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Dissociable correlates of recollection and familiarity within the medial temporal lobes

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Abstract

Regions in the medial temporal lobes (MTL) have long been implicated in the formation of new memories for events, however, it is unclear whether different MTL subregions support different memory processes. Here, we used event-related functional magnetic resonance imaging (fMRI) to examine the degree to which two recognition memory processes—recollection and familiarity—were supported by different MTL subregions. Results showed that encoding activity in the rhinal cortex selectively predicted familiarity-based recognition, whereas, activity in the hippocampus and posterior parahippocampal cortex selectively predicted recollection. Collectively, these results support the view that different subregions within the MTL memory system implement unique encoding processes that differentially support familiarity and recollection.

Keywords: Prefrontal; Inferior; Frontal; Hippocampus; Parahippocampal; Rhinal; Perirhinal; Medial; Temporal; Long-term; Episodic; Memory; Encoding; Subsequent; fMRI; Neuroimaging; Human

1. Introduction

It is well established that extensive damage to the medial temporal lobes (MTL) causes severe and relatively specific impairments in the ability to form new declarative memories. For example, amnesic patients with extensive MTL damage have been shown to exhibit deficits on explicit tests of free recall and recognition (Moscovitch & McAndrews, 2002; Yonelinas, Kroll, Dobbins, Lazzara, & Knight, 1998) but show intact performance on numerous measures of unconscious learning processes, such as skill learning, simple classical conditioning, and perceptual priming (Squire & Knowlton, 2000). The MTL regions that appear to be most critical for declarative memory formation are the hippocampal region (i.e., the dentate gyrus, CA 1–3, and the subicular complex) and the cortex of the parahippocampal gyrus (the entorhinal, perirhinal, and parahippocampal cortices). Based on anatomical differences between the hippocampal and parahippocampal regions (Lavanex & Amaral, 2000), several researchers have proposed that these subregions may implement distinct memory processes (Aggleton & Brown, 1999; Eichenbaum & Cohen, 2001; O'Reilly & Norman, 2002; O'Reilly & Rudy, 2001; Shastri, 2002). However, the characterization of how these regions might contribute to different aspects of declarative memory has been a topic of extensive controversy.

Results from numerous behavioral studies have supported the view that declarative memory is supported by at least two distinct processes: the assessment of an item's familiarity and the recollection of the context in which an item was encountered (Yonelinas, 2002). Based on an extensive review of neuropsychological and neurophysiological studies of recognition memory in rats, monkeys, and humans, Aggleton and Brown (1999) recently proposed that these two processes might depend on different MTL subregions. Specifically, these investigators hypothesized that, whereas the hippocampus supports recollection, regions within the parahippocampal gyrus support familiarity-based recognition. Similar predictions have been made based on other models of cortico-hippocampal interaction (Eichenbaum & Cohen, 2001; O'Reilly & Norman, 2002; O'Reilly & Rudy, 2001; Shastri, 2002).

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Other investigators, while acknowledging potential heterogeneity between MTL subregions, have suggested that these subregions may support familiarity and recollection to an equivalent degree. For example, Squire and Knowlton (2000) have suggested that familiarity and recollection may be functionally distinct, but that they are both forms of declarative memory that depend on integrated processing within the MTL. These investigators have suggested that dissociations between recollection and familiarity may reflect the disproportional dependence of recollection on strategic processing mediated by the prefrontal cortex (PFC) (Davidson & Glisky, 2002; Knowlton & Squire, 1995; Manns, Hopkins, Reed, Kitchener, & Squire, 2003). Consistent with this view, several neuropsychological studies suggest that recognition memory is relatively preserved in patients with PFC lesions, whereas performance is impaired on free recall and source memory tests that are thought to rely on recollection (for a review, see Ranganath & Knight, 2003).

Studies of amnesic patients with varying degrees of MTL damage have yielded conflicting results regarding whether different MTL regions support recollection and familiarity. Results from some neuropsychological studies have supported the view that the hippocampus is disproportionately critical for recollection, whereas parahippocampal regions can support familiarity-based recognition (Aggleton & Shaw, 1996; Baddeley, Vargha-Khadem, & Mishkin, 2001; Duzel, Vargha-Khadem, Heinze, & Mishkin, 2001; Holdstock et al., 2002; Mayes, Holdstock, Isaac, Hunkin, & Roberts, 2002; Yonelinas et al., 2002). However, results from other studies have suggested a similar role for both the hippocampus and parahippocampal regions in familiarity-based recognition and recollection (Manns et al., 2003; Stark & Squire, 2001, 2003).

In light of the difficulties in precisely specifying the locus and extent of lesions in amnesic patients, functional neuroimaging studies can provide a critical source of evidence regarding the nature of encoding processes implemented by different MTL subregions. Results from human neuroimaging studies have generally shown that encoding activity in the ventrolateral PFC, hippocampus, and the posterior parahippocampal cortex is enhanced for recollected items relative to forgotten items (Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998; Davachi, Mitchell, & Wagner, 2003; Davachi & Wagner, 2002; Fernandez et al., 1999; Henson, Rugg, Shallice, Josephs, & Dolan, 1999; Kirchhoff, Wagner, Maril, & Stern, 2000; Otten, Henson, & Rugg, 2001; Reber et al., 2002; Strange, Otten, Josephs, Rugg, & Dolan, 2002) as well as items that are recognized on the basis of familiarity (Brewer et al., 1998; Davachi et al., 2003; Henson et al., 1999). In contrast, robust correlates of familiarity-based recognition at encoding have not been identified (but see Davachi et al., 2003).

In previous neuroimaging studies, familiarity-related encoding activations may have been elusive because recognition memory is usually treated as a categorical variable (e.g., recollected versus recognized on the basis of familiarity versus forgotten). Thus, prior studies may have lacked adequate measurement sensitivity to detect changes of encoding activity that covaried with incremental changes in subsequent familiarity. Behavioral studies have indicated that, although recollection can be categorical (i.e., some items are recollected, while others are not), familiarity varies in a more continuous nature (i.e., differences in familiarity are reflected as a gradual change in recognition confidence; for a review see Yonelinas, 2002). Accordingly, in order to measure the neural correlates of familiarity, it may be more appropriate to use measures of memory that are sensitive to continuous changes in memory strength.

In the present study, we used event-related functional magnetic resonance imaging (fMRI) to determine how encoding processes within MTL subregions are related to familiarity and recollection. Subjects were scanned while they encoded a list of visually presented words (Fig. 1A). Half of the words were presented in red and half were presented in green. In a post-scan memory test, subjects were shown a series of studied words and novel foils and asked to indicate on a 1–6 scale how confident they were that the item was studied (i.e., recognition confidence judgments), and to indicate whether the item was studied in red or green (i.e.,

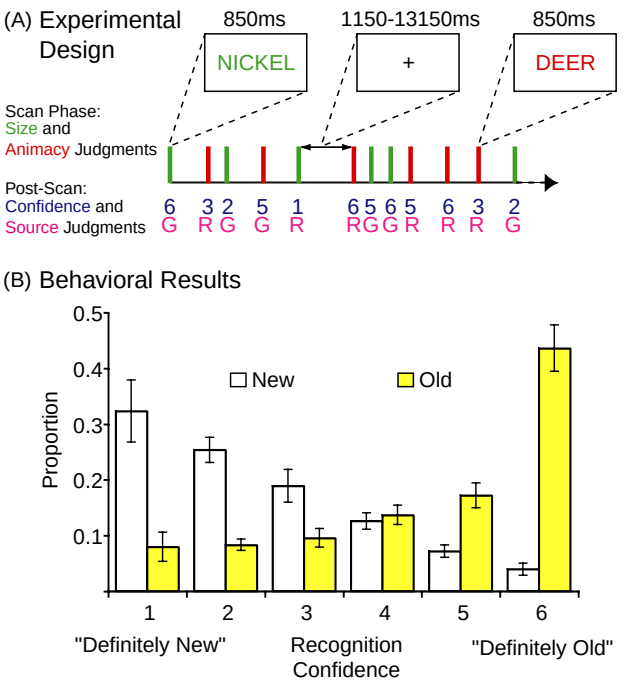

Fig. 1. Experimental design and behavioral results. (A) Schematic depiction of the sequence of events in one scanning run. During scanning, subjects viewed a series of words, and made either an animacy or size judgment for each, depending on the color in which the word was shown. After the scan session, subjects made recognition confidence (1: definitely new, . . . , 6: definitely old) and source memory (red or green) judgments for each word, and fMRI results during encoding were then analyzed as a function of these measures. (B) Mean proportions of studied ("old") and unstudied ("new") items endorsed at each confidence level. Error bars depict the standard error of the mean across subjects.

source memory judgments). Because the red and green items were presented in a mixed order during the study list they should be equally familiar at time of test, and it would be unlikely that subjects could use familiarity to make source judgments. Thus, differences in activation between items leading to accurate compared to inaccurate source judgments would reflect the encoding processes that are specific to recollection. In contrast, prior behavioral findings suggest that recollection leads to high confidence recognition responses whereas familiarity contributes to the entire range of recognition confidence in a graded manner (Yonelinas, 2001). Accordingly, familiarity was indexed as a continuous increase across confidence ratings 1–5.

2. Materials and methods

2.1. Participants

Thirteen neurologically intact right-handed native English speakers (seven females) aged 18–25 years participated in the study. These volunteers were recruited from the UC Berkeley and UC Davis student communities and were financially compensated for their participation.

2.2. Materials

Seven hundred and twenty nouns were selected from the MRC Psycholinguistic Database. All words were highly imageable (ratings greater then 500 on a scale from 100–700) and were selected to be unambiguous with respect to whether they were smaller/bigger than a shoebox and whether they were living/nonliving. Half of the words were randomly selected to serve as study items, with the constraint that they were balanced with the non-studied items for word frequency and word imageability.

2.3. Procedure

At the beginning of the experimental session, participants were scanned during performance of a visuomotor response task, in which a bimanual button press was made in response to a flashing checkerboard presented once every 20 s. Results from this task were used to derive an individual hemodynamic response function (HRF) (Aguirre, Zarahn, & D'Esposito, 1998).

Next, subjects performed six runs of word encoding. In each run, 60 words were presented at the center of the screen (half in red and half in green presented in a random order). Each word was presented for 850 ms followed by a fixation cross that was jittered from 1150 to 13,150 ms in 2000 ms intervals. To ensure that subjects later remembered the color of the items they were instructed that if the word was presented in green they were to decide whether it referred to an object that could fit in a shoebox (size judgment). If the word was presented in red, they were to indicate whether it referred to a living or nonliving object (animacy judgment). Yes/no decisions were made by pressing one of two buttons on a four-button fiber optic response device.

Immediately after the scanning session, subjects were presented with a self-paced recognition memory test containing a random mixture of studied words (360) and new words (360). The items were presented and responses collected on a laptop computer. For each word, subjects first rated how confident they were that the item was studied (1: sure it is new, ..., 6: sure it is old). They were instructed to spread their responses across the entire response scale, being careful to use all the response categories. For each item, they were also required to make a source memory judgment, indicating if the item was initially studied in green (i.e., the size judgment task) or red (i.e., the animacy task). If subjects felt they were unsure of the color of the word at study or if they felt that the word was not studied, they were instructed to guess.

2.4. MRI acquisition and processing

MRI data for seven volunteers were collected on a 1.5T Picker Medical Systems scanner at the Martinez VA Medical Center. Functional imaging was performed using a gradient echo echoplanar imaging (EPI) sequence sensitive to blood oxygenation level dependent (BOLD) contrast (TR = 2000, TE = 32, FOV = 240 mm, 64 × 64 matrix). Each functional volume consisted of 20 contiguous 5 mm axial slices oriented parallel to the AC–PC line. In addition, co-planar and high-resolution T1-weighted localizer images were also acquired. MRI data from six volunteers were collected on a 1.5T GE Signa scanner at the UC Davis Research Imaging Center. Functional imaging at this site was also done with a gradient echo EPI sequence (TR = 2000, TE = 40, FOV = 240 mm, 64 × 64 matrix), with each volume consisting of 24 contiguous 5 mm axial slices. Co-planar and high-resolution T1-weighted images were also acquired for each of these volunteers. fMRI data processing for all subjects included: motion correction using a six-parameter, rigid-body transformation algorithm provided by Statistical Parametric Mapping (SPM99) software, calculation of the global signal and power spectrum for each scanning run, and normalization of the time-series of each voxel by its mean signal value to attenuate between-run scaling differences.

2.5. Data analysis

Event-related BOLD responses were analyzed using a modified general linear model (Worsley & Friston, 1995). All models incorporated empirically derived estimates of intrinsic temporal autocorrelation (Zarahn, Aguirre, & D'Esposito, 1997), filters to attenuate frequencies above 0.25 Hz and below 0.01 Hz, and covariates to model the mean of each scanning run. RFs were estimated for each subject using empirically derived BOLD responses in the central sulcus during the visuomotor response task (Aguirre

et al., 1998). These HRFs were used to model BOLD responses to events in all subsequent analyses (Aguirre et al., 1998; Postle, Zarahn, & D'Esposito, 2000).

Responses during encoding trials were analyzed both as a function of subsequent recognition confidence and as a function of source memory accuracy. In the recognition confidence analyses, BOLD responses were modeled with six separate covariates corresponding to each subsequent recognition confidence category. In the source memory analyses, separate covariates were included to model responses to words subsequently judged "new" (i.e., words that evoked a 1, 2, or 3 confidence rating), words subsequently judged "old" (i.e., words that evoked a 4, 5, or 6 confidence rating), but for which the source memory judgment was incorrect, and words subsequently judged old for which the source memory judgment was correct.

Results from single-subject analyses were then entered into second-level *t*-tests treating subjects as a random variable. For these analyses, images of parameter estimates for each contrast of interest (i.e., linear combinations of β values from the regression analyses described above) were spatially normalized to the template from the International Consortium for Brain Mapping Project (Cocosco, Kollokian, Kwan, & Evans, 1997), resliced into 2 mm isotropic voxels, and spatially smoothed with an 8 mm Gaussian filter using SPM99 software. These normalized, smoothed subject-specific contrast images were then entered into a second-level group analysis—a one-sample *t*-test—in which the mean value across the group for each voxel was tested against zero. Significant regions of activation were identified using a two-tailed threshold of $P < 0.001$ and a minimum cluster size of at least eight contiguous voxels. Activations in Figs. 2 and 3 were overlaid on averaged T1-weighted images using the MRIcro software package (http://www.psychology.nottingham.ac.uk/staff/cr1/mricro.html). For archival purposes, results for all local maxima lying in gray matter (as visualized on the averaged T1 image) are summarized in Tables 1 and 2. However, we only discuss results obtained in regions in the MTL and PFC, given that this study was designed to test a priori hypotheses regarding the roles of these regions in recollection and familiarity. Follow-up region of interest (ROI) analyses were performed to characterize activity within MTL regions showing subsequent recollection or familiarity effects (see Section 3). In these analyses, the local maxima for the corresponding activations were used to define each

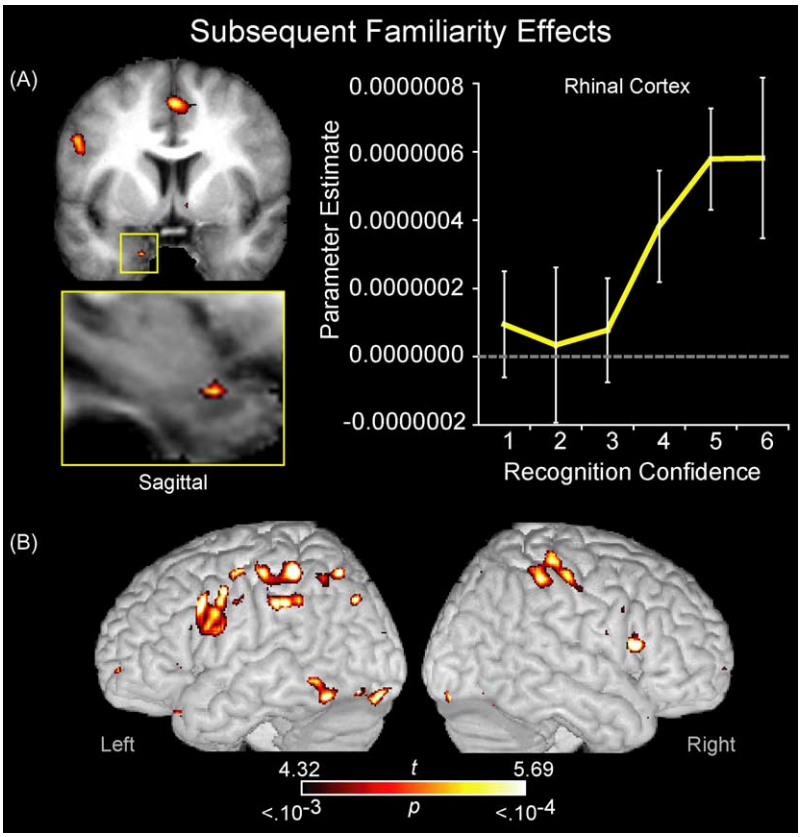

Fig. 2. Subsequent familiarity effects as indexed by linear increases in activity with increasing recognition confidence. (A) A region of the rhinal cortex (BA 36) that exhibited a subsequent familiarity effect is shown on an average of the spatially normalized T1-weighted scans from the group of subjects. A magnified view of this region is also shown in the sagittal plane. At right, parameter estimates indexing response amplitudes during encoding are plotted as a function of subsequent recognition confidence. Error bars depict the standard error of the mean across subjects. (B) Other regions of cortical activation are rendered on a template brain.

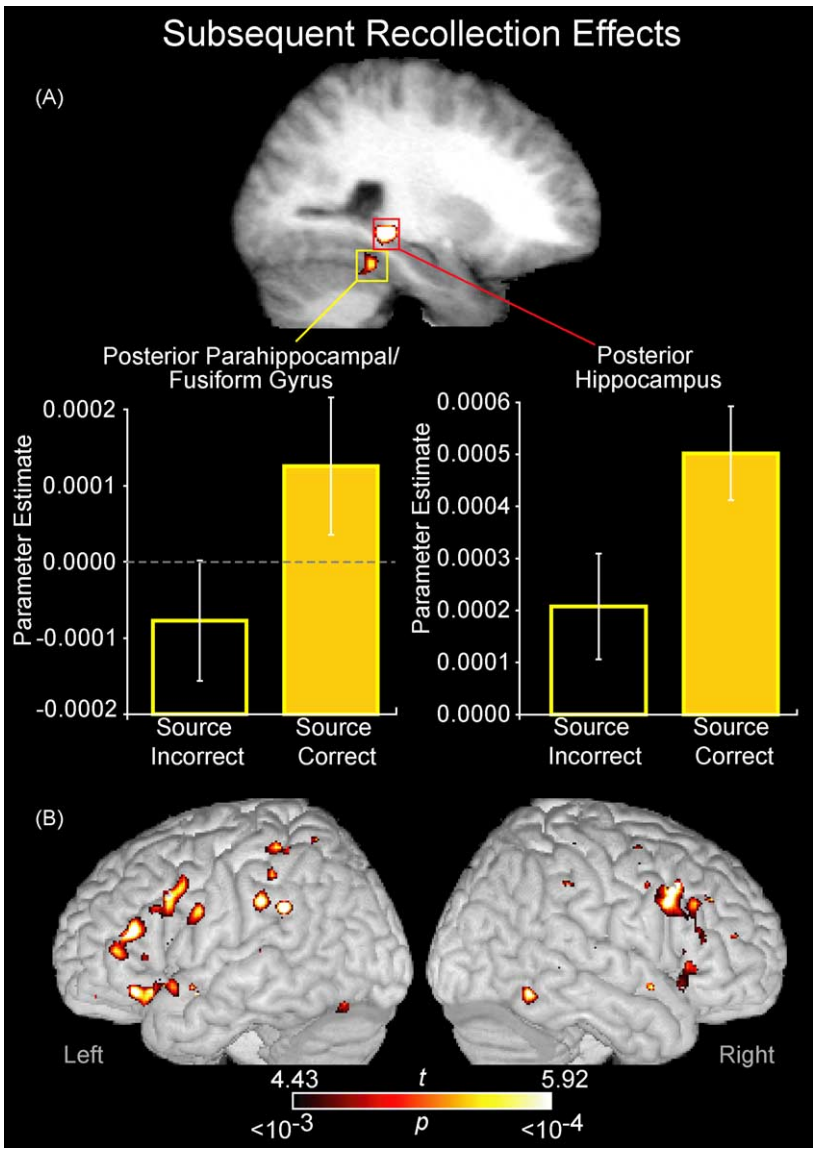

Fig. 3. Subsequent recollection effects as indexed by source memory accuracy. (A) Two MTL regions that exhibited subsequent recollection effects—the posterior hippocampus (shown within the red square) and the posterior parahippocampal cortex (shown within the yellow square)—are overlaid on an averaged T1-weighted image. Plots of the parameter estimates (indexing response amplitude) for recognized items eliciting correct (filled bars) vs. incorrect source judgments (open bars) are shown for each of these regions. (B) Other regions of cortical activation are rendered on a template brain.

ROI (similar results were obtained when the entire extent of activation was used to define each ROI). For these analyses, we additionally verified that similar effects were observed for subjects at each imaging site.

3. Results

3.1. Behavioral results

The distributions of recognition confidence ratings for studied and unstudied items are presented in Fig. 1B. The figure shows that the proportion of recognized items increased monotonically with recognition confidence. For non-recognized items (i.e., items eliciting a 1–3 confidence response), mean source accuracy (mean = 50.9%, S.D. = 6.7%) did not differ from chance [$t(12) < 1$]. However, for recognized items (i.e., items eliciting a 4–6 confidence response), source accuracy (mean = 67.8%, S.D. = 4.9%) was significantly above chance [$t(12) = 12.62$, $P < 0.001$], indicating that subjects were able to successfully recollect source information about many of the studied items. Examination of the data on a subject-by-subject basis revealed that only one subject failed to show above-chance source memory accuracy for recognized items. Accordingly, this subject's data was not included in the fMRI analyses of subsequent recollection effects described below. (We note, however, that inclusion or exclusion of this subject's data

Table 1
Regions exhibiting a subsequent familiarity effect, as indexed by recognition confidence

Region	BA	X	Y	Z	t
L. anterior parahippocampal gyrus	36	−18	6	−34	5.45
L. inferior frontal gyrus	44	−50	12	38	6.37
	6/44	−54	4	32	5.56
L. anterior superior frontal gyrus	10	−20	60	−2	5.26
L. gyrus rectus	11	−16	26	−26	5.52
R. anterior insula		34	18	14	7.94
L. fusiform gyrus	37	−50	−60	−16	5.88
L. inferior temporal gyrus	37	−50	−54	−8	5.55
L. precenteral gyrus	6	−34	0	44	6.89
L. superior frontal sulcus	6	−24	−8	54	5.74
Supplementary motor area	8	0	24	46	9.61
	6	−2	16	50	6.19
	6	0	4	54	5.93
L. inferior parietal lobule	40	−44	−36	36	6.36
		−46	−44	38	5.34
		−56	−30	38	6.27
		−44	−40	56	7.56
L. superior parietal lobule	7	−22	−68	54	6.43
		−28	−58	52	4.91
L. lingual gyrus	18	−10	−90	−16	6.4
		−14	−78	−14	6.37
L. cuneus	19	−26	−76	40	6.06
R. postcentral gyrus	2	46	−38	52	5.98
		44	−32	62	5.81
		52	−22	54	5.64
L. postcentral gyrus	3	−48	−24	54	5.82
R. cerebellum		16	−70	−18	7.44
R. caudate nucleus (head)		8	4	−6	5.31
L. anterior thalamus		−6	−4	8	5.16
L. medial thalamus		−4	−18	14	5.02
R. globus pallidus		18	−4	8	4.89

Note: These regions exhibited a linear relationship between encoding activation and subsequent recognition confidence across levels 1–5. R: right; L: left; BA: Brodmann's area.

Table 2
Regions exhibiting a subsequent recollection effect, as indexed by source memory accuracy

Region	BA	X	Y	Z	t
R. posterior hippocampus		26	−30	−4	8.71
R. posterior parahippocampal gyrus	37	30	−40	−16	5.33
L. inferior frontal gyrus	45	−52	38	16	5.97
	6/44	−48	0	28	5.43
R. inferior frontal gyrus	44	48	16	30	4.86
L. lateral orbital gyrus	47	−36	24	−12	5.63
R. inferior temporal gyrus	37	50	−56	−12	5.83
R. fusiform gyrus	37	44	−52	−20	4.98
L. superior temporal gyrus	38	−48	4	−10	6.32
		−48	12	−14	4.9
		−38	0	−12	8.7
R. superior temporal gyrus	38	64	6	−10	5.87
L. anterior insula		−32	18	−8	5.93
R. precentral gyrus	6	46	0	60	5.04
L. precentral gyrus	6	−40	−2	30	5.08
L. inferior parietal lobule	40	−52	−30	34	6.41
		−40	−40	48	5.18
R. inferior parietal lobule	40	48	−38	40	6.72
		36	−58	44	6.36
L. cuneus	17	−4	−94	8	8.62
L. mediodorsal thalamus		−16	−10	8	5.54

Note: These regions exhibited greater encoding activation for subsequently recognized words that elicited correct source judgments than for subsequently recognized words that elicited incorrect source judgments. R: right; L: left; BA: Brodmann's area.

from any of the analyses did not change the pattern of results.)

3.2. fMRI results

In order to identify regions whose encoding activity was associated with familiarity we examined the correlation between encoding activation and response confidence ratings 1–5 (i.e., computing a linear contrast of parameter estimates as follows: "5": +2; "4": +1; "3": 0; "2": −1; "1": −2). In order to identify regions related to recollection, we examined regions in which encoding activation for recognized items was significantly increased for items that elicited correct compared to incorrect source judgments.

Results from these analyses are summarized in Tables 1 and 2. As shown in Fig. 2A, a region showing familiarity-related encoding activation was observed in the left anterior medial parahippocampal gyrus (BA 36). Based on the location of this activation, and inspection of single-subject data, this region most likely corresponds to the rhinal cortex (i.e., either lying in peri- or ento-rhinal cortex (Amaral, 1999)). No other MTL region exhibited significant familiarity effects. However, regions in the hippocampus and in the right posterior collateral sulcus (spanning the posterior parahippocampal and fusiform gyri), shown in Fig. 3A, exhibited subsequent recollection effects. In addition, another region of activation related to recollection was observed in the MTL (MNI coordinates: 36, −24, −20), but upon inspection of its location on the averaged T1 image or on the single-subject T1-weighted images, it was unclear whether this area was within the hippocampus or within the posterior parahippocampal cortex. In light of this ambiguity, we do not comment further on this area.

The results from the above analyses suggest that different MTL subregions exhibited different patterns of subsequent memory effects. However, as we have previously shown (Ranganath & D'Esposito, 2001; Ranganath, Johnson, & D'Esposito, 2003), it is important to distinguish whether different patterns of activation in thresholded statistical maps reflect qualitative or merely quantitative differences in

response properties. Thus, to more extensively characterize the patterns of encoding activity within MTL subregions, ROIs were defined within the left rhinal, right hippocampal, and right posterior parahippocampal/fusiform regions identified above (see Section 2 for details).

First, we investigated whether the apparent dissociation observed between the three MTL subregions may have emerged as a result of the stringent statistical thresholds used to identify subsequent memory effects. Results of exploratory analyses within the rhinal cortex ROI did not reveal any trend toward greater activation for recognized items that elicited correct versus incorrect source judgments [$t(11) = -1.32$, $P > 0.2$]. Thus, we found no indications that activation in this region was predictive of recollection. Likewise, exploratory analyses within the hippocampus and parahippocampal/fusiform ROIs did not reveal a reliable relationship between encoding activation and subsequent familiarity [hippocampus: $t(12) = 1.79$, $P = 0.10$; parahippocampal/fusiform: $t(12) < 1$].

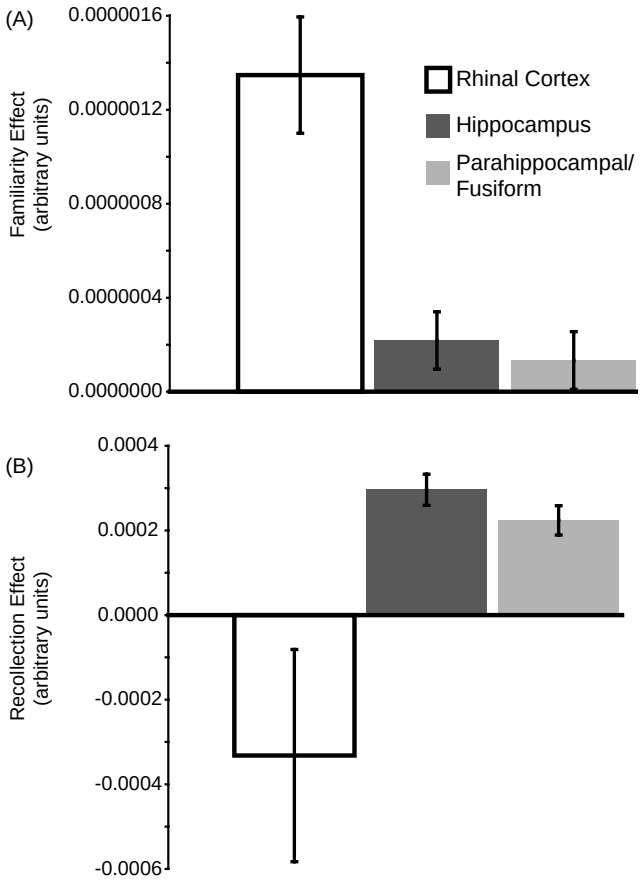

Fig. 4. Comparison of subsequent memory effects observed in rhinal, hippocampal, and parahippocampal ROIs. Bar graphs show relative magnitudes of (A) subsequent familiarity and (B) subsequent recollection effects observed in each ROI. Each plotted effect reflects a linear combination of β weights derived from GLM analyses (see Section 2 for details). Error bars depict the standard error of the mean across subjects.

To further explore the nature of the MTL activations, we compared the relative magnitudes of the familiarity and recollection effects across the three regions (see Fig. 4). This comparison was performed as a confirmatory analysis, in order to verify that the observed dissociation in subsequent memory effects across the three MTL regions reflected a qualitative difference in encoding activity patterns. To perform this analysis, the magnitudes of the recollection and familiarity effects were first z-transformed (using the mean effect pooled across subjects and ROIs) to allow comparisons of the recollection and familiarity related effects. Next, the rescaled effects were submitted to a Region (rhinal cortex versus hippocampus versus parahippocampal/fusiform) $\times$ Memory Effect (familiarity versus recollection) ANOVA. Results of this ANOVA revealed a significant Region $\times$ Memory Effect interaction [$F(2, 22) = 15.49$, $P < 0.005$], confirming that different patterns of encoding activation were observed in the three ROIs. Follow-up 2×2 ANOVAs revealed significant Region $\times$ Memory Effect interactions when the rhinal ROI was compared with the hippocampal ROI [$F(1, 11) = 15.97$, $P < 0.005$] and when the rhinal ROI was compared with the parahippocampal/fusiform ROI [$F(1, 11) = 15.95$, $P < 0.005$], but no significant interaction was observed when the hippocampal ROI was compared with the parahippocampal/fusiform ROI [$F(1, 11) < 1$]. This pattern of results confirms that the relative contributions of the rhinal cortex ROI to familiarity and recollection were indeed qualitatively different from those observed in the hippocampus and parahippocampal/fusiform ROIs.[1]

Finally, we note that, as described in Figs. 2B and 3B and Tables 1 and 2, subsequent memory effects were also observed in prefrontal, inferior temporal, and parietal cortical areas identified in other previous studies of memory formation (for reviews, see Buckner, Logan, Donaldson, & Wheeler, 2000; Paller & Wagner, 2002). Within the PFC, subsequent familiarity effects were observed in left orbitofrontal (BA 11) and frontopolar (BA 10) cortex, whereas subsequent recollection effects were observed within the anterior extent of left inferior frontal gyrus (BA 45) and in the lateral orbital gyrus (BA 47). Finally, a region in the posterior extent of the left inferior frontal gyrus (BA 6/44) exhibited both subsequent familiarity (local maxima: −54, 4, 32) and recollection (local maxima: −48, 0, 28) effects (see Fig. 5).

[1] It should be emphasized that these analyses were specifically intended to follow up on apparent dissociations between the loci of MTL regions identified in the thresholded statistical maps for subsequent recollection and familiarity effects. The results from these analyses confirmed that the pattern of encoding activity in the rhinal ROI identified in the familiarity contrast differed from the pattern observed in the hippocampal and parahippocampal ROIs that were identified in the recollection contrast. Although this outcome might not be surprising, given that these ROIs were selected on the basis of different contrasts, they nonetheless rule out the possibility that the different patterns of activation in these regions merely reflected a thresholding artifact.

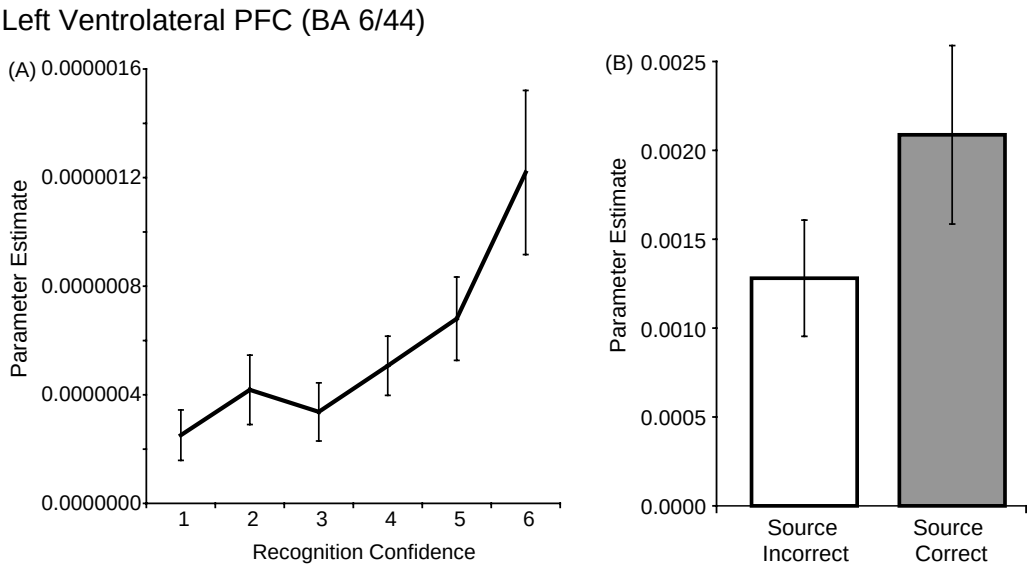

Fig. 5. Subsequent memory effects observed in left ventrolateral PFC (BA 6/44). (A) Encoding activation is plotted as a function of subsequent recognition confidence for the local maxima within left BA 6/44 ($X = -54$, $Y = 4$, $Z = 32$). (B) Encoding activation is plotted for recognized items eliciting correct (filled bar) vs. incorrect (open bar) source judgments for the local maxima within left BA 6/44 ($X = 48$, $Y = 0$, $Z = 28$). Error bars depict the standard error of the mean across subjects.

4. Discussion

In the present study, we used multiple methods to examine the neural correlates of memory formation within specific MTL subregions. Recognition confidence was explored as a parametric index of subsequent memory, yielding a sensitive measure of familiarity-based recognition. In addition, source memory accuracy provided a measure of subjects' ability to recollect qualitative information about study events. Our results revealed that encoding activity in distinct MTL subregions was differentially correlated with subsequent indices of familiarity and recollection. Furthermore, we observed that encoding activity in regions of PFC predicted subsequent familiarity and recollection. We discuss these findings and their implications below.

4.1. Distinct MTL subregions differentially contribute to familiarity and recollection

As noted earlier, recent research has suggested that hippocampal and parahippocampal regions may implement distinct encoding operations. Consistent with models proposing functional heterogeneity within the MTL (Aggleton & Brown, 1999; Eichenbaum & Cohen, 2001; O'Reilly & Norman, 2002; O'Reilly & Rudy, 2001; Shastri, 2002), we observed that encoding activity in a region in the left rhinal cortex specifically predicted familiarity-based recognition, but there was no indication that activity in this region was correlated with recollection. In contrast, encoding activity in regions in the posterior hippocampus and posterior parahippocampal cortex specifically predicted recollection, but activity in these regions did not reliably covary with subjective recognition confidence.

These findings add to accumulating evidence suggestive of a functional distinction between the hippocampus and the rhinal cortex. For example, results from one fMRI study revealed greater hippocampal and posterior parahippocampal activation during retrieval of source information than during item-recognition (Yonelinas, Hopfinger, Buonocore, Kroll, & Baynes, 2001). Results from another study showed that hippocampal activity during memory retrieval was selectively enhanced during recognition of items that were recollected relative to items that were recognized on the basis of familiarity (Eldridge, Knowlton, Furmanski, Bookheimer, & Engel, 2000). Finally, a recent analysis of results from four neuroimaging studies of memory retrieval showed that activity in the rhinal cortex differentiated between novel and familiar items, but was not sensitive to whether information about these items was recollected (Henson, Cansino, Herron, Robb, & Rugg, 2003). These findings suggest that rhinal and hippocampal regions exhibit dissociable patterns of activity at retrieval.

Concurrent with our investigation, another research group also used event-related fMRI to investigate the relationship between encoding activity in MTL subregions and source memory accuracy. Davachi et al. (2003) examined activity during a deep (visual imagery) encoding task that elicited high levels of recognition memory and a shallow (covert articulation) encoding task that elicited relatively poor memory performance. Their results showed that hippocampal activation for deeply encoded items was selectively enhanced if subjects correctly recalled encountering the item in the deep

encoding task. In contrast, perirhinal activation for deeply encoded items was enhanced if these items were subsequently recognized, regardless of whether subjects successfully recalled encountering them in the deep encoding task. Our results are consistent with the results of Davachi et al. (2003) suggesting that the hippocampus specifically contributes to source recollection. Our results further demonstrate that encoding activation in the rhinal cortex is directly related to familiarity-based recognition confidence ratings, and that rhinal and hippocampal regions make qualitatively distinct contributions to memory formation.

The sharp contrast between rhinal and hippocampal encoding activity observed here may seem surprising, given that most theoretical discussions of recollection and familiarity center around retrieval processing. Indeed, our findings raise the question of what types of encoding processes might be mediated by these regions. One possibility is that, whereas the rhinal and parahippocampal cortices encode the specific aspects of an event that can support familiarity in the absence of an adequate hippocampal representation, the hippocampus encodes the relations among these aspects (Eichenbaum & Cohen, 2001) that uniquely support conscious recollection (Moscovitch, 2000; Moscovitch & McAndrews, 2002). In support of this view, Davachi and Wagner (2002) found that encoding of the relations among triplets of words elicited greater hippocampal activation than did rote rehearsal of these words, whereas the opposite pattern was observed in the rhinal and parahippocampal cortices.

By this account, our findings of rhinal cortex activation associated with successful item recognition and hippocampal activation associated with successful source memory may reflect the differential reliance of these two measures on item versus relational processing (Eichenbaum & Cohen, 2001). However, the fact that encoding activity in the posterior parahippocampal cortex was sensitive to the successful recollection of source information suggests that the proposed role for the rhinal cortex in item-based encoding may not generalize to the posterior parahippocampal cortex. Indeed, although researchers have generally assumed a similar function for rhinal and parahippocampal cortical regions on the basis of parsimony, there has been little work to systematically compare the response properties of these two regions (Suzuki, 1999).

4.2. Prefrontal encoding activity associated with familiarity and recollection

In addition to examining activity within the MTL, we examined patterns of activity within the PFC, based on findings suggesting that the PFC may contribute disproportionately to recollection (Davidson & Glisky, 2002; Knowlton & Squire, 1995). However, as shown in Tables 1 and 2, subsequent memory effects related to both familiarity and recollection were observed within the PFC.

For example, frontopolar (BA 10) and medial orbitofrontal regions (BA 11) exhibited subsequent familiarity effects. These regions have been implicated in memory encoding (Frey & Petrides, 2000, 2002) and they are extensively interconnected with the rhinal cortex, where a subsequent familiarity effect was also observed. Although the present results do not suggest exactly how these regions contribute to familiarity-based recognition, the unique neuroanatomical connectivity of these areas suggests one possibility. As we have described elsewhere (Ranganath & Rainer, 2003), the orbital PFC and the rhinal cortex are among a small set of cortical areas that project to the cholinergic nuclei of the basal forebrain (Mesulam & Mufson, 1984). Given the role of acetylcholine in enhancing synaptic plasticity (Gu, 2002) and memory consolidation (Hasselmo, 1999), we have hypothesized that an orbitofrontal-rhinal circuit may act to modulate the encoding of items based on their relative novelty or distinctiveness (Kishiyama & Yonelinas, in press; Ranganath & Rainer, 2003). This hypothesis presents one potential mechanism by which orbitofrontal and rhinal cortical regions may modulate encoding in a way that subsequently impacts familiarity-based recognition.

Activation in many ventrolateral prefrontal areas predicted subsequent recollection. These areas spanned much of the left (BA 45/47) and right (BA 44) inferior frontal gyri. Finally, we note that activation in the posterior extent of the left inferior frontal gyrus (BA 6/44)—an area identified in numerous studies of verbal memory encoding (Buckner, 2003; Fletcher & Henson, 2001; Ranganath & Knight, 2003; Wagner, 1999)—predicted both subsequent recollection and familiarity (see Fig. 5). The precise contribution of these regions to memory encoding, and more generally to linguistic processing has been a topic of extensive debate (Gold & Buckner, 2002; Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997; Wagner, Pare-Blagoev, Clark, & Poldrack, 2001). Although some findings suggest that different subregions of the left inferior frontal cortex may implement different encoding processes (Gold & Buckner, 2002; Wagner et al., 2001), analyses on activity within these regions did not reveal any reliable qualitative differences between contributions of these subregions to recollection and familiarity (results available on request).

The present findings suggest that damage to the PFC may affect familiarity *and* recollection, in contrast to the view that the PFC uniquely contributes to recollection (Davidson & Glisky, 2002; Knowlton & Squire, 1995; Manns et al., 2003). Indeed, although not all PFC subregions exhibited both subsequent familiarity and recollection effects, most studies of patients with PFC lesions typically include patients with lesions that span multiple subregions (e.g., Janowsky, Shimamura, & Squire, 1989; McAndrews & Milner, 1991; Rapcsak, Polster, Glisky, & Comer, 1996; Stuss et al., 1994). Little work has been done in such studies to determine whether patients with PFC lesions exhibit familiarity deficits, however several studies have shown that such patients can exhibit particularly high false alarm rates on recognition tests (Delbecq-Derouesne, Beauvois, & Shallice, 1990; Rapcsak et al., 1998; Rapcsak et al.,

1996; Rapcsak, Reminger, Glisky, Kaszniak, & Comer, 1999; Schacter, Curran, Galluccio, Milberg, & Bates, 1996; Swick & Knight, 1999). These findings suggest that PFC lesions may impair familiarity-based recognition. Further work needs to be done to characterize the memory deficits exhibited by patients with PFC lesions, and the degree to which such deficits can be linked to impairments in specific encoding and/or retrieval processes. Nonetheless, the available evidence is consistent with the view that PFC implements executive control processes critical for accurate recollection and familiarity-based recognition memory (Ranganath & Knight, 2003).

5. Conclusions

In summary, the present results are consistent with the view that, although different MTL subregions play a joint role in the formation of complex episodic memories (Fell et al., 2001), each subregion implements distinct computations. Indeed, available evidence from neuroanatomy (Lavanex & Amaral, 2000), neurophysiology (Brown & Aggleton, 2001; Suzuki, 1999), neuroimaging (Davachi et al., 2003; Davachi & Wagner, 2002; Ranganath & D'Esposito, 2001), and neuropsychological (Aggleton & Brown, 1999; Eichenbaum & Cohen, 2001) studies is inconsistent with the view that the hippocampus, rhinal, and parahippocampal cortices implement the same types of processes. The present findings add to this picture by demonstrating that recollection and familiarity depend on different MTL subregions.

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