High-resolution fMRI Reveals Match Enhancement and Attentional Modulation in the Human Medial Temporal Lobe

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Abstract

■ A primary function of the medial temporal lobe (MTL) is to signal prior encounter with behaviorally relevant stimuli. MTL match enhancement—increased activation when viewing previously encountered stimuli—has been observed for goal-relevant stimuli in nonhuman primates during delayed-match-to-sample tasks and in humans during more complex relational memory tasks. Match enhancement may alternatively reflect (a) an attentional response to familiar relative to novel stimuli or (b) the retrieval of contextual details surrounding the past encounter with familiar stimuli. To gain leverage on the functional significance of match enhancement in the hippocampus, high-resolution fMRI of human MTL was conducted while participants attended, ignored, or passively viewed face and scene stimuli in the context of a modified delayed-match-to-sample task. On each "attended" trial, two goal-relevant stimuli were encountered before a probe that either matched or mismatched one of the attended stimuli, enabling examination of the consequences of encountering one of the goal-relevant stimuli as a match probe on later memory for the other (nonprobed) goal-relevant stimulus. fMRI revealed that the hippocampus was insensitive to the attentional manipulation, whereas parahippocampal cortex was modulated by scene-directed attention, and perirhinal cortex showed more subtle and general effects of attention. By contrast, all hippocampal subfields demonstrated match enhancement to the probe, and a postscan test revealed more accurate recognition memory for the nonprobed goal-relevant stimulus on match relative to mismatch trials. These data suggest that match enhancement in human hippocampus reflects retrieval of other goal-relevant contextual details surrounding a stimulus's prior encounter. ■

INTRODUCTION

The ability to discriminate between previously encountered and novel stimuli is an essential mnemonic function that depends on multiple neural mechanisms (Wagner, Shannon, Kahn, & Buckner, 2005; Simons & Spiers, 2003; Eichenbaum & Cohen, 2001; Gabrieli, 1998), including critical mechanisms subserved by the medial temporal lobe (MTL) (e.g., Mayes, Montaldi, & Migo, 2007; Preston & Wagner, 2007; Squire, Stark, & Clark, 2004; Ranganath & Rainer, 2003; Rugg & Yonelinas, 2003; Brown & Aggleton, 2001; Eichenbaum, 2000; Cohen & Eichenbaum, 1994; Scoville & Milner, 1957). One approach to investigating the functional neurobiology of recognition memory has been to examine the relationship between stimulus history (e.g., novel or familiar) and neural response direction (i.e., increased or decreased neural activity) during retrieval. Electrophysiological studies using this approach have revealed hippocampal and MTL cortical neurons that discriminate between novel and familiar stimuli through a firing rate increase to previously encountered stimuli (*match enhancement*) or through a firing rate increase to novel stimuli (*mismatch enhancement*) (e.g., Rutishauser, Mamelak, & Schuman, 2006; Xiang & Brown, 1998; Fried, MacDonald, & Wilson, 1997; Suzuki, Miller, & Desimone, 1997; Miller & Desimone, 1994; Rolls, Cahusac, Feigenbaum, & Miyashita, 1993; Otto & Eichenbaum, 1992). At a theoretical level, mismatch enhancement effects—in electrophysiological, regional CBF, and BOLD fMRI data—have garnered considerable attention, being linked to familiarity-based recognition decisions (e.g., Montaldi, Spencer, Roberts, & Mayes, 2006; Gonsalves, Kahn, Curran, Norman, & Wagner, 2005; Weis, Klaver, Reul, Elger, & Fernandez, 2004; Henson, Cansino, Herron, Robb, & Rugg, 2003; Brown & Aggleton, 2001; Curran, 2000), novelty detection (e.g., Kumaran & Maguire, 2006, 2007a, 2007b; O'Kane, Insler, & Wagner, 2005; Dolan & Fletcher, 1997; Knight, 1996; Stern et al., 1996; Tulving, Markowitsch, Craik, Habib, & Houle, 1996), and prediction error (e.g., Lisman & Grace, 2005; see also Shohamy & Wagner, 2008). By contrast, the functional significance of MTL match enhancement during recognition is less well characterized.

One recent perspective on MTL match enhancement is that this effect depends on the relationship between a test probe and an explicit goal state, wherein the increased response to matching test probes reflects a mnemonic signal

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marking the convergence of external inputs with internal goals (Duncan, Curtis, & Davachi, 2009). Supporting this view are data from two fMRI studies that revealed greater bilateral hippocampal activation for visual displays that matched versus mismatched an internally maintained representation or goal state (Duncan et al., 2009; Hannula & Ranganath, 2008). Importantly, Duncan et al. (2009) further demonstrated that hippocampal match enhancement does not reflect perceptual novelty per se, thus more tightly linking this enhanced hippocampal response to the match between a retrieval probe and an internally maintained representation.

Although offering a potential account of when match enhancement versus mismatch enhancement will be observed in the MTL, the hypothesis of Duncan et al. (2009) does not specify the mechanism(s) underlying the increased MTL response to match probes. One possibility is that when the probe stimulus matches an internal goal, the probe garners increased attention much like recognized stimuli have been posited to capture attention (Cabeza, Ciaramelli, Olson, & Moscovitch, 2008; cf. Hutchinson, Uncapher, & Wagner, 2009). From this perspective, MTL match enhancement might reflect a cascading feed forward effect of attentional gain enhancement into the MTL (Muzzio, Kentros, & Kandel, 2009). Alternatively, MTL match enhancement could reflect pattern completion (or episodic retrieval) of other goal-relevant contextual details that had co-occurred with the matching probe during its prior encounter. Extensive fMRI evidence indicates that hippocampal activation increases when retrieval cues trigger the successful recollection of event details (e.g., Kuhl, Shah, DuBrow, & Wagner, 2010; Yonelinas, Otten, Shaw, & Rugg, 2005; Eldridge, Knowlton, Furmanski, Bookheimer, & Engel, 2000). Thus, rather than reflecting an effect of attention, the hippocampal match enhancement observed in recent fMRI studies might reflect the increased probability that retrieval of contextual or event details will be triggered by a matching (vs. mismatching) retrieval probe (Cook, Marsh, & Hicks, 2006; Macken, 2002; Rajaram, 1996; Yonelinas & Jacoby, 1995). Importantly, this pattern completion account predicts that there should be specific mnemonic consequences when the probe stimulus matches (vs. mismatches) an internally maintained representation—namely, presentation of a matching probe should facilitate later memory for other goal-relevant contextual details that had co-occurred with the stimulus during its prior encounter.

The preceding proposed mechanisms underlying match enhancement assume that mnemonic goals can enhance MTL activation, either by increasing attention to the probe itself or by promoting the retrieval of other goal-relevant event details. Consistent with this assumption, recent fMRI data indicate that MTL retrieval responses are not automatically triggered by test probes but rather are modulated by goal-directed attention (e.g., Dudukovic & Wagner, 2007). Moreover, other data indicate that selectively attending to one stimulus (or one class of stimuli) while ignoring others results in (a) decreased neural activation in ventral temporal regions known to process the stimuli (or class of stimuli) being ignored, e.g., faces (fusiform cortex) or scenes (parahippocampal cortex), and (b) poorer explicit memory for the ignored stimuli (Yi, Kelley, Marois, & Chun, 2006; Gazzaley, Cooney, McEvoy, Knight, & D'Esposito, 2005; Gazzaley, Cooney, Rissman, & D'Esposito, 2005; Yi & Chun, 2005). Because distinct ventral temporal regions are thought to differentially project to and functionally influence specific subregions of parahippocampal gyrus—with cortical regions that represent faces and other objects putatively differentially projecting to perirhinal cortex and cortical regions that represent spatial stimuli putatively differentially projecting to parahippocampal cortex (Preston et al., 2010; Suzuki, 2009; Diana, Yonelinas, & Ranganath, 2008; Buffalo, Bellgowan, & Martin, 2006; Epstein, Harris, Stanley, & Kanwisher, 1999; Burwell & Amaral, 1998; Epstein & Kanwisher, 1998; Suzuki & Amaral, 1994)—an open question is whether attention modulates content-sensitive responses within MTL cortical regions and the hippocampal subfields to which they in turn project.

The current high-resolution fMRI study adopted a short-delay recognition memory paradigm that probes memory using a single stimulus that either matches or does not match one of two goal-relevant studied stimuli (Gazzaley, Cooney, McEvoy, et al., 2005). The primary goals were to examine whether match enhancement effects for face and scene stimuli are observed in specific subregions within the MTL and to test the hypothesis that encountering a matching probe has beneficial mnemonic consequences for other goal-relevant nonprobe stimuli that co-occurred with the probe at study. In particular, more accurate subsequent memory for the nonprobed goal-relevant stimulus on match relative to mismatch trials would provide evidence that match enhancement signals may reflect pattern completion. In the short-delay recognition paradigm, participants attended, ignored, or passively viewed face and scene stimuli, with the perceptual input being equivalent across the three conditions and only the goal varying. Thus, in addition to providing leverage on the nature of MTL match enhancement, this design also provided an opportunity to examine attention-specific responses within the hippocampus and MTL cortices. In so doing, the study sheds light on the intended and unintended neural and mnemonic consequences of an individual's mnemonic goals.

METHODS

Participants

Nineteen right-handed, native English speakers (12 women; age range = 18–28 years, mean = 21.6 years) were paid $60 for their participation. Data from three additional participants were excluded from analysis, one because of excessive motion (>8 mm across scans) and two because of poor behavioral performance (one failed to respond on more than half of the trials, and the other was less than

70% accurate on the two encoding tasks). None of the remaining participants moved more than 3 mm across scans. Informed consent was obtained from all subjects in accordance with the institutional review board at Stanford University.

Materials

The stimuli consisted of grayscale photographs of 476 novel faces (238 women, 238 men) and 476 novel scenes (238 indoor, 238 outdoor), which were 128 pixels wide × 150 pixels tall. Of these images, 325 faces and 325 scenes were used during the encoding task. The remaining images served as novel stimuli in the postscan recognition memory test.

Modified Delayed-match-to-sample Task

To examine the effects of goal-directed attention on MTL activation, we used the variant of Gazzaley, Cooney, McEvoy, et al. (2005) of the delayed-match-to-sample (DMS) short-delay paradigm for faces and scenes. Immediately before scanning, subjects were given detailed instructions and were shown a diagram of sample trials to ensure their understanding of the task. Subjects were then presented with 150 trials of the DMS task over the course of ten functional scans (15 trials/scan). Each trial consisted of a sample, delay, and probe period (Figure 1A). During the sample period, two faces and two scenes were presented sequentially in random order. The sex of the face and the type of scene (indoor vs. outdoor) were held constant within each trial; across trials, the frequency of male and female faces and of indoor and outdoor scenes was equivalent.

Each image was presented for 800 msec with a 200-msec blank screen ISI. Subjects were instructed to either (1) remember the faces and ignore the scenes ("faces"), (2) remember the scenes and ignore the faces ("scenes"), or (3) passively view the faces and scenes ("view"). After the presentation of the sample images, a fixation cross appeared on the screen for 8500 msec, after which a probe image was presented for 1000 msec followed by a blank screen for 500 msec. The probe was a novel or studied face (faces), a novel or studied scene (scenes), or a leftward or rightward arrow (view). During this 1500-msec probe period, subjects indicated whether the probe matched one of the sample stimuli on the current trial (faces/scenes) or they indicated the direction the arrow was pointing (view). The probe was a match 50% of the time and a novel item 50% of the time for the faces and scenes conditions. Similarly, the arrows in the view condition were evenly split between pointing leftward or rightward. All responses

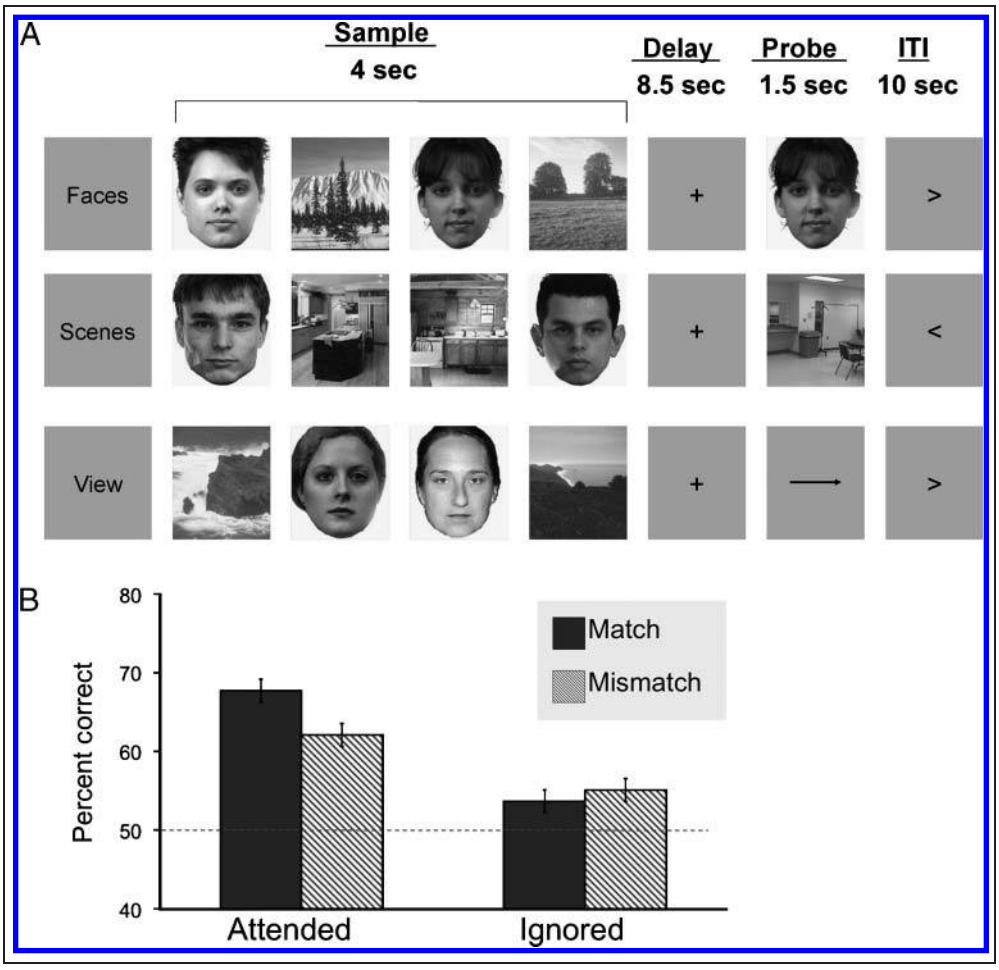

Figure 1. (A) The experimental design for the faces and scenes trials of the DMS task and for the view trials. (B) Forced-choice recognition memory accuracy for attended and ignored stimuli that initially appeared during the sample period of match versus mismatch trials. The dashed line indicates chance performance (50%). Error bars represent the within-subjects error terms.

were made using a keypad under the right hand. At the end of each trial, subjects engaged in a simple arrows task for 10 sec, which served as a baseline. The arrows task entailed pressing one of two keys to indicate the direction (left or right) an arrowhead was pointing (Stark & Squire, 2001).

The three conditions (faces, scenes, or view) alternated in miniblocks of five trials. Each scan consisted of three miniblocks, one of each condition, for a total of 50 trials per condition across the experiment. The order of miniblocks was counterbalanced across scans. Before each miniblock began, subjects were presented with a 2000-msec task cue (faces, scenes, or view), which informed them of how to direct their attention during the subsequent sample and delay periods. Subjects were asked to follow the current instruction on every trial until a new task cue appeared. The presentation of images was counterbalanced such that across subjects, each image appeared in each of the three conditions.

Recognition Memory Task

After scanning, subjects were given an unexpected memory test for the images seen during the modified DMS task. One face and one scene from each of the 150 DMS trials were pseudorandomly selected as target memory probes. Importantly, images that appeared more than once during the DMS task (i.e., the goal-relevant stimulus that appeared a second time as the probe on "match" trials) were not tested. Subjects were presented with 300 forced-choice recognition memory trials (150 faces, 150 scenes), each consisting of one studied image and one novel foil, matched for sex (faces) or scene type. On each trial, participants had 3000 msec to decide which of the two images had been encountered during the DMS task. They then rated their decision confidence as low, medium, or high; these confidence ratings were self-paced. Trials were presented in random order.

fMRI Data Acquisition

Functional imaging was performed on a 3-T Signa MRI system (GE Medical Systems, Milwaukee, WI). Before functional imaging, high-resolution, T2-weighted, flow-compensated, fast spin-echo anatomical images (repetition time = 3000 msec, echo time = 68 msec, 0.43 × 0.43 mm in-plane resolution) were acquired from 22 contiguous 3-mm slices perpendicular to the main axis of the hippocampus to allow for the segmentation of the hippocampal subfields (dentate gyrus/$CA_{2/3}$, CA_1, and subiculum) and MTL cortices (entorhinal, perirhinal, and parahippocampal). Functional images, colocalized to the anatomical images, were acquired using a high-resolution T2*-sensitive two-shot gradient-echo spiral in/out pulse sequence (repetition time/volume = 4000 msec, echo time = 34 msec, flip angle = 90°, field of view = 20 cm, 1.89 × 1.89 × 3.0 mm resolution; Glover & Law, 2001). A total of 930 functional volumes were acquired for each subject across ten functional scans of the modified DMS task. Two discarded volumes (a total of 8 sec) were collected at the beginning of each scan to allow for T1 stabilization. A bite bar was used to minimize head motion.

fMRI Data Analysis

All imaging data were preprocessed using SPM2 (Wellcome Department of Imaging Neuroscience, London). Functional images were corrected for differences in slice acquisition timing, followed by realignment to correct for motion. A mean T2*-weighted functional volume was computed during realignment, and the T2-weighted anatomical volume was coregistered to this mean functional volume. The imaging data were not normalized or smoothed to preserve the high spatial resolution.

Voxel-based statistical analyses were conducted in SPM2 at the individual subject level under the assumptions of the general linear model with volumes treated as a time series. A finite impulse response model was constructed for each subject to estimate the observed event-related hemodynamic responses for each of the five DMS conditions—faces-match, faces-mismatch, scenes-match, scenes-mismatch, and view—without making assumptions about the shape of the hemodynamic responses. For the model, we used six time points (bin size = 4 sec) starting with each trial's onset and ending with the onset of the subsequent trial. Incorrect trials were modeled separately and were not included in the analysis. In addition to the condition regressors, the general linear model included a basis set that served to high-pass filter the data and a covariate representing session effects. To further test the hypothesis that encountering a matching probe has beneficial mnemonic consequences for goal-relevant nonprobed items, an additional finite impulse response model was constructed to assess the relationship between probe period activation and subsequent memory performance for the nonprobed items on faces and scenes match and mismatch trials.

Group analyses were performed using an anatomically motivated ROI approach that targeted MTL subregions. Specifically, anatomically defined ROIs for the hippocampal subfields (dentate gyrus/$CA_{2/3}$, CA_1, and subiculum) and MTL cortical areas (entorhinal, perirhinal, and parahippocampal) were demarcated on each subject's high-resolution structural images using techniques adapted for analysis and visualization of MTL subregions (e.g., Preston et al., 2010; Zeineh, Engel, Thompson, & Bookheimer, 2003; Pruessner et al., 2002; Insausti et al., 1998; Amaral & Insausti, 1990; see also Carr, Rissman, & Wagner, 2010). For each ROI, data were averaged across all voxels within the region, and BOLD signal deconvolution was performed using MarsBaR (http://marsbar.sourceforge.net), thus allowing assessment of the percent signal change associated with each condition (relative to the baseline). Effects related to the sample/delay and probe portions of each trial were examined separately. To examine sample/delay attention-dependent effects, the integrated percent signal change

Table 1. Mean Accuracy and RT (msec; Restricted to Correct Trials) on the Three DMS Tasks, with Standard Deviations in Parentheses

	% Correct	*RT*
Faces		
Match	90.2 (9.9)	804 (111)
Mismatch	93.6 (8.6)	798 (92)
Scenes		
Match	83.0 (10.9)	868 (109)
Mismatch	97.6 (4.4)	831 (96)
View	99.6 (1.1)	574 (62)

was calculated from 4 to 12 sec after the trial onset (i.e., two to three repetition times), which spanned the trial period before probe onset (which occurred 12.5 sec after trial onset). When taken together with the 10-sec intertrial interval, this ensured that the estimate of the sample/delay response was unlikely to be contaminated by carryover of probe-related response of trial $N - 1$ and of the current trial. Probe-related activation was estimated as the percent signal change from 16 to 20 sec after trial onset and was used to examine match/mismatch and stimulus class effects. Importantly, because match enhancement or mismatch enhancement effects were defined by a probe-related factor (i.e., whether the probe matched or mismatched one of the goal-relevant samples), the observed effects were unlikely to be due to carryover of sample/delay period activity (if anything, any such carryover would have made it harder to identify match/mismatch enhancement).

BEHAVIORAL RESULTS

Performance on the Modified Delayed-match-to-sample Task

Accuracy, defined as percent correct [(Hits + CRs) / 2], differed between the three DMS conditions, $F(2, 36) = 25.25$, $p < .0005$, with participants responding more accurately to the arrow probes (view; 99.6) than to the face probes (faces; 92.0) and scene probes (scenes; 90.3). Accuracy on the faces and scenes trials did not significantly differ, $F(1, 18) = 2.06$, $p > .10$. However, participants were more accurate in mismatch trials than that in match trials, $F(1, 18) = 16.98$, $p = .001$ (Table 1). A significant interaction with stimulus type, $F(1, 18) = 19.72$, $p < .0005$, revealed significantly higher accuracy on mismatch than match scenes trials, $F(1, 18) = 38.51$, $p < .0005$, but a difference between mismatch and match faces trials that did not reach significance, $F(1, 18) = 1.63$, $p > .10$.

Because of technical difficulties, RT data were not collected from one participant. For the remaining participants, mean median RTs on correct trials differed between the three conditions, $F(2, 34) = 170.76$, $p < .0005$ (Table 1), with participants responding faster to the arrow probes than to the face probes and scene probes. For the latter conditions, participants were significantly slower in scenes than that in faces trials, $F(1, 17) = 50.77$, $p < .0005$. Moreover, although RT did not significantly differ between match and mismatch trials, $F(1, 17) = 3.09$, $p > .05$, there was a significant interaction with stimulus type, $F(1, 17) = 4.75$, $p < .05$. Specifically, RTs were significantly faster for mismatch than for match scenes trials, $F(1, 17) = 8.62$, $p < .01$, whereas RTs for match and mismatch faces trials did not differ ($F < 1$).

Recognition Memory Performance

The postscan two-alternative forced-choice recognition memory test revealed better memory for items that were attended as opposed to ignored or passively viewed, $F(2, 36) = 15.35$, $p < .0005$, and better memory for faces than scenes, $F(1, 18) = 7.93$, $p < .05$, with no Attention × Stimulus Type interaction, $F(2, 36) = 2.06$, $p > .10$ (Table 2). Specifically, recognition accuracy was higher for attended faces than for faces that were ignored or passively viewed, $F(2, 36) = 13.06$, $p < .0005$. Moreover, recognition accuracy for ignored and passively viewed faces did not significantly differ from each other, $F(1, 18) = 1.08$, $p > .10$, with memory for passively viewed faces not significantly differing from chance performance (50%), $t(18) = 1.71$, $p > .10$. Similarly, attended scenes were better remembered than scenes that were ignored or passively viewed, $F(2, 36) = 8.54$, $p = .001$. Moreover, memory for ignored and passively viewed scenes did not significantly differ from each other ($F < 1$), and memory for ignored scenes did not significantly differ from chance (50%; $t < 1.14$, $p > .10$).

Importantly, there was a significant Attention (attended, ignored) × Probe Type (match, mismatch) interaction, $F(1, 18) = 5.86$, $p < .05$ (Figure 1B). Specifically, recognition accuracy was superior for attended stimuli that had appeared in the sample period of match trials (67.7%) than for attended stimuli that had appeared in the sample period of mismatch trials (62.1%), $F(1, 18) = 10.98$, $p < .01$. This effect was present for both faces and scenes, as evidenced

Table 2. Mean Accuracy and Response Confidence (Correct Trials) on the Postscan Two-alternative Forced-choice Recognition Memory Test, with Standard Deviations in Parentheses

	Face Stimuli		*Scene Stimuli*	
	% Correct	*Confidence*	*% Correct*	*Confidence*
Attended	68.2 (11.3)	1.95 (.35)	61.5 (9.6)	1.96 (.37)
Ignored	56.8 (8.0)	1.63 (.28)	51.8 (7.0)	1.62 (.30)
Viewed	53.6 (9.2)	1.63 (.29)	53.1 (6.0)	1.64 (.32)

by the absence of a Stimulus Type × Probe Type interaction ($F < 1$), thus indicating that both attended faces and attended scenes from the sample period (i.e., the nonprobed goal-relevant stimuli) were remembered better if they had been followed by a probe that matched versus mismatched the other member of the goal-relevant sample set. We stress that these recognition test stimuli from attended trials had appeared only once during the modified DMS task—that is, they appeared during the sample period and *not* during the probe period. As such, processing of these stimuli during the sample/delay period was presumably comparable on match and mismatch trials, indicating that the superior subsequent memory for attended stimuli on match trials than on mismatch trials must be due to processes triggered by and occurring during the probe period. This behavioral pattern would be predicted if the match probe served to trigger pattern completion (retrieval) of the other attended item at the time of probe onset, as it is memory for this other attended item that is being assessed on the postscan recognition memory test. In contrast, memory for ignored stimuli did not differ for items that had originally appeared in the sample period of match (53.7%) versus mismatch trials (55.1%; $F < 1$; Figure 1B), and again, there was no Stimulus Type × Probe Type interaction ($F < 1$).

Mean recognition confidence ratings on correct trials were computed for each condition for both face and scene stimuli using a scale from 1 to 3, where 1 = *low confidence responses*, 2 = *medium confidence responses*, and 3 = *high confidence responses* (Table 2). Recognition confidence was highest for attended versus ignored or passively viewed stimuli, $F(2, 36) = 28.89$, $p < .0005$, with no difference for face versus scene stimuli ($F < 1$) and no Attention × Stimulus Type interaction ($F < 1$). Attended faces were more confidently recognized than ignored or passively viewed faces, $F(2, 36) = 29.78$, $p < .0005$, which did not significantly differ from one another ($F < 1$). Similarly, attended scenes were more confidently recognized than ignored or passively viewed scenes, $F(2, 36) = 14.58$, $p < .0005$, which did not significantly differ from each other ($F < 1$). Recognition confidence did not differ for stimuli that had appeared during the sample period of match versus mismatch trials ($F < 1$), and there was no Stimulus Type × Probe Type interaction, $F(1, 18) = 1.24$, $p > .10$, nor an Attention × Probe Type interaction ($F < 1$).

FMRI RESULTS

Match/Mismatch Effects

To examine the effect of probe type—either match or mismatch—on MTL activation during the DMS task, an ANOVA was performed on the probe period data from each anatomically defined ROI in the MTL cortex (i.e., parahippocampal, perirhinal, and entorhinal cortices) and hippocampus (i.e., dentate gyrus/$CA_{2/3}$, CA_1, and subiculum), with factors of Condition (faces, scenes), Probe Type (match, mismatch), and Hemisphere (left, right). Probe period as well as the below reported sample/delay period analyses were restricted to correct trials.

The effect of probe type differed between MTL cortical regions and subregions of the hippocampus, as evidenced by a significant Region (MTL cortex, hippocampus) × Probe Type interaction, $F(1, 18) = 6.10$, $p < .05$. Specifically, analyses of the probe period data from each MTL cortical region—that is, parahippocampal, perirhinal, and entorhinal ROIs—revealed neither a match enhancement effect (match > mismatch) nor a mismatch enhancement effect (mismatch > match) in any region (Fs < 3.15, ps > .05). Moreover, probe type did not interact with condition or with hemisphere (Fs < 2.43, $p > .10$) in the MTL cortex. In contrast, significant match enhancement effects were observed in CA_1 and in subiculum (Fs > 5.54, ps < .05), and there was a trend for match enhancement in dentate gyrus/$CA_{2/3}$, $F(1, 18) = 3.90$, $p = .064$ (Figure 2). Although probe type did not interact with condition in any hippocampal subregion (Fs < 1.10, ps > .10), match enhancement was more pronounced in left versus right CA_1, as evidenced by a Hemisphere × Probe Type interaction, $F(1, 18) = 6.22$, $p < .05$. By contrast, match enhancement effects did not significantly differ by hemisphere in dentate gyrus/$CA_{2/3}$ or in subiculum (Fs < 3.39, ps > .05).

If the significant match enhancement effects observed in CA_1 and subiculum reflect pattern completion, with a match probe triggering memory for the other attended stimulus from the sample set, then hippocampal activation during the probe period may predict the subsequent mnemonic fate of the other attended (but nonprobed) goal-relevant stimulus. Although this analysis is underpowered because of the limited number of trials available and thus interpretative

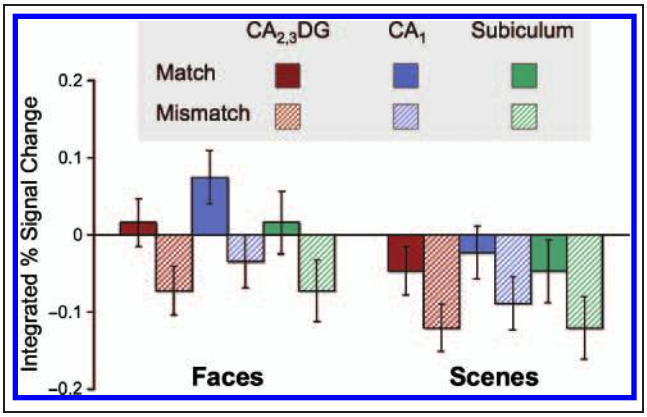

Figure 2. Probe period activation from anatomically defined hippocampal ROIs, collapsed across hemisphere. The bar graphs show integrated percent signal change from each ROI during the probe period (16–20 sec poststimulus onset) for match and mismatch face and scene probes. Match enhancement was more pronounced in left versus right CA_1, and a preference for face stimuli was present in right but not left dentate gyrus/$CA_{2,3}$. There were no other significant interactions with hemisphere. Error bars represent the within-subjects error terms.

caution is warranted, there was a trend in the right subiculum for an enhanced subsequent memory effect for the other nonprobed goal-relevant face on match versus mismatch face trials, $F(1, 18) = 3.88$, $p = .06$. In right subiculum, probe period activation during face match trials was associated with subsequent memory for the other attended face, $F(1, 18) = 5.48$, $p < .05$, whereas probe period activation during face mismatch trials did not predict subsequent memory for attended faces ($F < 1$). Thus, this subsequent memory effect observed in right subiculum on match trials may reflect pattern completion of the other nonprobed goal-relevant face. However, in contrast to the behavioral results and this fMRI subsequent memory effect for the nonprobed face on match trials, hippocampal activation during the probe period of scene match trials was not associated with enhanced subsequent memory for the nonprobed goal-relevant scene (Fs < 1).

Stimulus Class Effects

In addition to exploring match/mismatch effects during the probe period, we also examined stimulus class effects for face and scene probes (i.e., the effects of condition). Of the MTL cortical ROIs, parahippocampal cortex showed a strong stimulus class effect during the probe period, $F(1, 18) = 16.38$, $p = .001$, wherein both left and right parahippocampal cortex were more active during scene probes than face probes (Fs > 9.54, ps $\leq .01$). In contrast, no stimulus class effects were observed in perirhinal or entorhinal cortex (Fs < 1.56, ps $> .10$).

Of the hippocampal ROIs, only right dentate gyrus/$CA_{2/3}$ demonstrated a significant effect of stimulus class during the probe period, as evidenced by a significant Hemisphere × Condition interaction, $F(1, 18) = 5.93$, $p < .05$. Specifically, right dentate gyrus/$CA_{2/3}$ was more active during face probes than scene probes, $F(1, 18) = 4.56$, $p < .05$, whereas left dentate gyrus/$CA_{2/3}$ did not exhibit a stimulus class preference ($F < 1$). Although not significant, both right CA_1 ($p < .07$) and right subiculum ($p < .06$) also demonstrated trends for greater activation during faces versus scene probes.

Attention-dependent Effects

Parahippocampal, perirhinal, and entorhinal cortical ROIs were examined to assess whether there was an effect of attention during the sample/delay period. Specifically, we sought to determine whether activation in the MTL cortices varied depending on whether subjects were attending to faces (and ignoring scenes; faces), attending to scenes (and ignoring faces; scenes), or passively viewing both stimulus classes (view). As depicted in Figure 3, parahippocampal activation was significantly modulated by attention, $F(2, 36) = 12.41$, $p < .0005$, whereas activation in perirhinal and entorhinal cortices was not significantly modulated by this factor (Fs < 1.16, ps $> .10$). Both left and right parahippocampal cortex were modulated by scene attention, with greater activation for attended versus ignored scenes (Fs > 8.55, ps $< .01$) and attended versus passively viewed scenes (Fs > 25.67, ps $< .0005$). By contrast, although perirhinal cortex tended to show a more generalized attention-based activation increase, with greater activation on average when attending to faces and when attending to scenes than when passively viewing them, the effect of attention did not reach significance, $F(1, 18) = 2.31$, $p = .146$. Comparison of the parahippocampal and perirhinal patterns revealed a trend for a Region × Attention interaction, $F(2, 36) = 2.51$, $p = .095$, which again reflects that parahippocampal cortex was modulated by goal-directed attention to scenes, whereas the subtle effect of attention in perirhinal cortex was generalized across stimulus class.

In contrast to parahippocampal cortex and to a lesser extent perirhinal cortex, the anatomically defined ROIs for the hippocampal subfields, including dentate gyrus/$CA_{2/3}$, CA_1, and subiculum, were not significantly modulated by attention (Fs < 1.59, ps $> .10$). Comparison of the MTL cortical and hippocampal patterns revealed a significant

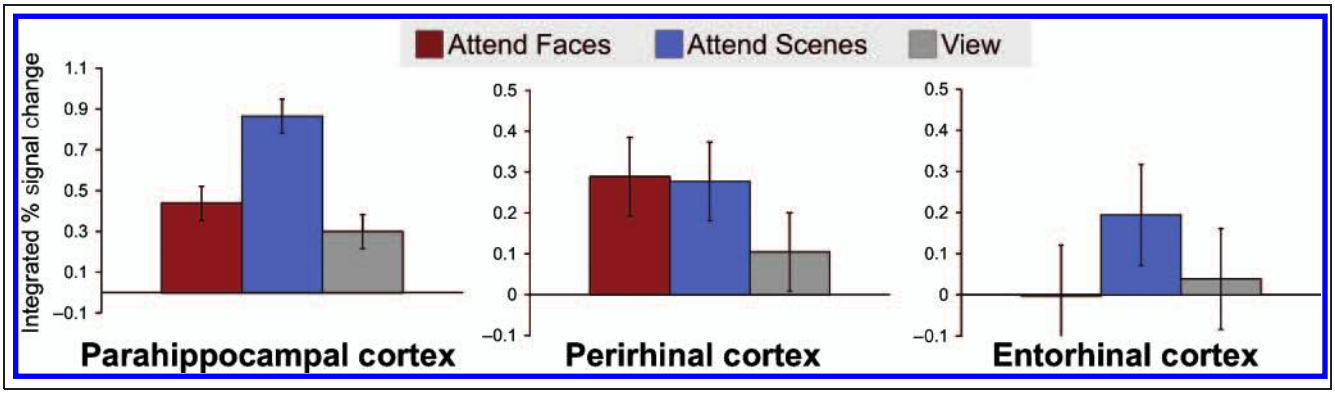

Figure 3. Sample/delay period activation from anatomically defined MTL cortical ROIs collapsed across hemisphere. The bar graphs show integrated percent signal change from ROIs during the sample/delay period (4–12 sec poststimulus onset). There were no significant Hemisphere × Attention interactions. Error bars represent the within-subjects error terms.

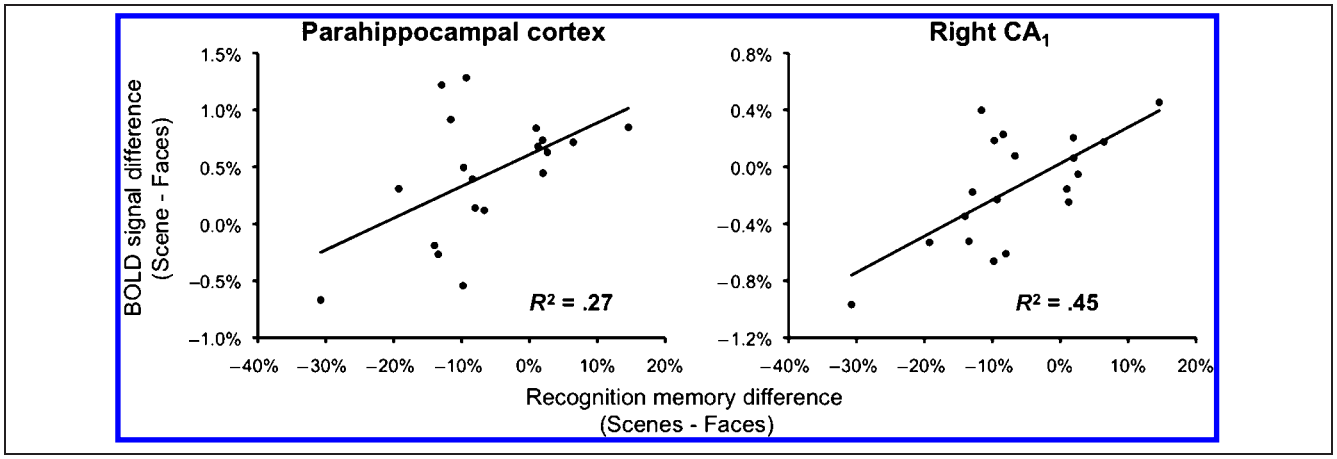

Figure 4. Regression plots displaying the integrated percent signal change difference between faces and scenes sample periods relative to the percent recognition memory difference for attended faces and attended scenes. The activation difference was positively correlated with the recognition memory difference in right CA_1 and both right and left parahippocampal cortex (the parahippocampal cortex data are rendered collapsed across hemispheres).

Region × Attention interaction between parahippocampal cortex and each of the hippocampal subfields (dentate gyrus/$CA_{2/3}$, CA_1, and subiculum; Fs > 11.29, ps < .0005); by contrast, none of the interactions between hippocampal subfields and entorhinal or perirhinal cortex reached significance (Fs < 1.80, ps > .10).

To test whether attention-induced changes in MTL activation during the sample/delay period were associated with subsequent performance on the postscan recognition memory test, we explored whether activation differences when attending to scenes compared with attending to faces correlated with overall recognition memory differences for scene versus face stimuli. Of the MTL cortical ROIs, activation differences in parahippocampal cortex during scenes versus faces sample/delay periods positively correlated with differences in recognition memory for scene versus face stimuli ($R^2 = .27, p < .05$; Figure 4); this correlation was significant for both left and right parahippocampal cortex (ps < .05). Within the hippocampus, although no subfield showed a main effect of attention, a positive correlation between attention-driven activation differences and subsequent scene versus face memory performance was nevertheless observed in CA_1 ($R^2 = .32, p < .05$). This effect was robust in the right hemisphere ($R^2 = .45, p < .005$; Figure 4) but not in the left hemisphere ($R^2 = .09, p > .10$). Attention-based activation differences in the other MTL ROIs did not correlate with differences in later memory performance (ps > .10).

DISCUSSION

The present study demonstrates that an individual's mnemonic goals have multiple behavioral and neural consequences. First, attended faces and scenes were more accurately and more confidently recognized than passively viewed or ignored faces and scenes (Yi et al., 2006; Gazzaley, Cooney, McEvoy, et al., 2005; Gazzaley, Cooney, Rissman, et al., 2005; Yi & Chun, 2005). Second, activation in parahippocampal cortex was modulated by the subject's mnemonic goals (Gazzaley, Cooney, McEvoy, et al., 2005; Gazzaley, Cooney, Rissman, et al., 2005), and the magnitude of attention-mediated differences in parahippocampal cortex activation correlated with differences in long-term memory for scene and face stimuli. Third, and more interestingly, goal-relevant but nonprobed faces and scenes were better remembered over the long term if they had been initially encountered in the sample period of match versus mismatch probed trials. Processing of these stimuli was presumably comparable during the sample/delay period; thus, this difference in long-term mnemonic outcome must derive from processes occurring during the probe period. Greater pattern completion (or recollection) of the goal-relevant nonprobed stimulus when encountering a match versus a mismatch probe can account for this novel behavioral finding. Fourth, probe period match enhancement was observed in all hippocampal subfields (dentate gyrus/$CA_{2/3}$, CA_1, and subiculum), which may reflect recollection of the nonprobed goal-relevant stimulus (Yonelinas et al., 2005; Dobbins, Rice, Wagner, & Schacter, 2003; Eldridge et al., 2000). Consistent with this account, in the right subiculum, probe period activation during face match trials predicted subsequent memory for the other attended but nonprobed face. Collectively, these data suggest that match enhancement signals in the human hippocampus reflect the retrieval of goal-relevant contextual or event details that co-occurred with the matching probe stimulus during its prior encounter.

Match Enhancement and Pattern Completion

Although match enhancement effects may reflect increased attention to a probe stimulus in response to a specific mnemonic goal, the present data would appear more readily accounted for by a pattern completion mechanism—which

refers to the completion of a conjunctive or relational representation of a set of items when cued with a single item (rather than completion of an item representation from partial input). Behaviorally, nonprobed goal-relevant stimuli were better remembered when they were initially encountered in the context of a match versus mismatch trial, supporting a specific prediction of the pattern completion account, namely, that exposure to a goal-relevant familiar stimulus would prompt the retrieval of other goal-relevant contextual details, including the nonprobed stimulus. An attentional account would not predict this pattern of data; in fact, it might predict the opposite: increased attention to a probed stimulus could potentially impair memory for a nonprobed, competing stimulus (Levy & Anderson, 2002). Moreover, at the neural level, match enhancement was observed in the hippocampus but not in the MTL cortices. This finding is informed by computational theories that posit that pattern completion is a fundamental hippocampal mechanism (e.g., O'Reilly & Rudy, 2001; McClelland, McNaughton, & O'Reilly, 1995), by previous fMRI studies demonstrating that recollection-based recognition is consistently associated with increased hippocampal activation (e.g., Yonelinas et al., 2005; Dobbins et al., 2003; Eldridge et al., 2000) and by neuropsychological data showing that the hippocampus is critical for tasks that require pattern completion of items associated at study even when memory is probed by a single item after a relatively short study test delay (Hannula, Ryan, Tranel, & Cohen, 2007; Hannula, Tranel, & Cohen, 2006; Olson, Page, Moore, Chatterjee, & Verfaellie, 2006).

A pattern completion account can also explain recent observations of increased hippocampal activation for visual displays that match versus mismatch a maintained goal representation (Duncan et al., 2009; Hannula & Ranganath, 2008). Exposure to an object display that matches an internally maintained goal representation may promote retrieval of other contextual details associated with the display, including thoughts or emotions that occurred at the time of encoding. Importantly, Duncan et al. (2009) demonstrated that hippocampal match enhancement is unaffected by perceptual novelty, suggesting that the pattern completion effects observed in the present study are unlikely to be automatic consequences of encountering a familiar stimulus; instead, they differentially occur when a stimulus matches a mnemonic goal. Moreover, Duncan et al. suggest that match enhancement may reflect reactivation of neurons that were active during the delay period. Our results provide evidence that the mechanism underlying match enhancement involves reactivation and further demonstrate that this mechanism may have lasting mnemonic consequences for associated goal-relevant details.

MTL Novelty Detection and Prediction Error

Given that prior recognition memory studies have observed robust mismatch enhancement or repetition suppression in the MTL cortex (e.g., Gonsalves et al., 2005; Weis et al., 2004; Henson et al., 2003; Curran, 2000), it may be somewhat surprising that the MTL cortex was not more active for mismatch versus match probes in the current study. Other short-delay paradigms have elicited mismatch enhancement in perirhinal or parahippocampal cortex in nonhuman primates (e.g., Brown & Aggleton, 2001; Miller & Desimone, 1994) as well as in humans in the context of continuous recognition tasks (e.g., Johnson, Muftuler, & Rugg, 2008; Kumaran & Maguire, 2006, 2007a; Brozinsky, Yonelinas, Kroll, & Ranganath, 2005). In recent short-delay relational memory paradigms, mismatch enhancement was not observed in response to goal mismatches or subtle perceptual mismatches (Duncan et al., 2009; Hannula & Ranganath, 2008); however, Duncan et al. (2009) did observe mismatch enhancement in the hippocampus and perirhinal cortex in response to more salient perceptual mismatches (i.e., novel objects and novel locations). Duncan et al. attributed these perceptual mismatch enhancement effects to the encoding of unpredicted, novel events that may have been highly salient because they only occurred on one-third of the probe trials (i.e., they may have been contextual oddballs, as in Knight, 1996). In the present study, by contrast, probe mismatches were present on half of the trials; thus, they were more predictable and less salient than the novel probes in the paradigm of Duncan et al., which could potentially account for the absence of mismatch enhancement in the present study. In addition, it could be that recognition decisions in the present paradigm were disproportionately accompanied by recollection, particularly given the nature of the encoding task in which two stimuli were encoded on every trial and may have been linked together in memory as paired associates. This is compatible with our interpretation of the match enhancement effects observed in hippocampus. Moreover, electrophysiological data suggest that pattern completion is associated with backward projecting signals originating in the MTL (Naya, Yoshida, & Miyashita, 2001). Thus, pattern completion in the hippocampus may yield a backward projecting signal to perirhinal cortex and parahippocampal cortex that offsets any novelty responses associated with the mismatching probe stimulus. Indeed, whereas some studies have observed repetition suppression in human perirhinal cortex during familiarity-based recognition, other studies suggest that perirhinal cortex is more active when subjects recollect features of events that are thought to project through perirhinal cortex to hippocampus (e.g., faces or objects; see Diana, Yonelinas, & Ranganath, 2007). Future studies are needed to adjudicate between these possibilities.

In a similar vein, the absence of mismatch enhancement in the hippocampal subfields may be viewed as surprising from at least two perspectives. In particular, given the importance of the hippocampus in novelty detection (e.g., Kumaran & Maguire, 2006, 2007a, 2007b; Dolan & Fletcher, 1997; Knight, 1996; Stern et al., 1996), including the prior observation of enhanced hippocampal activation in response to relational novelty (Köhler, Danckert,

Gati, & Menon, 2005) as well as the hypothesis that CA_1 mediates the detection of associative prediction errors (Lisman & Grace, 2005), one might expect mismatch enhancement in CA_1 and perhaps in other subfields of the hippocampus. However, consistent with the present findings, other recent high-resolution fMRI data suggest that the emergence of novelty encoding and pattern completion effects in human hippocampal subfields at least partially depends on task demands (Bakker, Kirwan, Miller, & Stark, 2008; Kirwan & Stark, 2007). Additional systematic evaluation of the interaction between goal states and hippocampal computations will undoubtedly shed further light on when the hippocampus is biased toward novelty encoding (or pattern separation), pattern completion, and the signaling of associative prediction errors.

Event Content, Attention, and the MTL

The present design also provided an opportunity to explore stimulus class effects in the MTL cortex and hippocampus. In accord with recent high-resolution fMRI data from human MTL (Preston et al., 2010), parahippocampal cortex demonstrated enhanced activation to scene versus face stimuli during the probe period, whereas perirhinal cortex and entorhinal cortex did not exhibit stimulus class sensitivity. Parahippocampal cortex has long been implicated in scene processing (Diana et al., 2008; Kirchhoff, Wagner, Maril, & Stern, 2000; Epstein et al., 1999; Epstein & Kanwisher, 1998), whereas the stimulus sensitivity of perirhinal cortex is less well specified. Although perirhinal cortex predominantly receives inputs from visual association cortices in the inferior temporal lobe that are important for visual–object processing (Suzuki, 2009; Burwell & Amaral, 1998; Suzuki & Amaral, 1994), recent evidence suggests that human perirhinal cortex may be involved in mnemonic processing of both visual object and spatial stimuli (Preston et al., 2010; Diana et al., 2008; Buffalo et al., 2006). Our findings add further evidence suggesting that perirhinal cortex may support more content-general encoding relative to parahippocampal cortex, although it should be noted that in this and many prior studies of scene encoding, the complex visual scene stimuli consisted of objects in space. Thus, it remains possible that perirhinal cortex may preferentially encode visual–object rather than visual–spatial representations. Other recent high-resolution fMRI data suggest that there may be a functional gradient along the rostral–caudal axis of human MTL cortex, with anterior perirhinal cortex supporting object processing and posterior parahippoacampal cortex supporting scene processing at the two ends of a continuum (Litman, Awipi, & Davachi, 2009; for a related finding, see Olsen et al., 2009). Anatomically defined perirhinal cortex may consist of a functional blend of more posterior voxels that are selective for scenes as well as anterior voxels that are selective for faces, which would contribute to the more content-general responses observed in the present study.

Given that mnemonic goals have been shown to modulate MTL activation, a secondary aim of the present study was to examine attention-specific encoding responses within the hippocampus and MTL cortices. In accord with previous findings, parahippocampal cortex was robustly modulated by scene-directed attention (Yi et al., 2006; Gazzaley, Cooney, McEvoy, et al., 2005; Gazzaley, Cooney, Rissman, et al., 2005; Yi & Chun, 2005). The present findings extend previous studies that focused on functional voxels within the parahippocampal cortex that were scene selective, as our data demonstrate that the anatomically defined parahippocampal cortical region is also modulated by scene-directed attention. By contrast, perirhinal cortex showed more subtle and general effects of attention, again suggesting that this region may mediate both visual object and spatial encoding (Preston et al., 2010; Diana et al., 2008; Buffalo et al., 2006). The hippocampal subfields were insensitive to the attentional manipulation, suggesting that if goal-directed attentional signals from MTL cortex propagate into the hippocampus, they modulate the hippocampus on a finer scale rather than broadly modulating the response of the hippocampal subfields.

The present data also revealed that parahippocampal cortical activation and CA_1 activation during the sample/delay period were related to long-term subsequent memory outcomes. Activation differences when attending to scenes versus faces were positively associated with differences in subsequent recognition memory for these scene and face stimuli. Research by Turk-Browne, Yi, and Chun (2006) has demonstrated that higher levels of tonic neural activity in the parahippocampal cortex immediately before scene encoding are associated with superior subsequent memory, suggesting that the level of attention allocated to a given stimulus strongly influences its mnemonic fate. Our results also demonstrate a potential link between goal-directed attention and subsequent memory, suggesting that increased stimulus-specific, goal-directed attention produces enhanced MTL activation, which in turn may result in better declarative memory. Although lesions of parahippocampal cortex appear differentially associated with mnemonic rather than perceptual deficits for spatial information (Epstein, DeYoe, Press, Rosen, & Kanwisher, 2001; Bohbot, Allen, & Nadel, 2000), the modulation of parahippocampal cortical activation by scene-directed attention may have affected the active representation of visual information during the sample/delay period, which fostered mnemonic encoding of the scenes.

The present findings provide novel leverage on the mechanisms underlying MTL match enhancement, demonstrating that these effects may reflect retrieval of other goal-relevant contextual details associated with a stimulus's prior encounter. This pattern completion appears to have functional consequences for the related details retrieved, rendering them more likely to be remembered over the long term. Whether these effects are automatic consequences of encountering goal-relevant probes that match past experience or are the consequences of strategically

engaged retrieval processes is an open question. Nevertheless, the present data build on an emerging literature that is beginning to specify the nature of match enhancement and mismatch enhancement signals in the MTL and in so doing advance understanding of how the MTL performs the remarkable feat of distinguishing the novel from the familiar.

Acknowledgments

This study was supported by the National Institute of Mental Health (grant no. R01-MH076932), the National Alliance for Research on Schizophrenia and Depression, and the Alfred P. Sloan Foundation.

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