

# Memory Strength and Repetition Suppression: Multimodal Imaging of Medial Temporal Cortical Contributions to Recognition

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## Summary

Declarative memory permits an organism to recognize stimuli that have been previously encountered, discriminating them from those that are novel. One basis for recognition is item memory strength, which may support the perception of stimulus familiarity. Though the medial temporal lobes are known to be critical for declarative memory, at present the neural mechanisms supporting perceived differences in memory strength remain poorly specified. Here, functional MRI (fMRI) and anatomically constrained magnetoencephalography (MEG) indexed correlates of graded memory strength in the human brain, focusing on medial temporal cortex. fMRI revealed a decrease in medial temporal cortical activation that tracked parametric levels of perceived memory strength. Anatomically constrained MEG current estimates revealed that strength-dependent signal reductions onset within 150–300 ms. Memory strength appears to be rapidly signaled by medial temporal cortex through repetition suppression (activation reductions), providing a basis for the subjective perception of stimulus familiarity or novelty.

## Introduction

Declarative memory—conscious memory for events and facts (Cohen and Eichenbaum, 1993; Squire, 1992)—allows an organism to bridge the temporal gap between the present and past. 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 at least partially depends on an assessment of memory strength, which can vary in

a continuous manner and which may underlie the subjective perception of stimulus familiarity (Wixted and 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 medial temporal lobe (MTL) structures—hippocampus and adjacent parahippocampal and perirhinal cortices—in item recognition (Baxter and Murray, 2001; Brown and Aggleton, 2001; Rugg and Yonelinas, 2003; Squire et al., 2004). While there is general agreement that the hippocampus is particularly important for remembering the relations between items and between items and context, there is less agreement about the neural substrates supporting 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 et al., 2003; Stark et al., 2002; Stark and Squire, 2003). By contrast, other studies document spared recognition following hippocampal-specific lesions (Baxter and Murray, 2001), with such lesions resulting in a differential impairment of relational memory and relative preservation of item recognition (Baddeley et al., 2001; Fortin et al., 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 and Aggleton, 2001; Yonelinas et al., 1998).

Support for a role of medial temporal cortex in item recognition comes from observations that in rats and monkeys lesions of perirhinal cortex result in consistent and often severe recognition memory deficits (Baxter and Murray, 2001; Brown and Aggleton, 2001). Furthermore, 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 and 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 hr), consistent with the hypothesis that they might support recognition discrimination based on item memory strength (Brown and 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 and Brown, 2003; Norman and O’Reilly, 2003).

Initial functional MRI (fMRI) studies in humans also

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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 et al., 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 et al., 2003) and during correct recognition of old items relative to old items incorrectly classified as new (Weis et al., 2004a, 2004b). While the magnitude of this activation reduction does not appear to track conscious recollection (Henson et al., 2003), at present it is unclear whether gradations in activation suppression relate to perceived differences in item memory strength or to nonconscious forms of memory (e.g., priming). Indeed, although it is possible that fMRI signal reductions in medial temporal cortex are a human analog 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 event-related potentials (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 MTL may contribute to the FN400, as initial evidence suggests that this region may be a source of the N400 (McCarthy et al., 1995), which differs when subjects encounter old compared to new items during recognition (Smith et al., 1986). However, as with fMRI activation reductions, there remains uncertainty about the relation between the FN400 and item memory strength. First, the FN400 effect is not always seen in ERP studies of recognition (Yovel and Paller, 2004). Second, data are mixed regarding whether the FN400 is modulated by manipulations that have clear effects on familiarity, such as levels of processing (Rugg et al., 1998, 2000; Wagner et al., 1997). Finally, gradations in the magnitude of the FN400 that track gradations in perceived item strength have yet to be established, though one study reported frontopolar signal differences from 300 to 450 ms post-stimulus onset across “remembered,” “known,” and “miss” recognition trials (Duarte et al., 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 et al., 2004; Tsivilis et al., 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 et al., 2001) and when comparing “remembered” and “known” test probes to “misses” (Duarte et al., 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 versus New-Old pairs) nevertheless result in comparable ERP deflections relative to New-New pairs (Tsivilis et al., 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 et al., 2004), and some have argued that the effect could reflect visual perceptual priming (Curran and Dien, 2003). Finally, though 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 et al., 2003).

The preceding review indicates that, while there are candidate fMRI and ERP responses that may relate to item memory strength, extant data have yet 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. The present study used a multimodal imaging approach that combined fMRI and *anatomically constrained* magnetoencephalography (aMEG) 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. Finally, 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 et al., 1998; Hintzman and Curran, 1994; McElree et al., 1999).

Subjects studied a series of faces, the memory for which was then tested via recognition. During the critical recognition test, subjects were presented old faces together with novel (unstudied) faces (see *Experimental Procedures*). For each, subjects made recognition decisions, indicating memory strength using a one-step “Remember”/“Know” procedure (Eldridge et al., 2002; Hicks and Marsh, 1999; Tulving, 1985). One group of subjects performed recognition while undergoing fMRI scanning and a second, independent group performed while undergoing MEG scanning. A third group participated in a behavioral experiment, wherein Remember (R), Know (K), and New responses were either preceded or followed by confidence ratings. This behavioral ex-

periment 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 and Stretch, 2004). That is, perceived memory strength—as indexed by confidence (Dunn, 2004; 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 aMEG signal are observed to onset early after test probe presentation. During data analysis, we remain neutral regarding the relation between perceived memory strength and the recollection/familiarity distinction, though as we argue in the Discussion, the obtained data are consistent with a neural correlate of item familiarity.

## Results

### Recognition Performance

All behavioral and region-of-interest neuroimaging analyses included the Hunyh-Feldt correction for nonsphericity where appropriate (denoted by  $p_{H-F}$ ). Recognition responses from the fMRI, MEG, and behavioral experiments were analyzed for studied and unstudied faces (see Experimental Procedures). 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 subjects do not have the opportunity to express this familiarity because the R and K response options are mutually exclusive (Yonelinas, 2002).

Both raw recognition responses and process estimates of recollection and familiarity revealed similar performance across the fMRI and MEG groups (Group × Performance, all F values < 1). R response rates were higher for studied than for unstudied faces [ $F(1,20) = 55.05$ ,  $p < 0.0001$ ], whereas raw K rates did not differ ( $F < 1.0$ ). Estimates of recollection and familiarity were both higher for studied than for unstudied faces (all F values > 6.32, all p values < 0.025). Collectively, these data demonstrate successful discrimination between studied and novel items (Figure 1A). Similar raw R and K probabilities and recollection and familiarity estimates were observed in the behavioral experiment [Group × Performance, all F values (2,48) < 1.13, all p values > 0.33], suggesting that all three groups treated the R/K distinction in a comparable manner.

In the behavioral study, R-hits were associated with higher confidence “old” responses than were K-hits [ $F(1,23) = 346.8$ ,  $p < 0.0001$ ], indicating greater memory strength for R-hits (Figure 1B). 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,

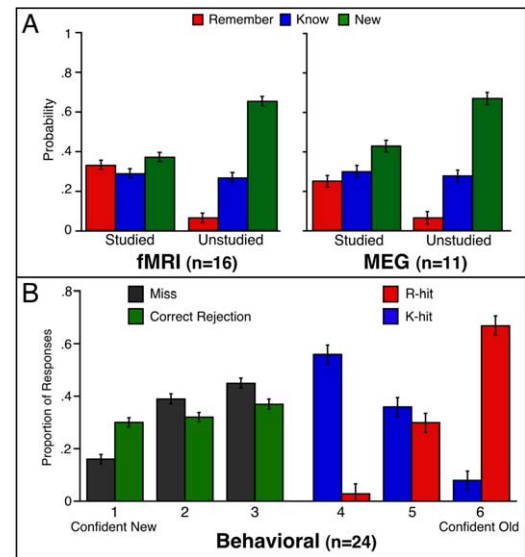


Figure 1. Behavioral Performance

(A) Probability of “Remember,” “Know,” and “New” responses to Studied and Unstudied faces in the fMRI and MEG experiments. (Note: Error bars in all figures denote within-subject SE.)

(B) Confidence ratings from the behavioral experiment. Plotted is the proportion of responses within each memory condition (Miss, CR, R-hit, and K-hit) given a particular confidence rating. (Note: proportions sum to 1.0 for each condition.)

1996; Dunn, 2004; Wixted and Stretch, 2004). Similarly, CRs were associated with modestly but reliably higher confidence “new” responses than were Misses [ $F(1,23) = 34.0$ ,  $p < 0.0001$ ]. Thus, although subjects 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). Thus, the conditions that were closer to the subjects’ 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).

### 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 2A). To assess the consistency of MTL normalization across subjects, which permits determination of the anatomical localization of this group-averaged MTL response projected to the individual subject level, the group-

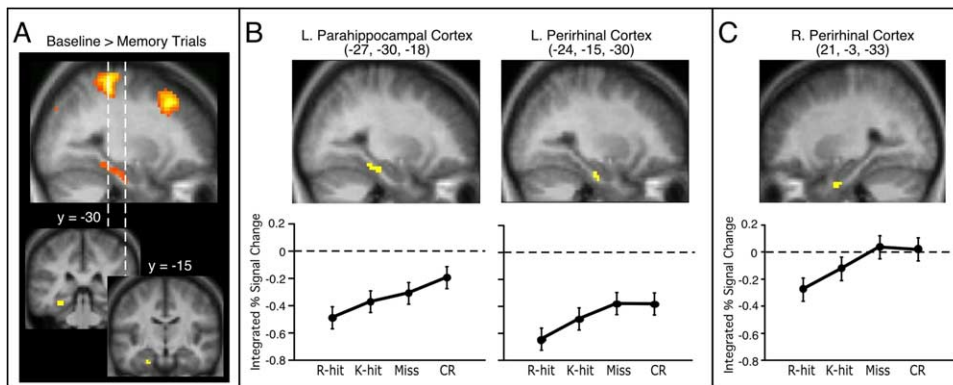


Figure 2. fMRI Results

(A) Activation along the collateral sulcus from the contrast of baseline > memory trials ( $p < 0.001$ ; five voxel extent). The coronal slices depict medial temporal regions of interest rendered on the group average anatomical image; the anterior region ( $y = -15$ ) corresponds 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 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 ( $p < 0.0025$ , uncorrected) showed a similar strength-dependent activation pattern.

averaged left medial temporal cortical response was projected onto each subject'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 all subjects. Anteriorly, this response included the medial bank of the collateral sulcus in 14 of the 16 subjects 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).

To examine the effect of perceived memory strength on activation levels in medial temporal cortex, the hemodynamic response (percent 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 versus 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 2B). Analyses of this perceived memory strength effect revealed a significant linear decline in left perirhinal cortex (MNI coordinates of  $-24, -15, -30$ :  $F(1,13) = 4.57$ ,  $p_{H-F} < 0.05$ ). This effect was also obtained when including data from all 16 subjects [ $F(1,15) = 5.66$ ,  $p_{H-F} < 0.05$ ] and when restricting the linear trend analysis to the R-hit, K-hit, and Miss condi-

tions [ $F(1,13) = 3.80$ ,  $p_{H-F} < 0.07$ ;  $F(1,15) = 5.31$ ,  $p_{H-F} < 0.05$ ]. Thus, in left perirhinal cortex, a graded decline was apparent across levels of perceived memory strength for studied faces. Similarly, a significant linear decline was observed in multiple foci within left parahippocampal cortex [ $-24, -21, -21$ :  $F(1,15) = 4.57$ ,  $p_{H-F} < 0.05$ ;  $-27, -30, -18$ :  $F = 8.25$ ,  $p_{H-F} = 0.01$ ; and  $-24, -39, -12$ :  $F = 3.71$ ,  $p_{H-F} = 0.06$ ]. This linear decline also tended to be reliable ( $-27, -30, -18$ :  $p_{H-F} = 0.09$ ) when the analysis was restricted to K-hits, Misses, and CRs, and activation during K-hits was reliably lower than CRs ( $p_{H-F} = 0.05$ , 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 subjects ( $n = 10$  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 ( $-24, -21, -21$ :  $p_{H-F} = 0.06$ ;  $-27, -30, -18$ :  $p_{H-F} = 0.08$ , 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 2C). Further analysis of the responses in this ROI revealed (1) that the monotonic decline was also observed when restricting the analysis to R-hits, K-hits, and Misses ( $p_{H-F} < 0.05$ ), (2) a trend for lower activation to K-hits relative to Misses ( $p_{H-F} < 0.08$ , one-tailed), and (3) reliably lower activation to K-based false alarms relative to Misses and CRs ( $p_{H-F} < 0.05$ , 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 and that these effects were not solely driven by R-hits.

In contrast to these strength-dependent activation reductions, exploratory voxel-based analyses revealed that no medial temporal region showed greater activation during R-hits versus K-hits or a graded *increase* in activation with increasing perceived memory strength (this was the case even at a lenient threshold,  $p < 0.01$ ). 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](#); [Yonelinas et al., 2005](#)), as R-hits did not differ from K-hits, nor did hippocampus show a graded effect that tracked perceived item memory strength. We suggest interpretative caution when considering the implications of these null 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 4A](#)). As we describe next, this result in right fusiform and the findings in left medial temporal cortex had parallels in the MEG correlates of recognition.

### MEG Results

MEG data were analyzed using each subject's cortical anatomy, obtained from MRI, to constrain localization of electromagnetic sources recorded at the scalp ([Dale et al., 1999, 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 aMEG 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 subject's MRI structural volume according to anatomical landmarks ([Figure 3A](#)) ([Amaral and 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 [Experimental Procedures](#)).

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  $\times$  Condition interaction, using four 150 ms time epochs from 0 to 600 ms post-stimulus onset [ $F(9,90) = 2.04$ ;  $p_{H-F} < 0.05$ ; [Figure 3B](#)]. Unpacking this interaction, analyses of mean amplitudes from 150 to 450 ms revealed a significant linear effect of perceived memory strength [ $F(1,10) = 4.27$ ,  $p_{H-F} < 0.05$ ] wherein MEG signal declined across the four conditions, from CRs to R-hits ([Figure 3C](#)). A similar linear effect during the 150–450 ms time window was observed in the left parahippocampal ROI [ $F(1,10) = 5.81$ ;  $p_{H-F} < 0.05$ ; [Figures 3B and 3C](#)], whereas no such linear effects were observed during this time window in the right medial temporal ROIs (all  $F$  values  $< 1.6$ , all  $p$  values  $> 0.2$ ).

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 (1) differences between the memory extremes (R-hits versus CRs) and (2) 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 ( $p < 0.05$ ) and a significant linear effect across the four conditions [ $F(1,10) = 4.57$ ;  $p_{H-F} < 0.05$ ]. In the late epoch, this region did not show a reliably different response to CRs relative to R-hits ( $p > 0.10$ ), and the linear effect did not reach significance [ $F(1,10) = 2.90$ ;  $p_{H-F} = 0.10$ ; [Figure 3C](#)]. Turning to the left parahippocampal ROI, in the early epoch the response was greater for CRs relative to R-hits ( $p < 0.05$ ), and there was a marginal linear effect across conditions [ $F(1,10) = 3.58$ ;  $p_{H-F} = 0.07$ ]. In the later epoch, CRs differed from R-hits ( $p < 0.05$ ), and there was a significant linear effect [ $F(1,10) = 6.44$ ;  $p_{H-F} < 0.05$ ; [Figure 3C](#)]. While these patterns suggest distinctions across the two epochs, the memory condition  $\times$  epoch interaction did not reach significance in either ROI [all  $F$  values (3,30)  $< 1.17$ , all  $p$  values  $> 0.16$ ]. Thus, strength-dependent signal differences were present in the left perirhinal and parahippocampal ROIs as early as the 150–300 ms window.

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 subject's average current estimates as a function of condition from 150 to 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 3D](#)). 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 coregistration 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 (for additional MEG data, see the [Supplemental Data](#) available online).

### 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 nonhuman animals, medial temporal cortex is thought to signal item recognition by reducing neural firing rates in response to previously encountered stimuli ([Brown and Aggleton, 2001](#)). Our fMRI data reveal

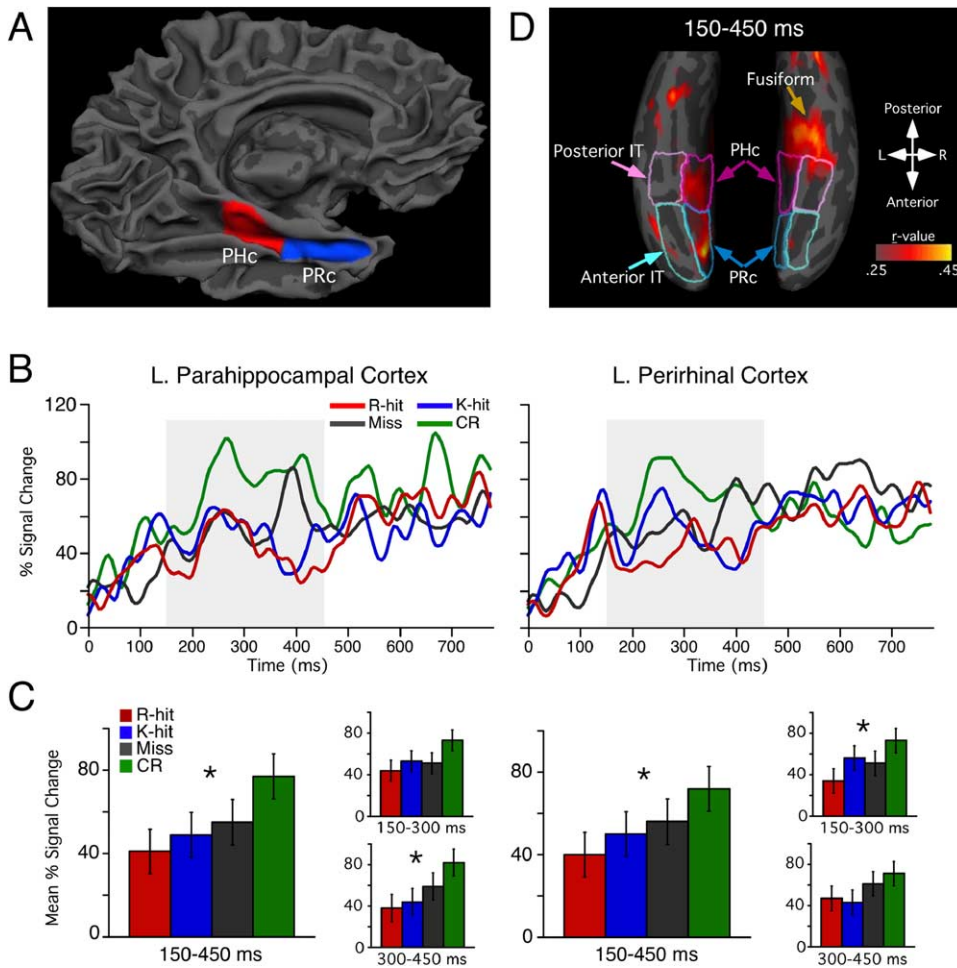


Figure 3. MEG Results

(A) Medial view of the folded reconstructed left hemisphere of an individual subject, showing anatomically defined perirhinal (PRc) and parahippocampal (PHc) cortical ROIs along the collateral sulcus.

(B) Anatomically constrained MEG (aMEG) current estimates derived from the left parahippocampal and perirhinal ROIs. Data are shown as percent change from the average of the prestimulus baseline as a function of time, in 5 ms increments (smoothed with a Gaussian kernel—25 ms FWHM—for presentation purposes). Shaded area corresponds to the 150–450 ms time window.

(C) Mean aMEG 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,  $p < 0.05$ )

(D) Linear regression map showing average strength-dependent effect across subjects. 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 subject, 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.

experience-dependent response reductions in medial temporal cortices when humans recognize faces that were previously encountered relative to faces that are novel (Henson et al., 2003; Weis et al., 2004a, 2004b). Moreover, the present fMRI findings provide 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 et al., 1998; Hintzman and Curran, 1994; McElree et al., 1999) and with single-unit data in animals revealing an early onset of repetition suppression (Brown and 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 and 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 1B).

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 and 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 and O'Reilly, 2003). Alternatively, graded repetition suppression may reflect an integrated response that blends information supporting both familiarity and recollection (Wixted and 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 and Aggleton, 2001), though additional single-unit data are required to definitively relate perirhinal repetition suppression to the perception of item familiarity in nonhuman 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 nonhuman animals and provides a critical link to mnemonic perception.

Second, extant fMRI data suggest 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. \(2003\)](#), 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 observation within this vein, wherein the magnitude of activation decreases in anterior and posterior medial temporal cortices tracks 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 indicate that more complex patterns of medial temporal cortical activation also can be observed during retrieval. Using a two-step R/K 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 R/K 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. However, 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. Finally, 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, and in contrast to these other retrieval studies, it is possible that the present one-step R/K method served to induce subjects 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 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

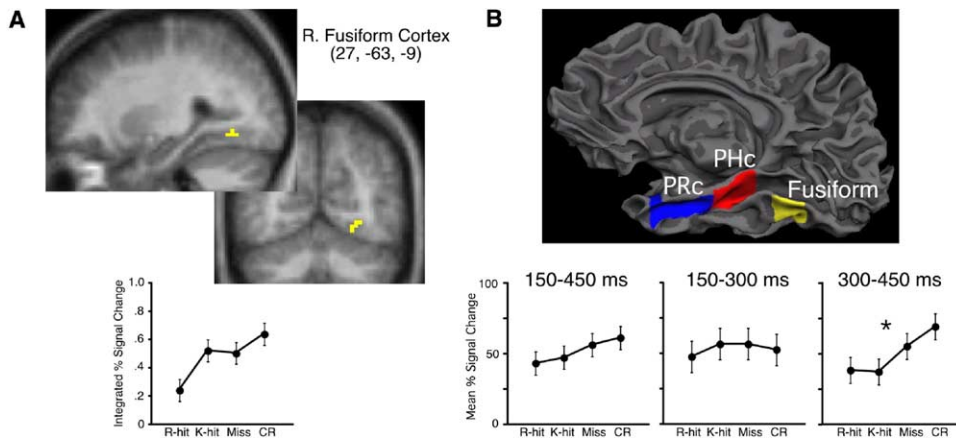


Figure 4. Responses in Right Fusiform Cortex

(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 ( $*p < 0.0025$ ).

(B) Right fusiform ROI and mean amplitudes of aMEG current estimates. There was a significant effect of perceived memory strength during the 300–450 ms epoch ( $*p < 0.01$ ).

deadline conditions (Hintzman et al., 1998; Hintzman and Curran, 1994; McEree et al., 1999). Accordingly, the present fMRI and MEG response reductions provide a possible human analog 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 MTL, 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 4), putatively near the fusiform face area (Kanwisher et al., 1997). Consideration of the MEG linear regression map also indicates that a strength-dependent response was present in a similarly localized right fusiform region (Figure 3D). 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 appear to rapidly signal knowledge about an item's relation to one's past.

#### Experimental Procedures

##### Subjects

A total of 51 subjects participated, 16 in the fMRI experiment (6 males; mean age of 22.1 years), 11 in the MEG experiment (4 males; 21.5 years), and 24 in the behavioral experiment (10 males; 20.7 years). All subjects gave informed consent and were remunerated for their participation, in accord with human subjects procedures approved by the institutional review boards at Stanford University, M.I.T., and Massachusetts General Hospital. fMRI data from an additional six subjects were not analyzed (three due to false alarm rates  $>0.50$ ; three due to having fewer than ten trials for a given condition); MEG data from three additional subjects 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 S1). 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).

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 Supplemental Results and Figure S1, subjects were insensitive to this subtle perceptual manipulation, treating Morphs in a comparable manner to that of studied faces. Accordingly, the behavioral and neuroimaging data analyses collapsed Parent faces and Morphs into a single “studied” condition.

### fMRI Behavioral Procedure

Subjects 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 S1).

Each study scan consisted of 45 face trials—40 critical nontarget faces and 5 presentations of a target face. On each trial, subjects intentionally encoded the face while simultaneously performing a target detection task that ensured attention to the stimulus. Specifically, subjects 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 subjects 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 subjects 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 subjects 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 subjects. On each test trial, the face was presented for 2000 ms, followed by 2000 ms of fixation; subjects 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 s, TE = 40 ms, 21 axial slices,  $3.125 \times 3.125 \times 5$  mm voxels, 1 mm interslice 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 Department 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 subjects' 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 subject 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 subject-by-subject 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 subjects as a random effect. Responses in a priori predicted medial temporal cortical regions were considered significant if they consisted of at least five contiguous voxels that exceeded an uncorrected threshold of  $p < 0.001$ . Left medial temporal cortical regions observed in the baseline > recognition contrast (see Results) were reliable at a corrected threshold ( $p < 0.05$ , small volume corrected). An additional contrast was performed to identify regions that showed a monotonic change according to perceived levels of memory strength (Figure 2C). For this more subtle contrast, MTL responses were considered significant if they consisted of at least five contiguous voxels that exceeded an uncorrected threshold of  $p < 0.0025$ .

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 ( $p < 0.001$ ) 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 subject 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 nonsphericity 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, subjects 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 subject's scalp were measured using several landmark locations on the head with a Polhemus FastTrack 3D digitizer (Polhemus Inc., Colchester, VT). Subjects 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 subject. High-resolution T1-weighted (MP-RAGE) anatomical MRI images were acquired for each subject in the MEG experiment for use in anatomically constrained MEG source localization.

### MEG Data Analysis

The basic MEG analysis procedure used here is described in detail elsewhere (Dale et al., 1999, 2000; Dale and Halgren, 2001; Liu et al., 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 subject 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 subject. 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 et al., 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 subject. Waveforms for all subjects were then entered into repeated-measures ANOVAs to assess patterns in the data that were consistent across subjects.

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 subject, and a linear regression was conducted on the four points. The *r* value at each location was then averaged across subjects by using a spherical morphing procedure to transform each subject's cortical surface to a standard spherical template (Fischl et al., 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 3D).

#### 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 subjects (*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 subjects 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 subjects (*n* = 12) performed recognition with the order of memory responses reversed. These subjects first made a remember/know/new response and subsequently made a confidence rating using the same six-point scale. Test order was varied across these two groups of behavioral subjects 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 (all *F* values < 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 1B).

#### Supplemental Data

The Supplemental Data for this article can be found online at <http://www.neuron.org/cgi/content/full/47/5/751/DC1/>.

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#### References

- Amaral, D.G., and Insausti, A.M. (1990). Hippocampal formation. In *The Human Nervous System*, G. Paxinos, ed. (San Diego, CA: Academic Press), pp. 711–755.
- Baddeley, A., Vargha-Khadem, F., and Mishkin, M. (2001). Preserved recognition in a case of developmental amnesia: implications for the acquisition of semantic memory? *J. Cogn. Neurosci.* 13, 357–369.
- Baxter, M.G., and Murray, E.A. (2001). Opposite relationship of hippocampal and rhinal cortex damage to delayed nonmatching-to-sample deficits in monkeys. *Hippocampus* 11, 61–71.
- Bogacz, R., and Brown, M.W. (2003). Comparison of computational models of familiarity discrimination in the perirhinal cortex. *Hippocampus* 13, 494–524.
- Brown, M.W., and Aggleton, J.P. (2001). Recognition memory: what are the roles of the perirhinal cortex and hippocampus? *Nat. Rev. Neurosci.* 2, 51–61.
- Cansino, S., Maquet, P., Dolan, R.J., and Rugg, M.D. (2002). Brain activity underlying encoding and retrieval of source memory. *Cereb. Cortex* 12, 1048–1056.
- Cohen, N.J., and Eichenbaum, H. (1993). *Memory, Amnesia, and the Hippocampal System* (Cambridge, MA: MIT Press).
- Curran, T. (2000). Brain potentials of recollection and familiarity. *Mem. Cognit.* 28, 923–938.
- Curran, T., and Dien, J. (2003). Differentiating amodal familiarity from modality-specific memory processes: An ERP study. *Psychophysiology* 40, 979–988.
- Dale, A.M. (1999). Optimal experimental design for event-related fMRI. *Hum. Brain Mapp.* 8, 109–114.
- Dale, A.M., and Halgren, E. (2001). Spatiotemporal mapping of brain activity by integration of multiple imaging modalities. *Curr. Opin. Neurobiol.* 11, 202–208.
- Dale, A.M., Fischl, B., and Sereno, M.I. (1999). Cortical surface-based analysis. I. Segmentation and surface reconstruction. *Neuroimage* 9, 179–194.
- Dale, A.M., Liu, A.K., Fischl, B.R., Buckner, R.L., Belliveau, J.W., Lewine, J.D., and Halgren, E. (2000). Dynamic statistical parametric mapping: combining fMRI and MEG for high-resolution imaging of cortical activity. *Neuron* 26, 55–67.
- Davachi, L., Mitchell, J.P., and Wagner, A.D. (2003). Multiple routes to memory: distinct medial temporal lobe processes build item and source memories. *Proc. Natl. Acad. Sci. USA* 100, 2157–2162.
- Desimone, R. (1996). Neural mechanisms for visual memory and their role in attention. *Proc. Natl. Acad. Sci. USA* 93, 13494–13499.
- Donaldson, W. (1996). The role of decision processes in remembering and knowing. *Mem. Cognit.* 24, 523–533.
- Duarte, A., Ranganath, C., Winward, L., Hayward, D., and Knight, R.T. (2004). Dissociable neural correlates for familiarity and recollection during the encoding and retrieval of pictures. *Brain Res. Cogn. Brain Res.* 18, 255–272.
- Dunn, J.D. (2004). Remember-know: A matter of confidence. *Psychol. Rev.* 111, 524–542.
- Eldridge, L.L., Knowlton, B.J., Furmanski, C.S., Bookheimer, S.Y., and Engel, S.A. (2000). Remembering episodes: a selective role for the hippocampus during retrieval. *Nat. Neurosci.* 3, 1149–1152.
- Eldridge, L.L., Sarfatti, S., and Knowlton, B.J. (2002). The effects of testing procedure on remember-know judgments. *Psychon. Bull. Rev.* 9, 139–145.
- Eldridge, L.L., Engel, S.A., Zeineh, M.M., Bookheimer, S.Y., and Knowlton, B.J. (2005). A dissociation of encoding and retrieval processes in the human hippocampus. *J. Neurosci.* 25, 3280–3286.
- Fischl, B., Sereno, M.I., Tootell, R.B., and Dale, A.M. (1999). High-

- resolution intersubject averaging and a coordinate system for the cortical surface. *Hum. Brain Mapp.* 8, 272–284.
- Fortin, N.J., Wright, S.P., and Eichenbaum, H. (2004). Recollection-like memory retrieval in rats is dependent on the hippocampus. *Nature* 431, 188–191.
- Henson, R.N., Cansino, S., Herron, J.E., Robb, W.G., and Rugg, M.D. (2003). A familiarity signal in human anterior medial temporal cortex? *Hippocampus* 13, 301–304.
- Hicks, J.L., and Marsh, R.L. (1999). Remember-know judgments can depend on how memory is tested. *Psychon. Bull. Rev.* 6, 117–122.
- Hintzman, D.L., and Curran, T. (1994). Retrieval dynamics of recognition and frequency judgments - evidence for separate processes of familiarity and recall. *J. Mem. Lang.* 33, 1–18.
- Hintzman, D.L., Caulton, D.A., and Levitin, D.J. (1998). Retrieval dynamics in recognition and list discrimination: Further evidence of separate process of familiarity and recall. *Mem. Cognit.* 26, 449–462.
- Holdstock, J.S., Mayes, A.R., Roberts, N., Cezayirli, E., Isaac, C.L., O'Reilly, R.C., and Norman, K.A. (2002). Under what conditions is recognition spared relative to recall after selective hippocampal damage in humans? *Hippocampus* 12, 341–351.
- Insausti, R., Juottonen, K., Soininen, H., Insausti, A.M., Partanen, K., Vainio, P., Laakso, M.P., and Pitkanen, A. (1998). MR volumetric analysis of the human entorhinal, perirhinal, and temporopolar cortices. *AJNR Am. J. Neuroradiol.* 19, 659–671.
- Jacoby, L.L. (1991). A Process dissociation framework - separating automatic from intentional uses of memory. *J. Mem. Lang.* 30, 513–541.
- Kanwisher, N., McDermott, J., and Chun, M.M. (1997). The fusiform face area: a module in human extrastriate cortex specialized for face perception. *J. Neurosci.* 17, 4302–4311.
- Kirwan, C.B., and Stark, C.E. (2004). Medial temporal lobe activation during encoding and retrieval of novel face-name pairs. *Hippocampus* 14, 919–930.
- Liu, A.K., Belliveau, J.W., and Dale, A.M. (1998). Spatiotemporal imaging of human brain activity using functional MRI constrained magnetoencephalography data: Monte Carlo simulations. *Proc. Natl. Acad. Sci. USA* 95, 8945–8950.
- Liu, A.K., Dale, A.M., and Belliveau, J.W. (2002). Monte Carlo simulation studies of EEG and MEG localization accuracy. *Hum. Brain Mapp.* 16, 47–62.
- Mandler, G. (1980). Recognizing - the judgment of previous occurrence. *Psychol. Rev.* 87, 252–271.
- Manns, J.R., Hopkins, R.O., Reed, J.M., Kitchener, E.G., and Squire, L.R. (2003). Recognition memory and the human hippocampus. *Neuron* 37, 171–180.
- McCarthy, G., Nobre, A.C., Bentin, S., and Spencer, D.D. (1995). Language-related field potentials in the anterior-medial temporal lobe: I. Intracranial distribution and neural generators. *J. Neurosci.* 15, 1080–1089.
- McElree, B., Dolan, P.O., and Jacoby, L.L. (1999). Isolating the contributions of familiarity and source information to item recognition: A time course analysis. *J. Exp. Psychol. Learn. Mem. Cogn.* 25, 563–582.
- Norman, K.A., and O'Reilly, R.C. (2003). Modeling hippocampal and neocortical contributions to recognition memory: a complementary-learning-systems approach. *Psychol. Rev.* 110, 611–646.
- Ranganath, C., Yonelinas, A.P., Cohen, M.X., Dy, C.J., Tom, S.M., and D'Esposito, M. (2004). Dissociable correlates of recollection and familiarity within the medial temporal lobes. *Neuropsychologia* 42, 2–13.
- Rugg, M.D., and Yonelinas, A.P. (2003). Human recognition memory: a cognitive neuroscience perspective. *Trends Cogn. Sci.* 7, 313–319.
- Rugg, M.D., Mark, R.E., Walla, P., Schloerscheidt, A.M., Birch, C.S., and Allan, K. (1998). Dissociation of the neural correlates of implicit and explicit memory. *Nature* 392, 595–598.
- Rugg, M.D., Allan, K., and Birch, C.S. (2000). Electrophysiological evidence for the modulation of retrieval orientation by depth of study processing. *J. Cogn. Neurosci.* 12, 664–678.
- Smith, M.E., Stapleton, J.M., and Halgren, E. (1986). Human medial temporal lobe potentials evoked in memory and language tasks. *Electroencephalogr. Clin. Neurophysiol.* 63, 145–159.
- Squire, L.R. (1992). Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. *Psychol. Rev.* 99, 195–231.
- Squire, L.R., Stark, C.E., and Clark, R.E. (2004). The medial temporal lobe. *Annu. Rev. Neurosci.* 27, 279–306.
- Stark, C.E., and Squire, L.R. (2003). Hippocampal damage equally impairs memory for single items and memory for conjunctions. *Hippocampus* 13, 281–292.
- Stark, C.E., Bayley, P.J., and Squire, L.R. (2002). Recognition memory for single items and for associations is similarly impaired following damage to the hippocampal region. *Learn. Mem.* 9, 238–242.
- Tsivivilis, D., Otten, L.J., and Rugg, M.D. (2001). Context effects on the neural correlates of recognition memory: An electrophysiological study. *Neuron* 31, 497–505.
- Tsivivilis, D., Otten, L.J., and Rugg, M.D. (2003). Repetition effects elicited by objects and their contexts: An fMRI study. *Hum. Brain Mapp.* 19, 145–154.
- Tulving, E. (1985). Memory and consciousness. *Can. Psychol.* 26, 1–12.
- Wagner, A.D., Gabrieli, J.D., and Verfaellie, M. (1997). Dissociations between familiarity processes in explicit recognition and implicit perceptual memory. *J. Exp. Psychol. Learn. Mem. Cogn.* 23, 305–323.
- Weis, S., Klaver, P., Reul, J., Elger, C.E., and Fernandez, G. (2004a). Temporal and cerebellar brain regions that support both declarative memory formation and retrieval. *Cereb. Cortex* 14, 256–267.
- Weis, S., Specht, K., Klaver, P., Tendolkar, I., Willmes, K., Ruhlmann, J., Elger, C.E., and Fernandez, G. (2004b). Process dissociation between contextual retrieval and item recognition. *Neuroreport* 15, 2729–2733.
- Wixted, J.T., and Stretch, V. (2004). In defense of the signal detection interpretation of remember/know judgments. *Psychon. Bull. Rev.* 11, 616–641.
- Xiang, J.Z., and Brown, M.W. (1998). Differential neuronal encoding of novelty, familiarity and recency in regions of the anterior temporal lobe. *Neuropharmacology* 37, 657–676.
- Yonelinas, A.P. (2002). The nature of recollection and familiarity: A review of 30 years of research. *J. Mem. Lang.* 46, 441–517.
- Yonelinas, A.P., Kroll, N.E.A., Dobbins, I., Lazzara, M., and Knight, R.T. (1998). Recollection and familiarity deficits in amnesia: Convergence of remember-know, process dissociation, and receiver operating characteristic data. *Neuropsychology* 12, 323–339.
- Yonelinas, A.P., Kroll, N.E., Quamme, J.R., Lazzara, M.M., Sauve, M.J., Widaman, K.F., and Knight, R.T. (2002). Effects of extensive temporal lobe damage or mild hypoxia on recollection and familiarity. *Nat. Neurosci.* 5, 1236–1241.
- Yonelinas, A.P., Otten, L.J., Shaw, K.N., and Rugg, M.D. (2005). Separating the brain regions involved in recollection and familiarity in recognition memory. *J. Neurosci.* 25, 3002–3008.
- Yovel, G., and Paller, K.A. (2004). The neural basis of the butcher-on-the-bus phenomenon: when a face seems familiar but is not remembered. *Neuroimage* 21, 789–800.
- Zola, S.M., Squire, L.R., Teng, E., Stefanacci, L., Buffalo, E.A., and Clark, R.E. (2000). Impaired recognition memory in monkeys after damage limited to the hippocampal region. *J. Neurosci.* 20, 451–463.