to constrain the location of dipoles used in the MEG source analysis. To compute the inverse solution, the cortical surface was subsampled into approximately 3000 dipole locations per hemisphere. Each of these dipole locations was then used to calculate the forward solution for three components per dipole (in the x, y, and z directions). These forward solutions were computed using a boundary element model, with the conductivity boundaries derived from the segmented MR images for each participant. The activation at each of these dipole locations was then estimated every 5 ms using a noise-sensitivity normalized, anatomically constrained linear estimation approach to the inverse solution (Dale et al., 2000). The noise covariance was defined as the MEG activity in the 250 ms prior to the presentation of the stimuli, averaged across all conditions. The noise normalization procedure reduces the variability in the point-spread function between dipole locations (Liu, Belliveau, & Dale, 1998), thereby increasing the consistency of spatial resolution of the inverse solution across brain regions.

To initially characterize the spatial specificity of the MEG patterns, using noise estimates we transformed the estimated dipole strengths into dynamic statistical parametric maps (dSPMs) (Dale et al., 2000). These maps indicate the statistical significance of estimated activity at each interval and cortical location averaged across all participants using cortical surface alignment of corresponding anatomical features

(Fischl, Sereno, Tootell, & Dale, 1999). For ROI analyses of the MEG data, which comprise the main analyses, minimum-norm estimates of the current contributions of all dipoles falling within a ROI were averaged and temporally downsampled into 5-ms time bins for each participant. Extracted waveforms for all participants were then submitted to repeated measures ANOVA to assess patterns in the data that were consistent across participants.

Results

Recognition Performance

Behavioral effects were considered reliable at an α-level of 0.05. Recognition response probabilities differed across Memory condition (Item+Source, Item Only, and FAs) for Imaged ($\underline{F}(2,18) = 16.37$) and Read trials ($\underline{F}(2,18) = 4.84$) (**Figure 1D**). Item recognition with source recollection (Item+Source) was greater than recognition without recollection (Item Only) and the corresponding FA rate (Imaged, $\underline{F}s(1,9) > 24.50$; Read, $\underline{F}s(1,9) > 7.02$). Item Only recognition levels for Imaged (.41) and Read trials (.37) were higher than the corresponding FA rate (Imaged, $\underline{F}(1,9) = 13.27$; Read, $\underline{F}(1,9) = 9.58$), when correcting for the opportunity to make such a response (Kahn, Davachi, & Wagner, 2004; Yonelinas & Jacoby, 1995). Finally, corrected recognition (collapsed across Item+Source and Item Only trials) was superior after Imaged (0.48) than after Read encoding (0.34) ($\underline{F}(1,9) = 13.61$), and recognition with recollection (Item+Source) was superior after Imaged than after Read encoding ($\underline{F}(1,9) = 17.63$). These differences in memory performance for the Imaged and Read encoded items motivated our subsampling the retrieval data for MEG analysis, thus ensuring that each of the critical memory conditions for studied items (Item+Source, Item Only, and Misses) contained an equivalent number of Imaged and Read items.

Reaction times (RTs) (**Figure 1E**), analyzed using a two-way ANOVA with factors of Encoding task (Imaged, Read, New) and Response type (Old-Imaged, Old-Read, New), revealed a main effect of Response type (F(2,18) = 4.52). RTs were faster for New (1496 ms) compared with Old-Read responses (1680 ms) (F(1,9) = 9.02), but did not reliably differ when comparing Old-Imaged (1595 ms) to New or Old-Read responses (Fs(1,9) < 2.58). The effect of Encoding task was not reliable (F < 1.50), though there was a reliable Encoding task × Response type interaction (F(4,36) = 4.24).

To explore the interaction, RTs were analyzed separately by encoding task. RTs differed across Memory condition (Item+Source, Item Only, Miss, and FA) for Imaged (F(3,27) = 3.05) and Read trials (F(3,27) = 4.64). For Imaged words, RTs were reliably faster for Item+Source compared with Item Only and with FA trials accompanied by the erroneous claim that the novel item had been imaged (FA–Imaged; Fs(1,9) > 5.19). RTs also revealed a trend for faster responses on Miss relative to Item Only trials (F(1,9) = 3.46, $p_{\text{H-F}} = .08$) and relative to FA–Imaged trials (F(1,9) = 3.84, $p_{\text{H-F}} < .07$). For Read words, RTs were reliably faster on Item+Source compared with Miss trials (F(1,9) = 6.82) and on Miss compared with FA–Read trials (F(1,9) = 6.41). There also was a trend for Misses to be faster than Item Only trials (F(1,9) = 3.40, $p_{\text{H-F}} < .09$), whereas Item+Source and Item Only trials did not differ (F < 1).

Spatiotemporal Correlates of Episodic Retrieval

MEG data were analyzed using each participant's cortical anatomy, obtained from MRI, to constrain the localization of electromagnetic sources recorded at scalp locations (Dale, Fischl, & Sereno, 1999; Dale et al., 2000). To be explicit, fMRI data did not contribute to the source solution. To initially characterize the spatial specificity of the MEG patterns, using noise estimates we transformed the estimated dipole strengths into dynamic statistical parametric maps (dSPMs) (Dale et al., 2000). These maps indicate the statistical significance of estimated activity at each interval and cortical location averaged across all participants using cortical surface alignment of corresponding anatomical features (Fischl, Sereno, Tootell, & Dale, 1999).

As a first step in the analysis, for each 150-ms temporal interval, an average of the statistic across participants was computed for the comparison of all retrieval trials relative to the pre-trial baseline. This analysis served to reveal regions sensitive to performance of the retrieval task, irrespective of memory status, thresholded at $p < 10^{-9}$ (**Figure 2**). The resulting group maps revealed initial responses emerging around 150–300 ms post-stimulus onset, inclusive of bilateral occipital regions and lateral and medial temporal cortices. Importantly, for present purposes, activity extended to include left medial and lateral parietal regions beginning around 300–450 ms. This response appeared to remain robust in the anterior portion of intraparietal sulcus and in medial parietal regions through approximately 750–900 ms, whereas the response in posterior intraparietal sulcus extended through the 1050–1200 ms interval. A later onsetting response, from approximately 600–1200 ms, was also observed in left middle frontal cortex.

Parietal Regions of Interest

Motivated by the dSPM patterns, targeted analyses adopted a region-of-interest (ROI) approach to assess whether the *a*MEG activity source-localized to lateral and medial parietal regions varied according to the mnemonic status of the recognition trial. ROIs were defined based on the above-threshold activity in the dSPMs at specific temporal intervals, using the dSPM of all retrieval trials vs. baseline to define the areal boundary of each ROI. The temporal intervals used to define the ROIs were chosen by qualitatively identifying the 150-ms interval with the most robust retrieval-related activity for each region. Note that this qualitative approach is unbiased with respect to memory condition, and thus does not prejudice the outcomes of the resulting ROI analyses.

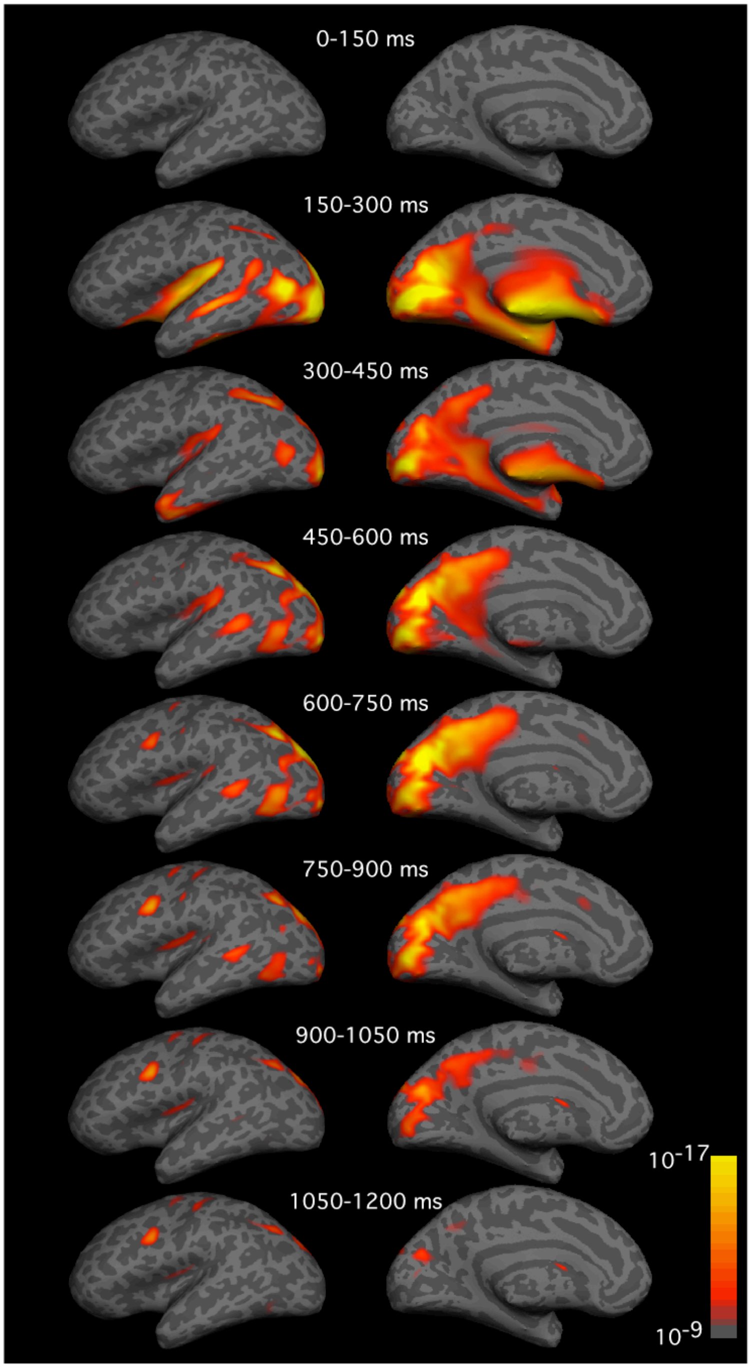

Figure 2. Group average dynamic statistical parametric maps (dSPMs) of estimated responses to episodic retrieval for the left hemisphere. An average of the statistic across participants was computed for the comparison of all retrieval trials relative to the pre-trial baseline for each 150-ms temporal interval, revealing regions sensitive to performance of the retrieval task, irrespective of memory status. The group dSPMs reveal initial responses emerging around 150-300 ms post-stimulus onset, inclusive of bilateral occipital regions and lateral and medial temporal cortices, with activity extending to include left medial and lateral parietal regions beginning around 300-450 ms. This response appeared to remain robust in the anterior portion of intraparietal sulcus and in medial parietal regions through approximately 750-900 ms, whereas the response in posterior intraparietal sulcus extended through the 1050-1200 ms interval. A later onsetting response, from approximately 600-1200 ms, was also observed in left middle frontal cortex.

Left lateral parietal ROIs were defined that corresponded to the posterior and anterior extents of the intraparietal sulcus (IPS; **Figure 3A**). These ROIs were defined based on the IPS activation at 300–450 ms, which was then divided into posterior and anterior portions by marking the anterior border of IPS activity on the 750–900 ms dSPM. Left medial parietal ROIs were defined to include retrosplenial, precuneus, and posterior cingulate foci (**Figure 4A**). These medial ROIs were defined by first demarcating the activation present on the medial wall of the left hemisphere at 600–750 ms. Subsequently, this medial region was subdivided into retrosplenial and precuneus areas by splitting the subparietal sulcus into dorsal and ventral portions. The precuneus ROI was then differentiated from the posterior cingulate ROI based on the border of the posterior cingulate sulcus immediately caudal to the marginal segment. Having defined these five parietal ROIs, the contribution of the dipoles within each ROI to the recorded MEG signals were computed, and the extracted MEG current estimates, averaged across dipoles within each ROI, were submitted to ANOVA.

Lateral Parietal Old–New Effects

Current estimates from the parietal ROIs were assessed for the presence of differential responses to old (hits) and new (CRs) recognition trials (old–new effects). Motivated by the onset and offset of retrieval-related activity in the dSPMs, and by *a priori* expectation that distinct recollection-sensitive and recollection-insensitive activation patterns would be obtained across parietal regions, two ANOVAs were computed on the current estimates (integrated across each 150-ms interval) with factors of Memory condition and Time epoch. The first ANOVA targeted old–new effects, comparing Hits (collapsed across Item+Source and Item Only) with CRs. The second ANOVA, designed to test whether old–new effects were influenced by source recollection, compared Item+Source, Item Only, and CR trials. For both analyses, the Time epochs covered the 300–900 ms or 300–1200 windows in 150-ms intervals, depending on the ROI. Anticipating the results, two classes of parietal regions were revealed: those showing an old–new effect sensitive to source recollection and those showing an old–new effect insensitive to recollection.

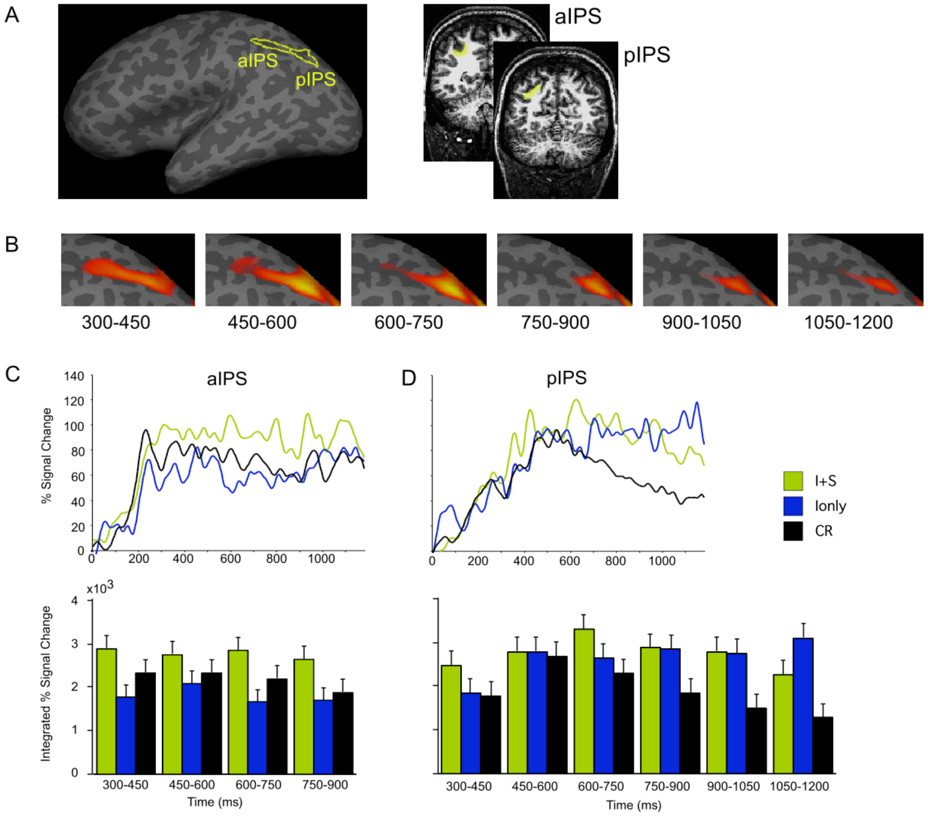

Figure 3. Lateral parietal old–new effects. *A*. Left lateral parietal targeted regions on interest (ROIs) were defined within the intraparietal sulcus (IPS) that corresponded to the anterior IPS (aIPS) and posterior IPS (pIPS). *B*. Group average dynamics statistical parametric maps (dSPMs) in the IPS between 300-1200 ms. The lateral parietal ROIs were defined based on the IPS activation at 300-450 ms, which was then divided into posterior and anterior portions by marking the anterior border of IPS activity on the 750-900 ms dSPM. *C,D*. Current estimates derived from the aIPS and pIPS ROIs. Data are shown as percent change from the average pre-stimulus baseline as a function of time, in 5 ms increments (smooth with a Gaussian kernel–25 ms FWHM–for presentation purposes). Integrated current estimated from aIPS and pIPS in the 300-900, and 300-1200, respectively, revealed an old–new effect that was sensitive to recollection in aIPS but not in pIPS.

Given the extended retrieval-related sensitivity of posterior IPS (pIPS) in the dSPMs (**Figures 2A**, **3B,** and **3D**), current estimates in this ROI were considered over the 300-to-1200 ms period. Current estimates in pIPS showed an old–new effect, as revealed by a main effect of Memory condition (Hits > CR: $\underline{F}(1,9) = 5.15$, $p_{\text{H-F}} < .05$). Unpacking this main effect by Time epoch, analyses revealed reliable differences at 750–900, 900–1050, and 1050–1200 ($\underline{F}s(1,9) > 8.58$, $ps_{\text{H-F}} < .05$), with there being a trend for a difference at 600–750, ($\underline{F}(1,9) = 3.78$, $ps_{\text{H-F}} < .1$) (**Figure 3D**).

While demonstrating an old–new effect, the differential response to hits in pIPS was not modulated by recollection success. Indeed, ANOVA revealed a non-significant effect of Memory condition when hits were decomposed according to recollection status (Item+Source, Item Only, and CR; $p_{\text{H-F}} > .14$). Moreover, consideration of the waveforms (**Figure 3D**) suggested that the response in pIPS was similar during Item+Source and Item Only trials, but with activation on the Item Only trials being temporally shifted relative to activation on Item+Source trials. Consistent with this interpretation, comparison of Item+Source, Item Only, and CR activation during the 600–750 and 1050–1200 intervals revealed a reliable Memory × Time interaction ($\underline{F}(2,18) = 4.15$, $p = .05$). This interaction reflected the cross-over activation pattern for Item+Source and Item Only trials during these intervals: (a) during the 600–750 interval, Item+Source differed from CR trials ($\underline{F}(1,9) = 5.97$, $p_{\text{H-F}} < .05$) but Item Only did not differ from CR trials ($\underline{F} < 1.0$), whereas (b) during the 1050–1200 interval, Item+Source and Item Only both differed from CR trials ($\underline{F}s(1,9) > 5.45$, $ps_{\text{H-F}} < .05$) with Item Only being marginally greater than Item+Source ($\underline{F}(1,9) = 4.04$, $p_{\text{H-F}} < .08$). Given the longer RTs on Item Only trials than on Item+Source trials, one interpretation is that a similar pIPS response was present across these two classes of hits, but with the response on Item Only trials being temporally delayed relative to that on Item+Source trials. This delay suggests that the response may be related to mnemonic monitoring or decision processes (see Discussion). Collectively, these analyses indicate that pIPS demonstrated old–new effects that reliably onset by 600–750 ms, with these effects being insensitive to source recollection.

In contrast to the extended retrieval-related response in pIPS, activation in anterior IPS (aIPS) appeared temporally more restricted in the dSPMs (**Figures 2A** and **3B**). Accordingly, current estimates in aIPS were considered over the 300-to-900 ms interval (**Figure 3C**). Consideration of the aIPS current estimates, when collapsing Hits across recollection status, failed to reveal a main effect of Memory condition (Hits and CR) or a Memory condition × Time epoch (300-to-900) interaction ($\underline{F}$s < 1). However, when hits were sorted according to recollection status (Item+Source, Item Only, and CR), aIPS showed a reliable effect of Memory condition ($\underline{F}(2,18) = 4.63$, $p_{\text{H-F}} < .05$). Unpacking this effect by Time epoch revealed reliably greater responses during Item+Source than during Item Only trials at 300–450, 600–750, and 750–900 ($\underline{F}\text{s}(1,9) > 8.48$, $p\text{s}_{H\text{-}F} < .05$), and a trend at 450–600 ($\underline{F}(1,19) = 4.16$, $p_{\text{H-F}} < .07$) (**Figure 3C**). Comparison of Item+Source to CR revealed a trend for a difference at 600–750 ($\underline{F}(1,9) = 4.40$, $p_{H\text{-}F} = .06$) and a reliable difference at 750–900 ($\underline{F}(1,9) = 5.45$, $p_{\text{H-F}} < .05$); Item Only and CR trials did not reliably differ at any interval ($p\text{s}_{\text{H-F}} > .11$). Thus, in contrast to pIPS, aIPS showed a difference during recognition accompanied with versus without source recollection that onset by 300–450 ms.

Consideration of the data in Figure 3C-D suggests that both aIPS and pIPS showed an early onsetting response (300–450 ms) that was sensitive to recollection, with this pattern being maintained in aIPS for the subsequent 450 ms whereas this pattern diverged to a recollection-insensitive effect in pIPS during this subsequent period. To assess whether the response patterns in pIPS and aIPS reliably differed, a three-way ANOVA was conducted with factors of ROI (pIPS and aIPS), Memory Condition (Item+Source, Item Only, and CR), and Time epoch (300-to-1200). This analysis revealed a marginally significant ROI × Memory Condition interaction ($F(2,18) = 3.37$, $p_{\text{H-F}} < .06$). Critically, pIPS showed no reliable difference between Item+Source relative to Item Only ($F < 1$) and a reliable difference between both Item+Source and Item Only relative to CR ($F\text{s}(1,9) > 7.49$, $p\text{s}_{\text{H-F}} < .05$), whereas aIPS showed a reliable difference between Item+Source relative to both Item Only and CR ($F\text{s}(1,9) > 4.97$, $p\text{s}_{\text{H-F}} < .05$) and no difference between Item Only and CR ($F < 1$). These data indicate that pIPS showed an old–new effect insensitive to recollection, whereas aIPS showed a recollection-selective effect.

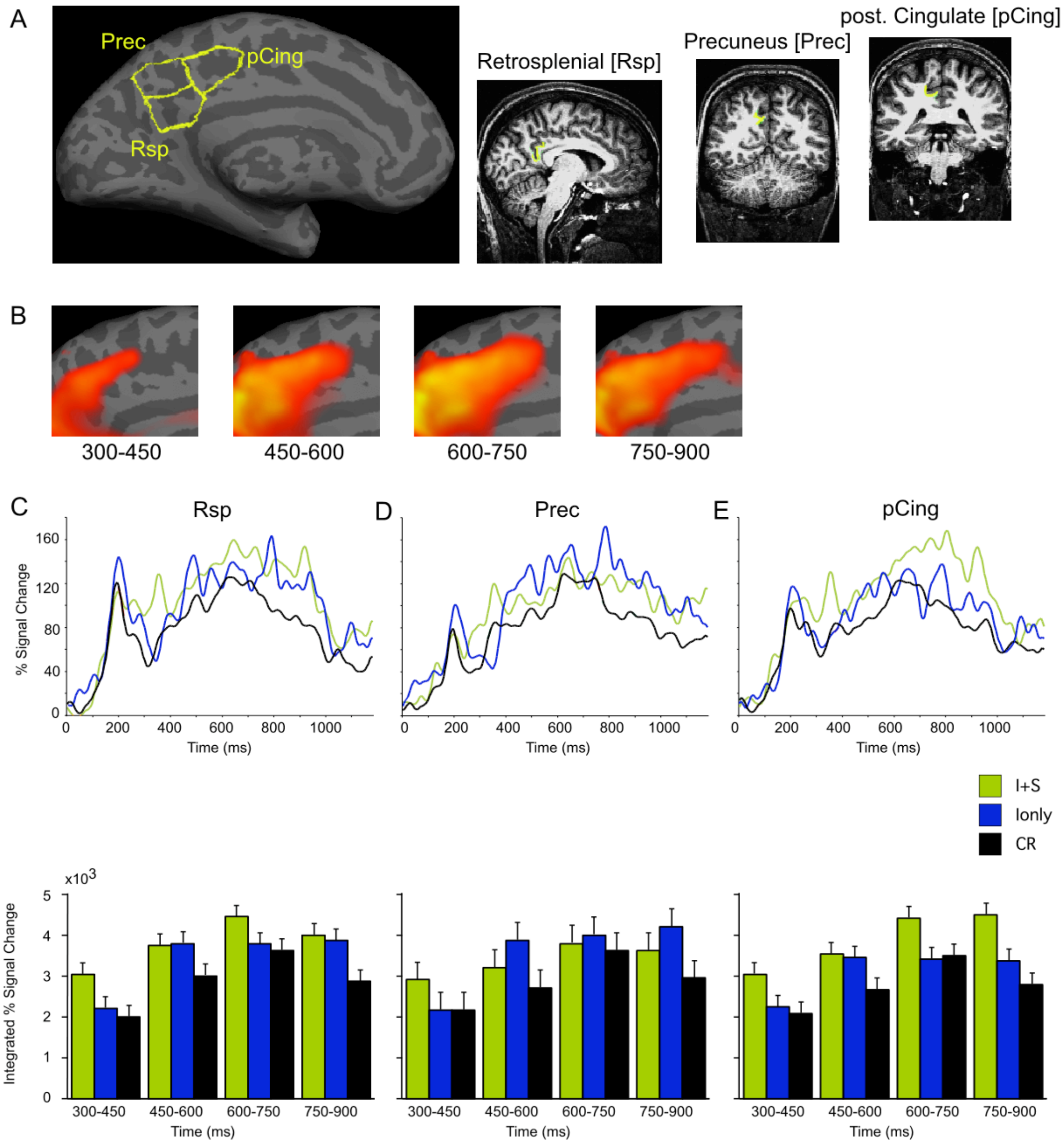

Figure 4. Medial parietal old–new effects. *A*. Left medial parietal targeted regions of interest (ROIs) were defined to include retrosplenial (Rsp), precuneus (Prec), and posterior cingulate (pCing) foci. *B*. Group average dynamics statistical parametric maps (dSPMs) in medial parietal between 300-900 ms. The medial ROIs were defined by first demarcating the activation present on the medial wall of the left hemisphere at 600-750 ms. Subsequently, this medial region was subdivided into retrosplenial and precuneus areas by splitting the subparietal sulcus into dorsal and ventral portions. The precuneus ROI was then differentiated from the posterior cingulate ROI based on the border of the posterior cingulate sulcus immediately caudal to the marginal segment. *C-E*. Current estimates derived from the Rsp, Prec and pCing ROIs. Data are shown as percent change from the average pre-stimulus baseline as a function of time, in 5 ms increments (smooth with a Gaussian kernel–25 ms FWHM–for presentation purposes). Integrated current estimates from Rsp, Prec, and pCing in the 300-900 ms time window, revealed an old–new effect that was sensitive to recollection in pCing but not in Rsp and Prec.

Medial Parietal Old–New Effects

The dSPMs suggest that medial parietal regions, including retrosplenial, precuneus, and posterior cingulate cortices, showed retrieval sensitivity during the 300–900 ms interval (**Figures 2B** and **4B**). Considering the retrosplenial ROI, an ANOVA with factors of Memory condition (Hits and CR) and Time epoch (300-to-900) revealed a reliable old–new effect ($F(1,9) = 6.84$, $p_{\text{H-F}} < .05$) (**Figure 4C**). Unpacking this main effect of Memory condition according to Time epoch, analyses revealed a reliable difference between Hits and CR at 450–600 and 750–900 ms ($Fs(1,9) > 5.78$, $ps_{\text{H-F}} < .05$), and a trend for a difference at 300–450 ms ($F(1,9) = 3.83$, $p_{\text{H-F}} < .08$). When Hits were sorted according to recollection outcome (Item+Source, Item Only, and CR), there was a trend for an effect of Memory condition ($F(2,18) = 3.20$, $p_{\text{H-F}} < .07$), which reflected a reliable difference between Item+Source and CR ($F(1,9) = 6.36$, $p_{\text{H-F}} < .05$), but no difference between Item Only and Item+Source or CR ($ps_{\text{H-F}} > .17$). Supplemental analyses revealed a reliable difference between Item+Source relative to CR ($F(1,9) = 7.57$, $p_{\text{H-F}} < .05$) and relative to Item Only ($F(1,9) = 4.97$, $p_{\text{H-F}} = .05$) at 300–450. By contrast, at 750–900 Item+Source reliably differed from CR ($F(1,9) = 9.04$, $p_{\text{H-F}} < .05$) but not from Item Only ($F < 1$), and Item Only reliably differed from CR ($F(1,9) = 6.82$, $p_{\text{H-F}} < .05$). Thus, while retrosplenial cortex showed an old–new effect that onset by 300–450 ms and was predominantly insensitive to recollection, at the earliest interval (300–450) this region showed a recollection-selective response. The precuneus ROI (**Figure 4D**), examined by ANOVA with factors of Memory condition (Hits and CR) and Time epoch (300-to-900), showed an old–new effect ($F(1,9) = 6.18$, $p_{\text{H-F}} < .05$). Unpacking this effect by Time epoch revealed a trend for a Hits > CR difference at 450–600 ($F(1,9) = 4.77$, $p_{\text{H-F}}$

$< .06$) and a reliable difference at 750–900 ($\underline{F}(1,9) = 6.83$, $p_{\text{H-F}} < .05$). However, when the precuneus response was analyzed in relation to recollection outcome (Item+Source, Item Only, and CR), the effect of Memory condition was not reliable ($p_{\text{H-F}} > .28$). Thus, the precuneus ROI showed an old–new effect that was insensitive to source recollection.

Turning to the posterior cingulate ROI (**Figure 4E**), current estimates showed an old–new effect, as revealed by a main effect of Memory condition (Hits > CR: $\underline{F}(1,9) = 15.04$, $p_{\text{H-F}} < .01$). Unpacking this main effect by Time epoch, analyses revealed reliable differences at 450–600 and 750–900 ($\underline{F}s(1,9) > 7.65$, $ps_{\text{H-F}} < .05$), and a trend for a difference at 300–450 ($\underline{F}(1,9) = 3.55$, $p_{\text{H-F}} < .08$). When Memory condition was sorted according to recollection outcome (Item+Source, Item Only, and CR), again there was an effect of Memory condition ($\underline{F}(2,18) = 8.74$, $p_{\text{H-F}} < .005$). Unpacking this effect revealed a reliable difference between Item+Source and Item Only trials at 600–750 and 750–900 ($\underline{F}s(1,9) > 6.33$, $\text{ps}_{H\text{-}F} < .05$), and a trend for a difference at 300–450, ($\underline{F}(1,9) = 3.96$, $p_{\text{H-F}} < .08$). Moreover, comparison of Item+Source to CR revealed reliable differences at 300–450, 600–750, and 750–900 ($\underline{F}s(1,9) > 5.29$, $ps_{H\text{-}F} < .05$), and a trend at 450–600 ($\underline{F}(1,9) = 4.55$, $p_{\text{H-F}} < .06$). Comparing Item Only to CR revealed a trend for a difference at 450–600 ($\underline{F}(1,9) = 3.79$, $p_{\text{H-F}} < .08$), but no other effects ($ps_{\text{H-F}} > .16$). Collectively, in contrast to the retrosplenial and precuneus ROIs, these analyses indicate that the mnemonic response in posterior cingulate was predominantly sensitive to recollection success.

To assess whether medial parietal response patterns reliably differed across these ROIs, a three-way ANOVA was conducted with factors of ROI (retrosplenial, precuneus, and posterior cingulate), Memory condition (Item+Source, Item Only, and CR), and Time epoch (300-to-900). This analysis did not reveal reliable ROI × Memory or ROI × Memory × Time interactions ($ps_{\text{H-F}} > .36$). Thus, while it appears that posterior cingulate was differentially responsive to recollection outcome whereas retrosplenial and precuneus cortices were sensitive to recognition independent of recollection, strong conclusions about functionally distinct responses across medial parietal regions cannot be drawn based on these analyses.

Actual or Perceived Oldness

For the parietal regions showing old–new effects that were insensitive to recollection outcome (i.e., pIPS, retrosplenial, and precuneus), the data discussed up to this point cannot distinguish between whether these old–new effects reflect correlates of the conscious perception that a test probe is old or correlates of non-conscious (implicit) memory consequences of past encounter (e.g., priming). To the extent that the old–new effects track conscious perception that a test probe was old, then we would expect that studied items not recognized as old (Misses) would elicit activation similar to novel items classified as novel (CRs), with Miss activation also being weaker than that for recognized items (e.g., Item+Source trials). By contrast, if the observed old–new effects reflect implicit memory phenomena, then greater parietal responses should be seen for Misses relative to CRs.

To test these two possibilities, for each of the five parietal ROIs, current estimates during Miss and CR trials were contrasted using ANOVA, with factors of Memory condition (Miss and CR) and Time epoch (300-to-900 or 300-to-1200, per the old–new contrasts). Critically, none of the ROIs showed a reliable effect of Memory condition nor an interaction ($ps_{\text{H-F}} > .19$) (**Figure 5**). Moreover, more directed consideration of the responses at particular time intervals revealed a limited set of reliable effects, with activation being greater for CR relative to Miss in the aIPS between 450–600, 600–750, and 750–900 ($Fs(1,9) > 6.51$, $ps_{\text{H-F}} < .05$); no other effects were reliable at any medial or lateral ROI. Collectively, these results argue strongly against the interpretation that the observed parietal old–new effects reflect non-conscious consequences of past encounter, supporting instead the conclusion that parietal activation tracks either perceived item familiarity or successful context recollection (depending on the region).

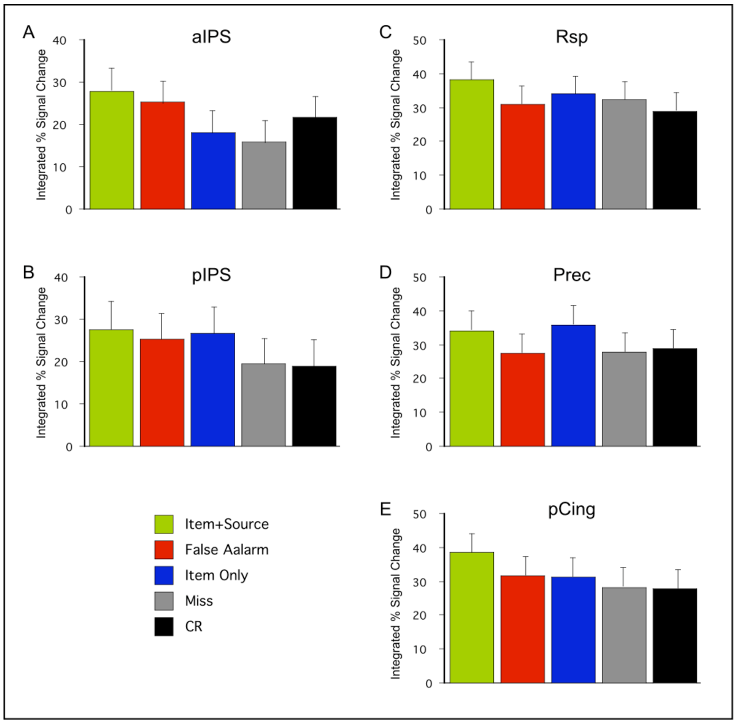

Figure 5. Left lateral and medial parietal regions showing an old–new effect in targeted regions of interest. *A-E.* Current estimated derived from anterior and posterior intraparietal sulcus (aIPS, and pIPS), as well as retrosplenial (Rsp), precuneus (Prec), and posterior cingulate (pCing), is depicted for perceived old items (Item+Source, False alarm, Item only) and perceived new (Miss, and CR).

To assess whether the parietal old–new effects generalize to comparisons of recognized studied items (e.g., Item+Source trials) with unrecognized studied items

(Misses), we conducted ANOVAs with factors of Memory condition (Miss and Item+Source) and Time epoch. These analyses revealed a main effect of Memory condition in aIPS ($\underline{F}(1,9) = 5.11$, $p_{H\text{-}F} = .05$), with there being a greater response for Item+Source relative to Miss trials at 300–450, 450–600, 600–750, and 750–900 ($\underline{F}s(1,9) > 5.38$, $ps_{H\text{-}F} < .05$) (**Figure 5**). The pIPS region demonstrated a Memory × Time interaction ($\underline{F}(5,45) = 2.73$, $p_{H\text{-}F} < .05$), with a reliably greater response to Item+Source relative to Miss trials at 600–750, 750–900, 900–1050, and 1050–1200 ($\underline{F}s(1,9) > 5.20$, $ps_{H\text{-}F} < .05$). Consideration of the medial parietal ROIs revealed no reliable main effects nor interactions for the retrosplenial and precuneus regions ($ps_{H\text{-}F} > .2$), nor did Item+Source and Miss trials differ at any of the targeted temporal intervals ($ps_{H\text{-}F} > .15$). In contrast, the posterior cingulate ROI demonstrated a reliable Memory effect ($\underline{F}(1,9) = 8.18$, $p_{H\text{-}F} < .05$), with a trend for a difference at 300–450 ($\underline{F}(1,9) = 3.11$, $p_{H\text{-}F} < .1$) and reliable differences at 600–750 and 750–900 ($\underline{F}s(1,9) > 10.32$, $ps_{H\text{-}F} < .01$). Together with the preceding comparisons of Misses to CRs, these differences between Item+Source and Miss trials at lateral and medial parietal regions indicate that Misses track CRs rather than hits. The implication of these outcomes is that parietal activation tracks memory perception rather than the actual memory history of a test probe.

*Parietal Responses During False Alarms*

Parietal responses during false recognition (i.e., endorsing a novel item as old; FA) may serve to reveal whether FAs are sometimes accompanied by recollection or whether they entirely reflect above-criterion familiarity (e.g., Kahn, Davachi, & Wagner, 2004; Slotnick & Schacter, 2004). Leading models of recognition memory assume that FAs are based exclusively on recognition without recollection (i.e., above-criterion familiarity) (Jacoby, 1991; Wixted & Stretch, 2004; Yonelinas, Dobbins, Szymanski, Dhaliwal, & King, 1996). We tested this assumption by considering the current estimates during FAs in parietal regions showing an old–new effect that tracks recollection. To the extent that FAs are recollection-free, the current estimates in these regions during FAs should fail to differ from the response to Item Only trials. By contrast, if FAs are sometimes accompanied by misbound/illusory recollection, then their current estimates should track those of Item+Source trials, being greater than activation during Item only trials.

For the two parietal regions showing recollection-sensitivity (aIPS and posterior cingulate), sensitivity to false recollection was tested using an ANOVA with factors of Memory condition (Item+Source, Item only, and FA) and Time epoch (300-to-900). Current estimates in the aIPS ROI revealed a main effect of Memory condition ($\underline{F}(2,18) = 5.61$, $p_{\text{H-F}} < .05$), wherein there were reliable differences between Item+Source and Item only trials ($\underline{F}(1,9) = 10.40$, $p_{\text{H-F}} < 05$) and between FA and Item only trials ($\underline{F}(1,9) = 5.73$, $p_{\text{H-F}} < .05$), but no difference between Item+Source and FA ($\underline{F} < 1$) (**Figure 5A**). Supplementary analyses comparing FA and Item Only responses revealed reliable differences at 300–450, 600–750, and 750–900 ($\underline{F}\text{s}(1,9) > 9.42$, $p\text{s}_{\text{H-F}} < .01$) and a trend for a difference at 450–600 ($\underline{F}(1,9) = 3.02$, $p_{\text{H-F}} < .1$). Finally, comparison of Item+Source to FA revealed no reliable differences at any of the time intervals ($p\text{s} > .17$). Accordingly, in aIPS, the response to FA resembled that of recognition accompanied by recollection (Item+Source) as opposed to recognition based solely on familiarity (Item Only).

In contrast to aIPS, a similar analysis of the current estimates in posterior cingulate failed to reveal a main effect of Memory or an interaction ($ps_{H\text{-}F} > .18$) (**Figure 5E**). Thus, while both aIPS and posterior cingulate demonstrated a recollection-selective response when comparing Item+Source to Item Only trials, only the former region provided evidence for a recollection-like pattern during FAs. The nature of this divergence in the pattern of response to FAs across these lateral and medial regions remains unclear at present. One possibility is that, in general, the magnitude of the old–new effects at medial parietal regions were qualitatively more modest than those at lateral parietal regions, perhaps making it more difficult to find a difference between FA and Item Only trials in medial regions. Consistent with this possibility, when FA were compared to Hits and CRs in regions showing recollection-insensitive old–new effects, FAs clearly tracked Hits in pIPS (i.e., FA > CR; **Figure 5B**) but did not track Hits or differ from CR in retrosplenial and precuneus regions (**Figure 5C-D**).

Discussion

PET and fMRI studies have demonstrated that episodic retrieval is accompanied by activation in left lateral and medial parietal structures when comparing *old* (hits) to *new* (CR) items during recognition, with such findings appearing consistent with ERP data revealing differential old–new responses at parietal electrode sites (for reviews see, Rugg & Allan, 2000; Wagner, Shannon, Kahn, & Buckner, 2005). The present results advance understanding of these parietal mnemonic responses in three important ways. First, the present findings begin to bridge the gap between fMRI observations of functionally distinct subregions within the parietal lobe that are differentially sensitive to recollection success and perceived familiarity (Wheeler & Buckner, 2004; Yonelinas, Otten, Shaw, & Rugg, 2005), and ERP observations of parietal old–new effects that are sensitive primarily to recollection (e.g., Duzel, Yonelinas, Mangun, Heinze, & Tulving, 1997; Paller & Kutas, 1992; Rugg et al., 1998; Smith, 1993; Trott, Friedman, Ritter, Fabiani, & Snodgrass, 1999; Wilding, Doyle, & Rugg, 1995; Wilding & Rugg, 1996). Our data indicate that distinct MEG responses, source localized to subregions of lateral and medial parietal cortex, can functionally dissociate. In particular, while the aIPS and posterior cingulate demonstrated an old–new effect that was selective to recollection, paralleling earlier observations with ERP, the pIPS, retrosplenial, and precuneus regions demonstrated an old–new effect that was insensitive to recollection. These data are broadly consistent with fMRI observations suggesting that multiple memory-sensitive subdivisions exist within the left parietal lobe. Second, we considered whether the old-new effects in regions showing recollection insensitivity are due to implicit memory processes (i.e., priming) or explicit awareness of past stimulus encounter. Results revealed that the memory effects in pIPS do not reflect implicit processes, but rather depend on conscious perception that the stimulus is familiar. Finally, consideration of the current estimates in aIPS revealed evidence that parietal responses during false alarms resemble those during veridical recognition accompanied by recollection, complementing prior fMRI data suggesting that false recognition is based partially on illusory recollection.

Parietal Correlates of Recollection

ERP old–new effects at parietal sensors track recollection (e.g., Duzel, Yonelinas, Mangun, Heinze, & Tulving, 1997; Paller & Kutas, 1992; Rugg et al., 1998; Smith, 1993; Trott, Friedman, Ritter, Fabiani, & Snodgrass, 1999; Wilding, Doyle, & Rugg, 1995; Wilding & Rugg, 1996), although the anatomical sources of these effects have been unclear due to the limited spatial resolution of EEG. The present anatomically constrained MEG data provide novel evidence suggesting that old–new effects that track recollection may emerge from aIPS and posterior cingulate.

The pattern observed in the aIPS demonstrated a relatively early onsetting (300-450 ms) old–new effect that was sensitive to recollection, with this effect extending for approximately 600 ms. Similarly, the posterior cingulate cortex demonstrated a sensitivity to recollection that was most prominent between 600-900 ms, though this response also tended to onset as early as 300-450 ms. These recollection-selective old–new effects correspond temporally to the well-documented ERP parietal old–new effect that emerges at approximately 400 ms and extends for 400-600 ms (e.g., Duzel, Yonelinas, Mangun, Heinze, & Tulving, 1997; Paller & Kutas, 1992; Rugg et al., 1998; Smith, 1993; Trott, Friedman, Ritter, Fabiani, & Snodgrass, 1999; Wilding, Doyle, & Rugg, 1995; Wilding & Rugg, 1996). Though MEG and EEG index partially complementary sources (see below for further discussion), the qualitative similarities between the present MEG responses and these prior ERP old–new effects provide suggestive evidence that neural sources for the ERP effects may indeed originate in lateral and/or medial parietal regions.

Parallels also exist between the present MEG responses in aIPS and posterior cingulate and prior fMRI measures of retrieval-related parietal activation. In particular, the present measures of aIPS activation converge with fMRI data showing parietal sensitivity to recollection, as evidenced by greater activation during Source-Hits compared to Source-Misses (Dobbins, Rice, Wagner, & Schacter, 2003; Herron, Henson, & Rugg, 2004). This fMRI source recollection effect was observed in left parietal cortex, just superior and anterior to the IPS. Given constraints on the spatial resolution of MEG, it is possible that the present aIPS observations have a similar parietal source as these earlier fMRI findings. Medially, our MEG observed posterior cingulate pattern is consistent with multiple fMRI studies demonstrating a recollection-sensitive pattern in the posterior cingulate (Eldridge, Knowlton, Furmanski, Bookheimer, & Engel, 2000; Henson, Rugg, Shallice, Josephs, & Dolan, 1999; Wheeler & Buckner, 2004; Yonelinas, Otten, Shaw, & Rugg, 2005).

Recent fMRI studies have also revealed a recollection-sensitive response in inferior parietal lobule—lateral and ventral to the IPS—as evidenced by greater activation when comparing “remember” to “know” responses or “remember” to high-confidence “know” responses (Wheeler & Buckner, 2004; Yonelinas, Otten, Shaw, & Rugg, 2005). As illustrated in Figure 3, consideration of the dSPMs of retrieval-related activation failed to reveal an MEG marker of episodic retrieval performance in parietal cortex lateral and inferior to the IPS. Given that MEG is differentially sensitive to sources that are parallel to the scalp, it is possible that the present study lacked sensitivity to detect signals arising from inferior parietal lobule.

Parietal Correlates of Perceived Familiarity

Recent fMRI studies have observed additional lateral and medial parietal regions that show old–new effects that track the perception that the test probe is old or familiar, independent of recollection outcome. In particular, the IPS was observed to respond similarly to "remember" and "know" responses as compared with CR (Wheeler & Buckner, 2004), and to not differentiate between "remember" responses and high confidence "know" responses (Yonelinas, Otten, Shaw, & Rugg, 2005). The present pattern in pIPS would appear to parallel these earlier fMRI finding. In particular, the pIPS demonstrated an old–new effect that did not track recollection, with this response reliably onsetting at 600-750 ms and extending for another 450-to-600 ms.

The pattern observed in retrosplenial cortex and precuneus appeared to differ from that observed in the posterior cingulate (though reliable memory × region interactions were not obtained, and thus interpretative caution is warranted). Both the retrosplenial cortex and precuneus demonstrated an old–new effect that was insensitive to source recollection, with the exception that the retrosplenial ROI also demonstrated an early onsetting (300-450 ms) sensitivity to recollection that was not sustained in later intervals. In an fMRI variant of this paradigm (Chapter 3), we observed activation in the precuneus for Hits relative to CR. While spatially neighboring, the locus of this fMRI precuneus effect does not appear to overlap with the precuneus ROI observed presently (**Figure 6A**). Again, this modest divergence could reflect differences in the spatial resolutions of the imaging methods and/or with between-group anatomical or functional variance. Interestingly, a recent multi-study conjunction analysis computed from seven fMRI studies (Wagner, Shannon, Kahn, & Buckner, 2005) revealed a precuneus locus that shows better overlap with the present MEG responses, suggesting that any divergence with our prior fMRI study may be more apparent than real (**Figure 6B**). Consistent with this interpretation, the present recollection-insensitive old–new effects in medial parietal regions converge with (a) a recent fMRI study by Yonelinas et al. (2005) observing a recollection-insensitive old–new response in precuneus, and (b) a fMRI-identified region reported by Henson et al. (1999), near the retrosplenial and precuneus ROIs explored presently, that was more active for "know" than for "remember" responses. The present MEG results add to these fMRI observations by demonstrating that an early component of this medial parietal response may be sensitive to recollection, with posterior medial parietal activation then been predominantly non-selective for recollection in the 450-to-900 ms interval.

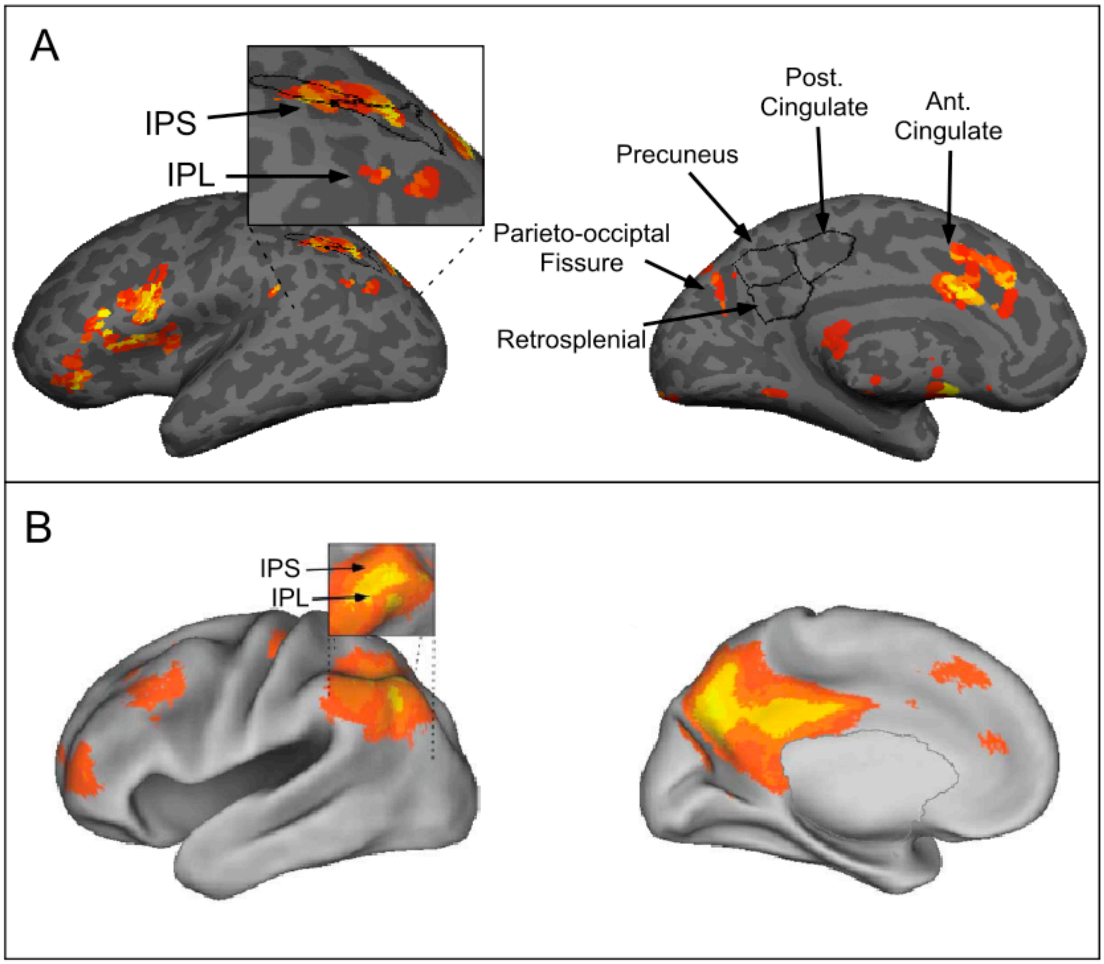

Figure 6. Convergence across fMRI and MEG of parietal old–new responses. *A*. Left parietal cortex showing an old–new effect in the fMRI version of the present experiment (Kahn et al., 2004), with MEG targeted regions of interest including anterior and posterior intraparietal sulcus (aIPS, and pIPS), as well as retrosplenial (Rsp), precuneus (Prec), and posterior cingulate (pCing). *B*. Convergence analysis of the old–new effect reproduced from Wagner, Shannon, Kahn, and Buckner (2005). Consistent old–new effects are plotted based on their reproducibility across studies. Old–new effects were identified at a threshold of $p <$ .001 in seven separate event-related fMRI contrasts. All contain direct comparisons of hits and correct rejects (CR) during recognition tasks. Voxels independently significantin 4 or more of the 7 contrasts are shown (yellow=7 of 7). Clear convergence is observed in lateral parietal (inferior parietal and a small focus in superior parietal) and the medial surface of the parietal lobe extending from precuneus into posterior cingulate and retrosplenial cortex. The midline region within the outlined area is not part of the cortical surface and is therefore masked.

Familiarity-gated Recollection Attempt

As reported in Chapter 3, greater activation was observed in the IPS during Hits compared with CRs in parietal cortices regardless of the outcome of recollection (see also, Wheeler and Buckner, 2003). It was suggested that parietal subregions mediate control processes that guide recollection attempts, with these processes being gated/disengaged when the recognition probe is perceived to be of low familiarity. Indeed, we observed that the IPS demonstrated old–new effects with greater activation during Hits compared with CRs, but no differential activation during Hits versus FAs and Misses versus CRs. Thus, it was concluded that the IPS is insensitive to the true memory status of the probe, because it was engaged to the extent that above-criterion familiarity (perceived familiarity) was elicited.

The present MEG data further support the results obtained with fMRI, extending these findings by documenting that pIPS activation dissociates from that in aIPS. As with our fMRI data, the pattern of current estimates in the pIPS suggest that activation in this region correlates with perceived familiarity. Two observations motivate this conclusion. First, FAs in this region tracked Hits (with or without recollection), indicating that activation in this region relates to or depends on the perception of stimulus familiarity. Second, the onset of the pIPS during hits accompanied with recollection preceded the onset of the response during hits not accompanied with recollection. This pattern tracked the reaction times to these trial types, suggesting that the activation pattern might not directly relate to recovered knowledge but rather may relate to working with any recovered information to arrive at a decision.

Taken together, our MEG data bear a striking resemblance to the observed functional subdivisions of parietal cortex in fMRI studies. With the exception of the lateral inferior parietal lobule, the patterns observed here track those revealed by fMRI, though we note that definitive conclusions about source localization based on *a*MEG are not possible. As previously suggested, the lack of response in the inferior parietal lobule may be due to the sensitivity of MEG to sources that are parallel to the scalp, in contrast to EEG, which is particularly sensitive to sources perpendicular to the scalp (Cohen & Halgren, 2003; Hämäläinen, Hari, Ilmoniemi, Knuutila, & Lounasmaa, 1993). If this interpretation is correct, it is possible that the left parietal old-new effects seen between 400-800 ms in ERPs originate in the lateral inferior parietal region observed with fMRI, complementing the presently observed effects in IPS. Consequently, MEG together with ERP may be needed to provide a fuller temporal description of the signals observed with fMRI. Future studies recording simultaneously from MEG and EEG may test this hypothesis.

False Recognition and Recollection

An old–new effect sensitive to recollection was observed in the aIPS. Importantly, current estimates during FAs in aIPS tracked those of hits accompanied by recollection (i.e., Item+Source trials). The similarity of the current estimates during Item+Source and FA trials, and the diverge of these responses from those of Item Only trials and CRs, suggest that, in the present experiment, false recognition was partially based on false recollection.

A body of behavioral and neuroimaging evidence suggests that, at least on some occasions, false recognition can be accompanied by illusory recollection. Behavioral data indicate that false recognition can be accompanied by illusory recollection when new items are conceptually related to studied items (Roediger & McDermott, 1995; Schacter, Norman, & Koutstaal, 1998). Neuroimaging studies suggest that false recognition of related new items can be accompanied by MTL activation that resembles that seen during veridical recognition, whereas regions that represent domain-specific details may be differentially engaged during veridical, but not false, recognition (Cabeza, Rao, Wagner, Mayer, & Schacter, 2001; Schacter et al., 1996). Critically, in an fMRI variant of this paradigm (Chapter 3), FAs appeared to be at least partially based on recollection, as revealed through observation of region-specific reactivation for falsely recognized items that were accompanied by source judgments.

The current observation of false recollection during FAs, as indexed by aIPS responses, has important implications for models of recognition. Recognition memory theorists, although differing in their accounts, agree that FAs are based on above-criterion familiarity in the absence of recollection (Jacoby, 1991; Wixted & Stretch, 2004; Yonelinas, Dobbins, Szymanski, Dhaliwal, & King, 1996). These theorists disagree on the specific account for "remember" responses made to novel items, with Yonelinas et al (1996) suggesting that remember-FAs reflect guessing, while Wixted and Stretch (2004) argue that they reflect high-confidence familiarity responses. Importantly, both accounts argue that FAs are not accompanied by false recollection. The present observation indicates that there are occasions in which this assumption may not hold.

It might be tempting to argue that the present aIPS response to FAs is consistent with the Wixted and Stretch account because hits accompanied with recollection are also likely to be associated with high familiarity, thus providing a familiarity-account of the similarity between FAs and Item+Source current estimates. However, the presence of two distinct regions within the IPS, each showing a binary response (recollection insensitive vs. recollection sensitive), rather than a single region showing gradations that correlate with gradations in familiarity signals would appear to argue against this interpretation. Thus, we suggest that, consistent with our fMRI report, the MEG current estimates are consistent with FAs being at least partially based on false recollection.

Understanding Memory-related Parietal Activation

Classical accounts of parietal function imply that parietal engagement during retrieval may be related to spatial attention and/or motor intention (Colby & Goldberg, 1999; Mesulam, 1999). However, a recent test of these possibilities by Shannon and Buckner (2004) suggests that parietal old–new responses are unlikely to reflect a simple target choice (i.e., motor intention) because greater activation during hits than during CRs was seen irrespective of whether participants responded to hits or to CRs. In contrast, spatial attention mechanisms may provide an account for observed parietal old–new effects that are sensitive to recollection. From that perspective, parietal sensitivity to episodic recollection may reflect the directing of attention to internal activated representations (*attention to internal representations hypothesis*) (Wagner, Shannon, Kahn, & Buckner, 2005), in line with theories that implicate parietal cortex in spatial attention (Colby & Goldberg, 1999).

However, as we have recently argued (Wagner, Shannon, Kahn, & Buckner, 2005), attention to internal representations may not be able to account for all parietal responses. One possible addition role of parietal cortex in episodic retrieval may be to accumulate "evidence" in the service of guiding a decision about the mnemonic status of the retrieval cue (*mnemonic accumulator hypothesis*). Motivated by results from non-human primates suggesting that LIP neurons integrate sensory signals in preparation for action (e.g., Shadlen & Newsome, 2001; Sugrue, Corrado, & Newsome, 2004), we have speculated that the role of the IPS in humans may extend to performing a similar function on mnemonic signals. Such a role would be compatible with models of episodic retrieval (Ratcliff, 1978) that posit that evidence is accumulated in the service of a signal-detection memory decision.

The present data offer some support for the mnemonic accumulator hypothesis: Our results show a functional subdivision in the lateral parietal lobe with pIPS correlated with recognition decisions, while the attention to internal representations may better account for aIPS responses that track recollection- but not familiarity-based recognition. At present, however, definitive conclusions are not possible, and thus future studies are needed to further characterize the response properties of these parietal subregions, as are targeted studies designed to test whether these parietal regions make necessary contributions to episodic retrieval. The present data added to an emerging story about potential parietal involvement in remembering the past, and suggest that when its all been written, the role of parietal cortex in retrieval will be multi-faceted.

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Chapter 5

Conclusions

The experiments and theoretical framework described in this thesis advance understanding of how the brain supports episodic retrieval. Specifically, these experiments build upon cognitive models that suggest that episodic retrieval can be decomposed into multiple subprocesses. Implicit in these models is the notion that the processes underlying episodic retrieval can be broadly classified into two complementary classes: (1) *recovery processes* that serve to reactivate stored memories, making information from a past episode readily available, and *(2) control processes* that serve to guide the retrieval attempt and monitor/evaluate information arising from the recovery processes. Guided by this framework, we adopted a multi-modal imaging approach, combining fMRI and MEG to gain insight into the spatial and temporal properties of the neural mechanisms supporting episodic retrieval.

In Chapter 2 of this thesis, we combined fMRI and MEG to characterize recovery processes, specifically asking whether we can identify neural structures that signal item memory strength, supporting the perception of familiarity. We observed that MTL regions demonstrate strength-dependent signal reductions, suggesting that they play a significant role in coding for item familiarity. The experiment described in Chapter 3 utilized fMRI to examine the neural signature of recollection. In particular, we asked whether retrieval of contextual details involves reactivation of neural structures engaged at encoding, in both sensory and non-sensory processing regions of the brain. The results demonstrated that reactivation occurs during the recollection of episode-specific information. Further, leveraging on this pattern of reactivation (referred to as the recapitulation neural signature), our fMRI experiment also tested whether false recognition may be accompanied by recollection. We found that neural markers of "recapitulation" occur for falsely recognized items, suggesting that, at least in some cases, false recognition is accompanied by misbound or illusory recollection.

Outstanding questions related to the spatio-temporal characteristics of control processes during episodic retrieval were addressed in Chapters 3 and 4. In particular, Chapter 3 examined whether retrieval-related activity in parietal and prefrontal cortices is sensitive to recollection success, and thus related to recovery processes, or whether such activity is insensitive to recollection success, implicating these regions in control processes that guide episodic retrieval. The results resolved this controversy by demonstrating that processing in prefrontal and parietal regions is likely gated by perceived familiarity. Thus, although activation in these regions is sensitive to recognition success, we conclude that the mechanisms supported by these structures are engaged when attempting to recollect the past, irrespective of the success of such an attempt, with perceived familiarity being a pre-requisite for this neural engagement. Chapter 4 described the companion MEG experiment, illuminating the temporal characteristics of parietal responses during episodic retrieval. The results revealed medial and lateral parietal correlates of retrieval, with recollection-sensitive and recollection-insensitive patterns of parietal activation being consistent with engagement of selective attention mechanisms during recollection and with parietal cortices playing a role in accumulating emerging mnemonic evidence in the service of arriving at a recognition memory decision. These observed MEG data also suggest that false recognition can be based on misbound/illusory recollection, supporting the results obtained with fMRI in Chapter 3.

Collectively, these studies contribute to an emerging anatomical and temporal “blueprint” of the cascade of neural events that accompanies attempts to remember the past. The results from each of these experiments shed light on the neural mechanisms subserving episodic retrieval, further elucidating how different brain regions contribute to recovery vs. control processes.

Recovery Processes

Neural Processes Underlying the Perception of Familiarity

The ability to recognize stimuli that were previously encountered and to discriminate such “old” stimuli from novel stimuli is key to episodic retrieval. Behavioral evidence indicates that this ability is partially based on an assessment of memory strength, which is thought to vary in a continuous manner and to underlie the subjective perception of familiarity. A fundamental question is what are the neural mechanisms that elicit gradations in the subjective experience of familiarity.

In Chapter 2, we used fMRI and MEG to examine the contribution of medial temporal cortical responses to perceived memory strength. Faces were incidentally encoded during a target detection task. Participants were scanned (with either fMRI or MEG) during a subsequent recognition memory test, which included studied faces, unstudied faces that were perceptually similar to studied faces, and dissimilar unstudied faces. Participants responded "remember," "know," or "new" to each test face.

We hypothesized that strength-dependent gradients observed in medial temporal neural structures reflect processing that supports the perception of item familiarity. The fMRI data revealed experience-dependent response reductions in medial temporal cortices when humans recognize faces that were previously encountered relative to faces that are novel. Moreover, the magnitude of this repetition reduction in human medial temporal cortex varied in a continuous manner and correlated with different mnemonic perceptions — that is, greater reductions were associated with the perception of stronger item recognition.

Anatomically constrained MEG measures obtained with the same paradigm indicated that these strength-dependent response reductions are seen as early as 150-300 ms post-stimulus onset, consistent with behavioral data indicating that humans have rapid access to information about item memory strength (Hintzman & Curran, 1994) and with single unit data in animals revealing an early onset of repetition suppression (Brown & Aggleton, 2001).

The fMRI data further demonstrated correlates of familiarity in regions outside the MTL. Right fusiform cortex, putatively near the fusiform face area (Kanwisher, McDermott, & Chun, 1997), showed decreasing activation with increasing perceived memory strength. The MEG data indicated that a strength-dependent response was present at around 300-450 ms, in a similarly localized right fusiform region, as well. This finding suggests that the MTL interacts with other cortical regions in the service of episodic retrieval. Given that these gradations are observed at a later time relative to face processing computations observed at 100-200 ms post-stimulus onset (e.g., Liu, Harris, & Kanwisher, 2002; Liu, Higuchi, Marantz, & Kanwisher, 2000; Sams, Hietanen, Hari, Ilmoniemi, & Lounasmaa, 1997), it is possible that they reflect computations that are different from early perceptual effects, such as experience-dependant tuning of representational cortices that contributes to recognition decisions, or alternatively that mnemonic responses in MTL feed back to these regions. At present, it remains unclear whether experience-dependent lateral cortical changes, and their interactions with such changes in MTL, are necessary for the perception of familiarity. The observation of memory strength effects in fusiform cortex motivates future research aimed at understanding the functional role of these patterns.

Recapitulation and Episodic Recollection

Recollection critically depends on processes that make available representations of contextual details surrounding an event at encoding. The experiment in Chapter 3 aimed to understand the neural mechanisms supporting such processes. To this end, fMRI indexed neural responses while participants recognized incidentally encoded items, including recollecting the task performed with each item at encoding (imagery or phonological processing). The experiment directly tested the idea that reactivation of sensory-specific cortex during retrieval occurs during recollection of domain-specific information, and that this reactivation underlies recollection-based memory decisions.

Critically, bilateral parahippocampal cortices were differentially activated during accurate recollection of having engaged in scene imagery at encoding. These structures were also differentially active during imagery at encoding and when passively viewing scenes, suggesting that task-sensitive recollection effects mark the “recapitulation” of neocortical representations that were present at encoding. This result suggests that recovery processes specified in cognitive models of recognition memory putatively rely on long-term storage of representations in the same brain structures involved in the initial processing during encoding. It remains unclear, however, whether neocortical recapitulation is necessary for recollection, and thus is the basis of the recollective experience.

The experiment in Chapter 3 additionally revealed that recapitulation effects can be seen in non-sensory regions during recollection of the cognitive operations performed on a stimulus at encoding. Specifically, the left posterior ventrolateral PFC (pVLPFC) was differentially engaged during recollection of having performed the phonological processing task. This result implicates non-sensory brain regions in mnemonic function, in particular in relation to verbal information processing, suggesting that these regions are likely to play a crucial role in episodic retrieval.

Recently, a first step in establishing the necessity of PFC for episodic encoding was established in a study using single-pulse transcranial magnetic stimulation (TMS), targeting pVLPFC (Kahn et al., 2005). Single-pulse TMS allows temporary disruption of relatively localized neural regions and thus allows an examination of whether a particular region is *necessary* for specific cognitive functions. In this study, we tested whether pVLPFC is necessary for the formation of episodic memory for verbal stimuli. A prior fMRI study revealed that the magnitude of pVLPFC activation during the encoding of novel and familiar words predicted whether the words would be later remembered or forgotten (Clark & Wagner, 2003). At encoding, participants made 2-or-3 syllable judgments about visually presented familiar (English) and novel (pseudo-English) words. Guided by the fMRI results, single-pulse TMS was applied using frameless stereotaxy to pVLPFC or to its right hemisphere homologue at various post-stimulus onset times (250ms – 600ms). A surprise recognition memory test for the studied words was administered following encoding; participants indicated whether they recognized seeing the word at encoding with high or medium confidence, or whether the word was not present during the study episode. Transient disruption of pVLPFC during encoding revealed that subsequent memory for familiar words was impaired by disruption of left pVLPFC, expressed as a decline in subsequent recognition confidence, with the critical contribution of left pVLPFC to encoding being strongest at 380 ms.

Taken together with the finding of a role for left pVLPFC in recapitulation (as described in Chapter 3), these data suggest that neural activity in left pVLPFC at encoding affects the formation of a memory trace that includes phonological processing details. The finding that high-confidence responses were particularly sensitive to disruption further suggests that these changes in left pVLPFC are more likely related to episodic recollection, rather than to item familiarity. Thus, these data support the necessity of non-sensory regions to episodic encoding. However, necessity at encoding does not imply necessity at retrieval. Future research aimed at characterizing recapitulation can build on this result. For example, combining disruption at encoding and imaging at retrieval can reveal whether patterns of activation differ for remembered and forgotten items. If the recapitulation hypothesis is correct, then differential recollection-related retrieval activity will be observed as a function of the stimulation parameters at encoding.

Evidence for the occurrence of recapitulation has now been reported in several studies generalizing the phenomenon across different paradigms and establishing the effect in multiple regions of the brain (Nyberg, Habib, McIntosh, & Tulving, 2000; Prince, Daselaar, & Cabeza, 2005; Slotnick & Schacter, 2004; Vaidya, Zhao, Desmond, & Gabrieli, 2002; Wheeler, Petersen, & Buckner, 2000). Future studies are necessary. However, to theoretically and experimentally refine understanding of the exact role recapitulation plays in episodic retrieval. One key question is to what degree recapitulation is necessary to retrieve the contextual details surrounding an event. In its extreme, the 'recapitulation hypothesis' might suggest that recollection of contextual details cannot occur without the reactivation of regions in which those representations were processed. For instance, recollection of details of a friend's house will necessitate reactivation of neural regions underlying the processing of scenes and places. Such a hypothesis would be in line with a recent proposal by Eichenbaum and Cohen (2001), suggesting that memory is a fundamental property of the brain's ongoing processing activities. Alternatively, it is possible that at encoding, representations are transformed such that they do not rely on regions necessary for initial processing. This alternative predicts, for example, that sensory processing regions alone may play a differential role in episodic retrieval (e.g., Slotnick & Schacter, 2004). Future imaging and neural disruption studies will help determine the specificity, extent, and necessity of neural recapitulation for episodic recollection.

Neural Markers of False Recognition

Some theories of memory function assume that false recognition – erroneously stating that a novel item has been previously encountered – is not accompanied by recollection (Yonelinas, 1997; Yonelinas *et al*., 2002). Whether false recognition involves recollection, or not, has remained an open question. In Chapters 3 and 4 of this thesis, we addressed this question. Specifically, in Chapter 3 we reasoned that to the extent that neural recapitulation effects reflect recollection, one can empirically examine whether false alarms are accompanied by false recollection (as indexed by false recapitulation). In Chapter 4, we reasoned that if MEG current estimates bear a similarity to current estimates for veridical recognition accompanied with recollection, with both patterns diverging from current estimates during recognition without recollection, this would lend further support for the conclusion that false recognition can be accompanied by illusory recollection.

Consistent with this prediction, in Chapter 3 we found that the "recapitulation" responses observed in parahippocampal cortex and left pVLPFC during veridical recollection were also observed during false recognition (false "Imaged" or "Read" judgments, respectively). This parallel between the activation patterns during veridical recollection and false recognition provides important new evidence that false alarms may be at least partially based on false recollection. Interestingly, the "recapitulation" responses observed in bilateral parahippocampal cortices during false recognition were weaker than those observed during veridical recollection, suggesting that false recognition is not always accompanied by recollection, or is accompanied by recollection of fewer details. Further, in Chapter 4 we observed that current estimates in the anterior intraparietal sulcus demonstrated sensitivity to veridical recollection. Critically, false alarms tracked this response and differed from familiarity-based recognition, suggesting that false recognition is accompanied at least partially by recollection.

The present observations of false recollection during false alarms have important implications for models of recognition. Current prominent models of recognition assume that false alarms are based on above-criterion familiarity in the absence of recollection (Jacoby, 1991; Wixted & Stretch, 2004; Yonelinas, Dobbins, Szymanski, Dhaliwal, & King, 1996). To the extent that neural "recapitulation" effects mark recollection, then, at a minimum, the present findings indicate that there are instances in which this assumption is violated. A critical goal for future research is to determine the conditions in which false alarms are partially based on recollection (Dodson, Koutstaal, & Schacter, 2000; Schacter, 1996, 1999).

In summary, the experiments described in Chapters 2, 3 and 4 indicate that the ability to recover information regarding a prior episode includes an early-onsetting graded familiarity signal that emerges from MTL cortex. Further, episodic recollection appears to involve neural 'recapitulation' in sensory- and process-related regions activated during encoding. Interestingly, such recapitulation responses were also found to accompany false recognition, suggesting that false recognition may be accompanied by misbound/illusory recollection. These imaging data, taken together with initial evidence from TMS, strongly suggest that neural recapitulation is fundamental to the ability to recollect details about past episodes. Critically, the discrepancy between present models of recognition memory and our data indicate that revision of current theories of recognition is necessary.

Control Processes

Prior studies have demonstrated that PFC plays an important role in episodic retrieval. In particular, PFC neural mechanisms were implicated in attempts to recognize that an item was previously encountered, to recollect contextual details, and to a more limited extent, with successful recognition and/or successful recollection. Interestingly, recent neuroimaging studies have also begun to implicate regions in left medial and lateral parietal cortex in similar or correlated processes (e.g., Dobbins, Rice, Wagner, & Schacter, 2003; Henson, Rugg, Shallice, Josephs, & Dolan, 1999; Wheeler & Buckner, 2003, 2004). These observations have led to the speculation that the parietal lobe may contribute to episodic retrieval by allocating attention to internally generated mnemonic representations and by integrating or accumulating mnemonic evidence to guide recognition memory responses (for review see, Wagner, Shannon, Kahn, & Buckner, 2005).

The specific nature of the contributions of PFC and parietal cortex to episodic retrieval, and particularly the situations in which these neural mechanisms are engaged, have remained controversial. From one perspective, it has been suggested that activity in PFC and parietal cortex is gated by the perception that an item was previously encountered. According to this hypothesis, additional PFC processing will be allocated only to items perceived to be old or familiar (Dobbins, Foley, Schacter, & Wagner, 2002; Dobbins, Rice, Wagner, & Schacter, 2003; Wheeler & Buckner, 2003). Alternatively, it has been suggested that the PFC and parietal lobe are sensitive to, or signal, retrieval success and thus are perhaps serving to recover information, rather than guide other recovery processes (Donaldson, Petersen, & Buckner, 2001; Henson, Rugg, Shallice, Josephs, & Dolan, 1999; Konishi, Wheeler, Donaldson, & Buckner, 2000).

The experiments reported in Chapters 3 and 4 provide initial insight into the circumstances in which PFC and parietal neural processes are engaged, as well as the circumstances that initiate or abort their engagement. In particular, these fMRI and MEG experiments examined whether regions showing differential activity to old vs. new items (old–new effects) support processes that are sensitive to recollection success or recollection attempt. Specifically, we examined whether activation in these regions might be sensitive to the *perception* that information is old or familiar, regardless of the true mnemonic status of the item. The results showed that regions in left PFC, including left dorsolateral, ventrolateral, frontopolar, as well as in left parietal cortex, including the posterior intraparietal sulcus, are sensitive to the perceived familiarity of test items, and not to recollection success.

Intriguingly, as revealed in Chapter 4, the parietal lobe demonstrated a more nuanced pattern of activity with a posterior-anterior division: medial and lateral posterior regions were insensitive to recollection, while anterior regions were sensitive to recollection. This pattern of results suggests that subregions in the parietal lobe differentially correlate with specific aspects of episodic retrieval. One possibility is that regions insensitive to recollection support mnemonic integration or evaluation in the service of guiding recognition memory decisions, whereas regions sensitive to recollection may reflect the allocation of attention to internal representations emerging as a consequence of recollection. Future experiments designed to directly test these possibilities are required to more precisely characterize the role of these parietal regions in retrieval.

It is interesting to note that despite the fact that the MEG study in Chapter 4 used a paradigm identical to that used with fMRI in Chapter 3, we found some inconsistencies in activity between the studies. In particular, the responses in left PFC regions that were observed with fMRI failed to emerge as significant in the MEG experiment. One possible explanation for this discrepancy is that PFC responses are more variable in time relative to parietal responses, making them less detectable using method with high temporal resolution. Consistent with this possibility, ERP studies have also tended to observe left parietal effects, with frontal effects associated with recollection attempt and/or success being less predictably obtained. Notably, since recognition performance levels were virtually identical between our fMRI and MEG experiments, it seems less likely that these discrepancies are the result of different neural patterns across the two studies due to differences in memory performance. Future investigations and novel methodological approaches to MEG data analysis may serve to resolve this discrepancy.

Spatio-temporal "Blueprint" of Episodic Retrieval: Future Directions

In the research program described here, we adopted a multi-modal neuroimaging approach that enabled the targeting of distinct aspects of the multi-faceted act of remembering the past. The obtained data contribute to an emerging anatomical and temporal "blueprint" documenting the cascade of neural events that unfold during attempts to remember, as well as when such attempts are met with success or lead to memory errors. In the course of framing this research within the context of cognitive models of retrieval, the obtained neural data served, in turn, to constrain these cognitive theories, raising a number of questions for future investigation.

Recapitulation and Episodic Retrieval

Several open questions remain regarding the necessity of neural recapitulation in episodic retrieval, and the relation between sensory/non-sensory processing and mnemonic representations. To test the necessity of recapitulation in recollection, future studies may capitalize from using visual processing and/or imagery, for instance, to drive participants to use the lateral occipital complex (LOc) in object recognition vs. MT in motion processing. Subsequently, TMS can be used to disrupt processing at encoding and retrieval under these conditions. This approach will help establish whether regions necessary for processing are also necessary for long-term storage of these representations, and thus identify whether neocortical recapitulation is necessary for the recollective experience. The studies described in this thesis illustrate the benefits of combining fMRI, MEG/EEG, and TMS; such an approach can also be adopted in the future to identify the timecourse of recapitulation.

Retrieval from Episodic Memory and Executive Control Processes

The research in this thesis, as well as work by others, argues that retrieval depends on prefrontal and parietal mechanisms that might support forms of cognitive control (e.g., Buckner & Wheeler, 2001; Dobbins, Foley, Schacter, & Wagner, 2002; Rugg & Wilding, 2000; Wagner, 2002). That is, in addition to pattern matching and pattern completion processes that occur in reaction to an initial retrieval cue (supported by hippocampus/MTL), additional processing on the retrieval cue or initial products of the retrieval attempt may provide additional retrieval cues. Recent neuroimaging studies propose a division of labor for PFC in such processes.

The evidence presented in Chapters 4 suggests that the parietal lobe plays a significant role in episodic retrieval. Multiple subregions were implicated in distinct control processes in the service of retrieval. Future studies using TMS will be helpful in further advancing understanding of the time course and anatomical localization of PFC and parietal processes. Results from such studies promise to provide direct evidence regarding whether these regions are necessary for episodic retrieval. As such, it is anticipated that the present body of findings will constrain theory, motivate future experimentation, and ultimately will lead to an understanding of the neural mechanisms that support our ability to accurately remember our past, as well as why remembering can be error prone.

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