Neuron, Vol. 31, 865–873, September 13, 2001, Copyright ©2001 by Cell Press

Medial Temporal Lobe Activity Associated with Active Maintenance of Novel Information

Charan Ranganath[1] and Mark D'Esposito
Helen Wills Neuroscience Institute and
Department of Psychology
University of California, Berkeley
Berkeley, California 94720

Summary

Using event-related functional magnetic resonance imaging, we investigated the role of medial temporal regions during active maintenance of information over short delays or working memory. In experiment 1, we observed sustained bilateral hippocampal activation during maintenance of novel faces across a short delay period but not during face encoding or recognition. In contrast, we observed transient right parahippocampal activation during encoding and recognition but not during maintenance. We replicated these findings in experiment 2 and further determined that anterior hippocampal activation was greater during maintenance of novel than familiar faces. Our results reveal the importance of medial temporal lobe regions for the active maintenance of novel information in the absence of perceptual stimulation.

Introduction

Substantial evidence from neuropsychology, neurophysiology, and neuroimaging suggests that the hippocampus and surrounding regions of the medial temporal lobes are critical for the formation and retrieval of long-term memories (LTM) for facts and events or declarative memory (Milner et al., 1998). In contrast, little research has been performed to determine whether the hippocampal formation also contributes to the active maintenance of information over short delays or working memory (WM). Although patients with medial temporal lobe lesions exhibit intact retention of familiar information across short intervals (Cave and Squire, 1992; Sidman et al., 1968; Wickelgren, 1968), findings from neuropsychological studies suggest that, at least under some circumstances, the hippocampus may be essential for WM.

For example, performance on tasks such as trial-unique delayed matching or nonmatching to sample requires the retention of a novel, complex visual stimulus across a delay period (Mishkin and Delacour, 1975). Human and nonhuman primates with large medial temporal lesions (including the hippocampus and surrounding cortex) may exhibit intact performance on these tasks when the delays are very short (4 s or less) but can exhibit deficits at delay lengths as short as 6–15 s (Aggleton et al., 1992; Baxter and Murray, 2001; Buffalo et al., 1998; Holdstock et al., 1995; Murray and Mishkin, 1986; Owen et al., 1995; Squire et al., 1988; Zola-Morgan and Squire, 1985; Zola-Morgan et al., 1989, 1993). Although no primate single-unit recording studies have examined medial temporal activity during trial-unique delay tasks, findings from similar paradigms suggest that cells in the hippocampus, perirhinal, and entorhinal cortex are active during short memory delays (Cahusac et al., 1989; Kreiman et al., 2000; Miller et al., 1993; Miyashita and Chang, 1988; Suzuki et al., 1997; Watanabe and Niki, 1985).

If processes supporting active maintenance of visual information were spared following medial temporal damage, why was performance impaired at such short delays? In these studies, stimuli were typically complex, novel, "junk objects" that were used on one trial and then discarded. Thus, the medial temporal lobes may not be necessary for rehearsal of simple, familiar stimuli (Cave and Squire, 1992; Sidman et al., 1968; Wickelgren, 1968), but they may be necessary for the active maintenance of novel information during memory delays.

Understanding the temporal dynamics of medial temporal activity during delay task performance can provide insights into the functional organization of medial temporal lobe regions, as well as the relationship between WM and LTM. For example, many researchers have proposed that WM maintenance is accomplished by activating LTM representations (Fuster, 1995; Kimberg et al., 1997; Petrides, 1989). Thus, one might expect to see medial temporal activity during the delay period when novel information is being maintained. Prior neuroimaging studies have reported hippocampal activity associated with the performance of WM tasks (Curtis et al., 2000; Eliot and Dolan, 1999; Friedman and Goldman-Rakic, 1988; Haxby et al., 1995; Sybirska et al., 2000), but it was unclear from these studies whether activation could be attributed to sensory or mnemonic processes. Here, using event-related functional magnetic resonance imaging (fMRI) methods to identify temporal patterns of brain activity within a trial (see Experimental Procedures) (D'Esposito et al., 1999; Postle et al., 2000; Zarahn et al., 1997b), we compared the response properties of different medial temporal regions during the performance of WM and LTM tasks.

Results

In experiment 1A, we assessed medial temporal lobe activation in eight participants while they performed a delayed-recognition task with novel grayscale face stimuli (see Figure 1A). On each trial, a sample face was shown, and participants were asked to retain a mental image of the face over a 7 s delay period. Next, a probe face was presented, and participants decided whether it matched the sample face. In accord with prior neuropsychological studies, faces in the WM task were novel and trial unique (Mishkin and Delacour, 1975).

To rule out the possibility that maintenance activity observed during WM task performance was related to incidental LTM encoding, we performed an additional experiment in the same session. In experiment 1B, participants performed intentional encoding and recognition

[1]Correspondence: charan@socrates.berkeley.edu

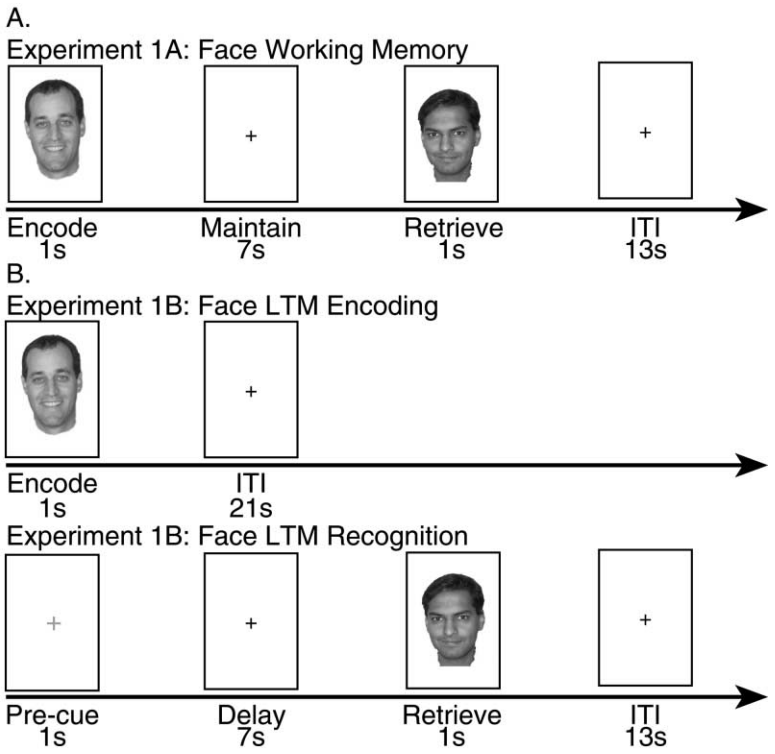

Figure 1. Examples of Each Trial Type

(A) Schematic depiction of a single trial of the delayed recognition task used to assess WM in experiments 1A and 2.

(B) Schematic depiction of a single trial of the face encoding and face recognition tasks used to assess LTM in experiment 1B.

tasks with novel faces, in order to assess encoding and retrieval activation within the context of LTM tasks (see Figure 1B). The stimuli and temporal parameters of the LTM and WM trials were matched so that activity during these tasks could be directly compared.

Behavioral results showed that participants were highly accurate at identifying same ($M = 97.7\%$, $SD = 2.8\%$) and different ($M = 97.2\%$, $SD = 2.6\%$) faces on WM trials. Similarly, participants were able to accurately identify studied ($M = 88.9\%$, $SD = 7.9\%$) and novel ($M = 85.6\%$, $SD = 9.9\%$) faces on LTM retrieval trials. A two-way ANOVA of these results with test condition (WM versus LTM) and item type (match/studied versus non-match/unstudied) revealed that accuracy was significantly higher on WM than LTM trials [$F(1,7) = 13.89$, $p < 0.01$]. Analyses of reaction times (RTs) during WM and LTM retrieval trials revealed a similar pattern of results. Mean RTs for match and mismatch faces on WM trials were 825.9 ms ($SD = 266.9$) and 785.8 ms ($SD = 199.8$), respectively. RTs for studied and novel faces on LTM trials were 1433.3 ms ($SD = 395.3$) and 1494.3 ms ($SD = 375.1$), respectively. RTs were significantly slower on LTM than on WM trials [$F(1,7) = 49.32$, $p < 0.001$].

FMRI results, shown in Figure 2, revealed bilateral anterior hippocampal activation during the delay period of the WM task. Consistent with evidence suggesting right hemisphere specialization for face processing (Kelley et al., 1998), delay activation appeared to be more extensive and larger in magnitude on the right anterior hippocampus than on the left. A followup analysis confirmed that delay activation was significantly greater at the right hippocampal local maxima than at the left hippocampal local maxima [$t(7) = 6.82$, $p < 0.0005$]. These hippocampal regions were not reliably activated during the encoding or retrieval phases of the WM or LTM tasks. Outside of the medial temporal lobes, the left anterior inferior frontal gyrus (BA 47; x, y, z = −30, 26, −10; $t(7) = 8.59$, number of voxels = 5), the right medial frontal gyrus (BA 9; x, y, z = 4, 49, 30; $t(7) = 8.02$, number of voxels = 2), and the left superior temporal gyrus (BA 22; x, y, z = −68, −23, −10; $t(7) = 6.78$, number of voxels = 3) were reliably activated during the delay period of the WM task. As shown in Figures 2 and 3, voxels in the parahippocampal gyri extending into the fusiform gyri (BA 35/36/37) were activated during the encoding and response phases of the WM and LTM tasks. The locus of activation in a region of the right parahippocampal gyrus during the LTM encoding task was particularly close to parahippocampal regions reported to show differential activity during encoding according to whether an item is subsequently remembered (Kirchhoff et al., 2000; Wagner et al., 1998).

To better understand the time course of activation in these regions, regions of interest (ROIs) were defined corresponding to the right hippocampal voxels activated during the delay period of the WM task and right parahippocampal voxels activated during the LTM encoding task. Unsmoothed single-subject time series data were trial averaged within these ROIs and averaged across subjects. Results, shown in Figure 4A, revealed that right hippocampal activation during WM trials exhibited a single peak 7 s after the onset of the memory delay and remained above the pretrial baseline throughout the remaining trial period. Given evidence that the hemodynamic response in the hippocampus (Eldridge et al., 2000), as in other regions (Aguirre et al., 1998; Miezin et al., 2000), peaks 4–6 s and returns to baseline 8–10 s after stimulus onset, this response likely reflected sustained activity in the anterior hippocampus during the memory delay period. Thus, the qualitative temporal

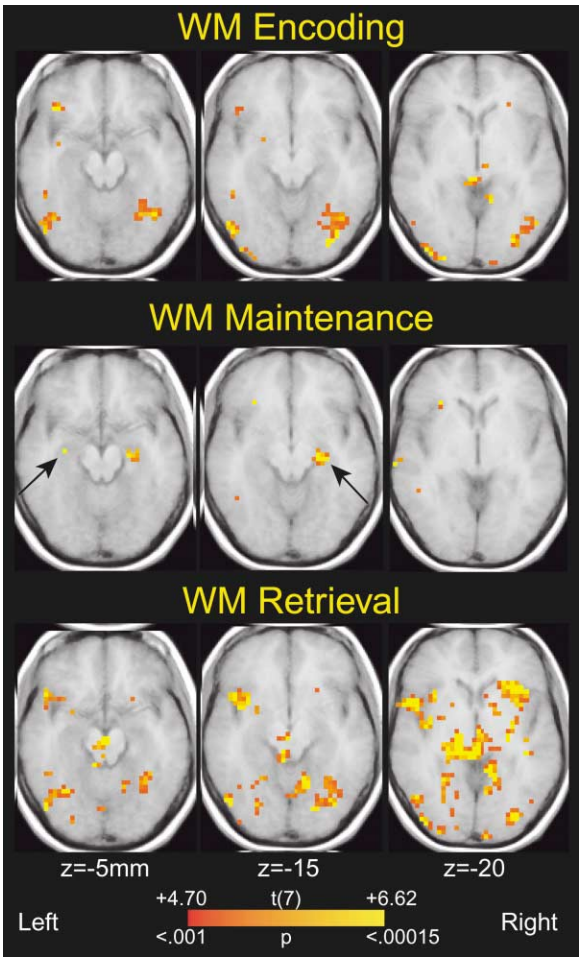

Figure 2. Medial Temporal Activation during WM Trials

Regions activated during the encoding, maintenance, and retrieval phases of WM trials in experiment 1A are displayed on an average of the spatially normalized anatomical images from the eight participants. Black arrows point to right ($x = 30$, $y = -22$, $z = -15$, $t(7) = 14.89$) and left ($x = -30$, $y = -15$, $z = -20$, $t(7) = 7.34$) anterior hippocampal regions activated during the WM delay period. Colored pixels exceeded a threshold of $t(7) > +4.70$, $p < 0.001$ one-tailed, uncorrected. Pixels shown in bright yellow met or exceeded a threshold of $t(7) > 6.62$, corresponding to a one-tailed threshold of $p < 0.05$, corrected for multiple comparisons.

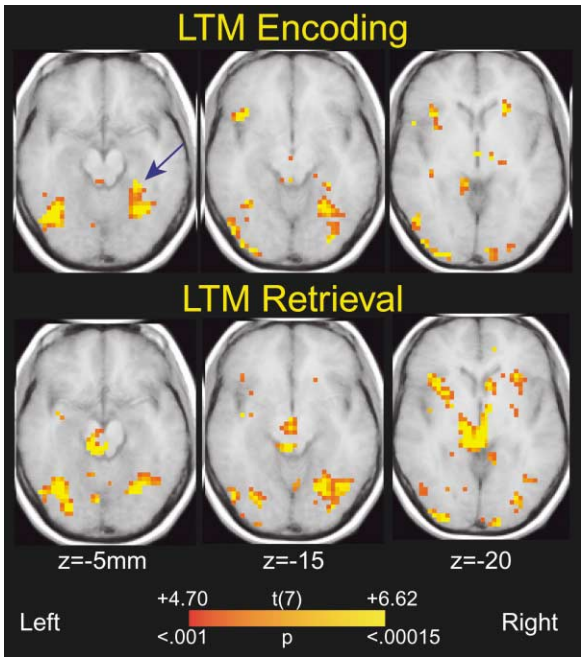

Figure 3. Medial Temporal Activation during LTM Trials

Regions activated during LTM encoding and retrieval trials in experiment 1B are shown. The blue arrow points to a region spanning the right parahippocampal and anterior fusiform gyri that was activated during LTM encoding ($x = 30$, $y = -41$, $z = -20$, $t(7) = 7.97$).

pattern of anterior hippocampal activity during the WM trial period was fully consistent with the statistical results presented earlier.

It could be argued that the delay period activation we observed in the hippocampus was a prolonged hemodynamic response solely associated with incidental encoding driven by the presentation of the cue face. Alternately, the response could have reflected anticipation of the upcoming test face during the memory delay. Evoked responses of this region during LTM trials, however, were not consistent with these hypotheses. As shown in Figure 4A, no reliable activation was observed in this region during LTM encoding or retrieval trials, despite the fact that participants actively processed faces during encoding trials and anticipated test faces during retrieval trials. These findings demonstrate that the requirement to actively maintain information during the memory delay was necessary to elicit the sustained activation pattern we observed during WM trials.

In contrast to the responses for the anterior hippocampus, right parahippocampal activation during WM trials, shown in Figure 4B, peaked 6 s after the onset of the encoding face, briefly returned to baseline, and subsequently peaked again 6 s following onset of the test face. This region also exhibited transient activation peaking 6 s after faces were presented during LTM encoding and retrieval trials. Prior results suggest that the hemodynamic response in parahippocampal regions has a peak latency of 4–6 s (Kirchhoff et al., 2000; Wagner et al., 1998) and returns to baseline 8–10 s after stimulus onset, suggesting that activity in the parahippocampal ROI was associated with encoding and retrieval of faces presented during both WM and LTM tasks.

Prior neuroimaging studies have reported medial temporal activation associated with encoding or retrieval of information (Cohen et al., 1999). The present results, however, demonstrate that hippocampal activity can reflect the maintenance of information in the absence of perceptual stimulation. Accordingly, our findings suggest that hippocampal activity plays a role in bridging memory delays. But in light of the fact that anterior hippocampal activation is not frequently observed during WM or LTM tasks (Cohen et al., 1999; Stern and Hasselmo, 1999), these findings raised an important question: under what circumstances does the hippocampus participate in WM tasks?

Unlike most neuroimaging studies of object WM, the

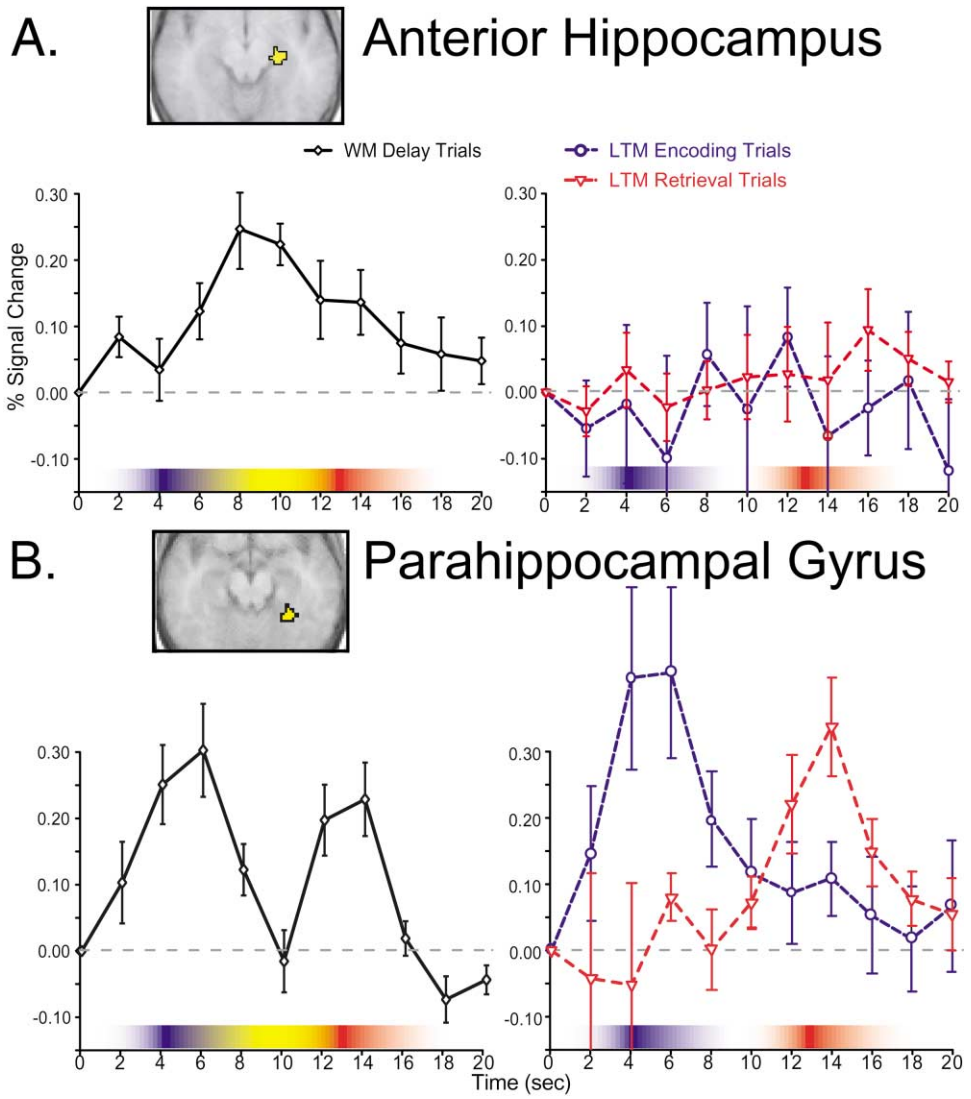

Figure 4. Hippocampal and Parahippocampal Regions Exhibit Temporally and Functionally Distinct Activity Patterns

Graphs depict the time course of (A) right anterior hippocampal and (B) right parahippocampal/fusiform signal changes during experiments 1A and 1B. Trial-averaged responses were scaled to a percent signal change value relative to trial onset. Error bars denote the standard error of the mean across participants. A color gradient shown in the background depicts when responses related to transient encoding (blue), sustained active maintenance (yellow), and transient retrieval (red) processes would be expected to peak, assuming a 4–6 s peak latency for the hemodynamic response (Aguirre et al., 1998; see Eldridge et al., 2000; Kirchhoff et al., 2000; Wagner et al., 1998, for evidence that this assumption is valid for the hippocampus and parahippocampal gyrus). At left, results are shown for WM trials performed in experiment 1A, and, at right, results are shown for LTM encoding and retrieval trials performed in experiment 1B. Results showed that the right anterior hippocampal region exhibited sustained activity associated with WM maintenance but not during encoding or retrieval epochs of WM or LTM trials. In contrast, the parahippocampal/fusiform region exhibited transient increases in activity associated with encoding and retrieval across both WM and LTM tasks.

stimuli we used were complex and novel. As stated earlier, the medial temporal lobes may be more essential for WM for novel than well-learned stimuli. For example, patients with hippocampal lesions exhibit attenuated electrophysiological responses to novel stimuli (Knight, 1996). Several functional neuroimaging studies have also demonstrated that posterior medial temporal regions are more active during encoding of novel than familiar information (Gabrieli et al., 1997; Kirchhoff et al., 2000; Stern et al., 1996). Based on these findings, we hypothesized that activity in the anterior hippocampal and parahippocampal regions activated in experiment 1A would be modulated by the novelty of information to be maintained. Furthermore, we predicted that the anterior hippocampal region would be more active during maintenance of novel than well-learned information, whereas the parahippocampal/fusiform region would be more active during encoding and retrieval of novel than well-learned information.

We tested this hypothesis in experiment 2 by comparing activity during maintenance of novel versus well-learned faces. Prior to scanning, seven volunteers performed 40 practice trials of the WM task used in experiment 1A but with a set of four faces repeatedly used as

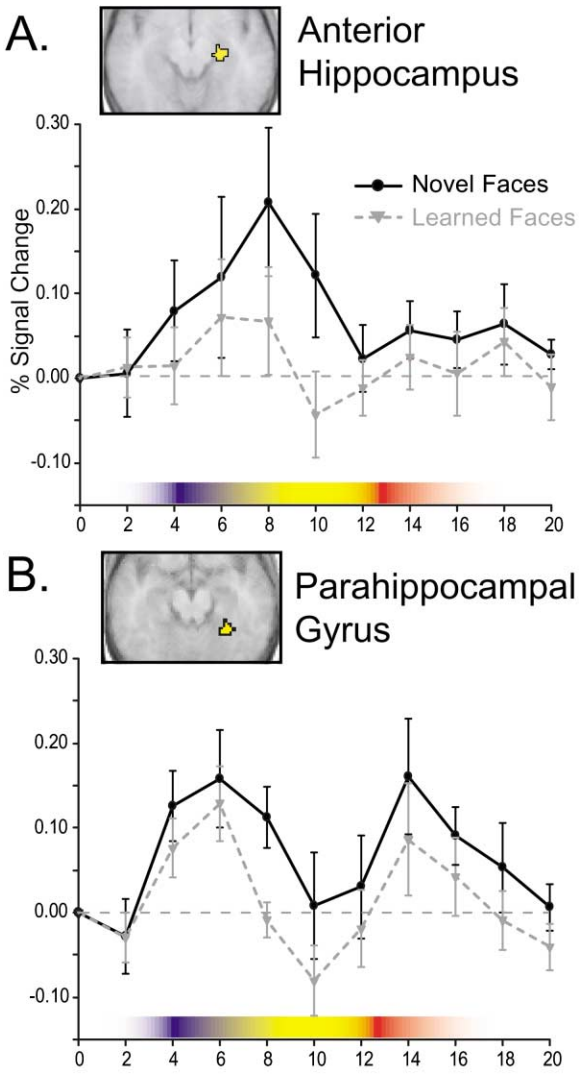

Figure 5. Task-Related Hippocampal and Parahippocampal Activity Is Modulated by Stimulus Novelty

Graphs depict the time course of (A) right anterior hippocampal and (B) right parahippocampal/fusiform signal changes during novel and familiar WM trials in experiment 2. Results showed that the right anterior hippocampal region exhibited greater delay period activity during novel than familiar WM trials. In contrast, the parahippocampal/fusiform region showed greater encoding and retrieval activity during novel than familiar trials.

stimuli. They performed the same task in the scanner, with novel, trial-unique stimuli on half the trials and cue and probe stimuli from the set of well-learned faces on the other trials. The trial order was randomized so that participants could not predict whether a trial would have novel or familiar faces as stimuli.

Behavioral results from experiment 2 revealed a similar pattern of results to those observed in experiment 1A. Behavioral results showed that participants were highly accurate at identifying matching ($M = 96.4\%$, $SD = 3.0\%$) and nonmatching ($M = 97.6\%$, $SD = 3.3\%$) faces on trials with learned face stimuli. Similarly, participants were able to accurately identify same ($M = 97.2\%$, $SD = 2.2\%$) and different ($M = 98.8\%$, $SD = 2.2\%$) faces on trials with novel face stimuli. No accuracy differences were observed between items in any condition [all $F(1,7)s < 2.62$, all $ps > 0.15$]. Mean RTs for match and mismatch faces on learned face trials were 929.1 ms ($SD = 381.1$) and 985.0 ms ($SD = 375.3$), respectively. Mean RTs for match and mismatch faces on novel face trials were 915.5 ms ($SD = 338.1$) and 914.9 ms ($SD = 367.2$), respectively. RTs did not reliably differ between items in any condition [all $F(1,7)s < 1.85$, all $ps > 0.20$].

We restricted our statistical analyses to results from the right anterior hippocampal and parahippocampal ROIs, defined a priori in experiment 1. Results, shown in Figure 5A, revealed that right anterior hippocampal activation again peaked 7 s following onset of the memory delay during novel face trials, as in Experiment 1A. Delay period activation in the hippocampal ROI was significant during maintenance of novel faces [$t(6) = 2.59$, $p < 0.05$] but not during maintenance of well-learned faces [$t(6) < 1.2$]. Furthermore, delay period activation in the right hippocampus was significantly greater during novel face trials than during familiar face trials [$t(6) = 3.71$, $p = 0.005$]. This region was not reliably activated during the encoding or retrieval phases for novel or familiar faces, and no differences between the two trial types were observed during these periods [all $t(6)s < 1.1$].

Results for the parahippocampal ROI, shown in Figure 5B, revealed that activation in this region peaked 6 s after the onset of the encoding face and subsequently peaked again 6 s after onset of the test face on novel and familiar face trials. This region was significantly activated during both the encoding [novel faces: $t(6) = 5.78$, $p < 0.001$; learned faces: $t(6) = 4.6$, $p < 0.005$] and retrieval [novel faces: $t(6) = 3.86$, $p < 0.005$; learned faces: $t(6) = 2.54$, $p < 0.05$] phases of the tasks. In accord with previous results (Kirchhoff et al., 2000), encoding activity in this region was greater during novel than familiar face trials [$t(6) = 4.99$, $p = 0.001$]. Furthermore, activity during the retrieval phase was greater during novel than familiar face trials [$t(6) = 2.66$, $p < 0.05$]. This region was not reliably activated during the delay period for novel faces [$t(6) < 1.2$] and showed a decrease in delay period activation for familiar faces [$t(6) = 2.93$, $p = 0.01$]. Furthermore, the difference in delay activation between novel and familiar face trials was not significant in this region [$t(6) < 1.1$].

Discussion

In experiment 1, we observed a double dissociation between the response properties of anterior hippocampal and parahippocampal regions. The hippocampus exhibited sustained delay period activation during WM trials, whereas the parahippocampal gyrus exhibited transient activation during encoding and retrieval periods of both WM and LTM trials. We replicated the findings of experiment 1A in experiment 2 and further demonstrated that activation in these regions was greater for novel than for familiar faces. These findings suggest that medial temporal lobe activity associated with WM is modulated by the novelty of the information to be remembered.

The present findings strongly suggest that the hippo-

campus is engaged when novel information must be actively maintained. However, it is conceivable that maintenance of faces during WM trials elicited enhanced encoding relative to the intentional learning strategies engaged during the LTM encoding trials. If so, delay period activation during WM trials might also be linked to LTM encoding. Because long-term retention of faces encountered during WM trials was not assessed, this possibility could not be directly evaluated. Nonetheless, available evidence from lesion studies suggests that, in addition to encoding, medial temporal regions may be necessary for the maintenance of novel information over short delays (Aggleton et al., 1992; Baxter and Murray, 2001; Buffalo et al., 1998; Holdstock et al., 1995; Murray and Mishkin, 1986; Owen et al., 1995; Squire et al., 1988; Zola-Morgan and Squire, 1985; Zola-Morgan et al., 1989, 1993). Although no lesion study has used an identical paradigm to the one presented here, our findings converge with some results indicating that the human medial temporal lobes may be necessary for the retention of complex, novel objects across comparable delays (Buffalo et al., 1998; Holdstock et al., 1995; Owen et al., 1995).

Our results also add to accumulating evidence that the hippocampus may play a different role in memory than surrounding cortical regions (Aggleton and Brown, 1999; Cabeza et al., 2001; Gabrieli et al., 1997). One interpretation of these results might be that, whereas parahippocampal regions are important for LTM, hippocampal regions are more important for WM. However, this conclusion is inconsistent with results from numerous lesion studies suggesting that both hippocampal and parahippocampal regions are essential for some aspects of declarative LTM (see Milner et al., 1998). Instead, an emerging view is that parahippocampal and perirhinal regions mediate object processing that is sensitive to the relative novelty of an item (Gabrieli et al., 1997; Miller et al., 1993; Parker et al., 1998). Thus, differences in parahippocampal activity during perception of novel versus familiar faces may be critical for familiarity-based recognition memory (Aggleton and Brown, 1999; Gabrieli et al., 1997; Parker et al., 1998). In contrast, the hippocampus may be more critical for representing relations between multiple items or multiple features of a complex, novel item (Cohen et al., 1999; Eichenbaum et al., 1999; Fried et al., 1997; Johnson and Chalfonte, 1994; O'Reilly et al., 1999). These binding processes could enable the encoding and recall of novel information as well as the context in which familiar information was last encountered (Cohen et al., 1999; Eichenbaum et al., 1999; Johnson and Chalfonte, 1994). We suggest that the same hippocampal binding mechanisms that enable recollection in the absence of bottom-up perceptual stimulation supported the active maintenance of novel faces in this study (Fuster, 1995).

If this is the case, why weren't anterior hippocampal regions activated during the LTM retrieval task in experiment 1B? Indeed, findings from this study and numerous others have shown reliable parahippocampal activation during LTM encoding and retrieval tasks, but fewer studies have reported activation in the hippocampus proper during such tasks (Cohen et al., 1999; Stern and Hasselmo, 1999). Of the few studies that reported hippocampal activation, most employed blocked-trial designs and fixed-effects statistical models, which offer increased statistical power but drastically limit the inferences that can be drawn from the results. (Aguirre and D'Esposito, 1999; Josephs and Henson, 1999). One explanation for this pattern of results is that the hippocampus utilizes sparse representations (Fried et al., 1997; O'Reilly et al., 1999; Stern and Hasselmo, 1999), so blood oxygenation level-dependent (BOLD) signal changes associated with hippocampal activity may be smaller than responses seen in other areas. Accordingly, transient activation of hippocampal networks during LTM tasks may be insufficient to evoke reliable hemodynamic responses, whereas prolonged activation of these networks during memory delays (perhaps through feedback from prefrontal networks) is sufficient to do so. Consistent with this hypothesis, one event-related fMRI study of episodic retrieval that encouraged sustained recollective processing reported hippocampal activation (Eldridge et al., 2000), whereas another event-related fMRI study using a similar paradigm but with a shorter trial duration did not (Henson et al., 1999).

The present results highlighted the role of medial temporal regions in memory, but results from numerous studies have shown that prefrontal cortex is also critical for active memory (D'Esposito et al., 2000; Fuster, 1997). For example, in this study and others (Courtney et al., 1998; Courtney et al., 1997), sustained prefrontal activation was observed during active maintenance of faces. Some researchers have proposed that prefrontal and medial temporal regions play complementary roles in both WM and LTM tasks, with prefrontal regions critical for the selection and activation of context-relevant information stored in hippocampal-cortical memory networks (Fuster, 1995; Mitchell et al., 2000; O'Reilly et al., 1999; Suzuki et al., 1997). Based on these ideas, O'Reilly, Braver, and Cohen implemented computational models of memory in which prefrontal regions are critical for biasing activity in posterior cortical regions, and medial temporal regions are critical for binding elements of novel associations (O'Reilly et al., 1999). Consistent with our results, their work suggests that tasks requiring rapid access to and storage of novel information will require both prefrontal biasing and hippocampal binding functions.

In the present study, we demonstrated that the human hippocampus, thought to be important for recollection of newly learned information, was active during rehearsal of novel information. Results from previous studies suggest that posterior cortical regions important for representing object and spatial information are also active during object and spatial WM tasks (Chafee and Goldman-Rakic, 1998; Fuster and Jervey, 1982; Postle and D'Esposito, 1999, 2000). Collectively, these findings cast doubt on the idea that the neural mechanisms of WM maintenance and LTM representation are distinct (Baddeley, 1986). Instead, our view is that WM maintenance is the outcome of controlled activation of distributed LTM networks (Fuster, 1995). The neural implementation of such processes clearly requires interaction between prefrontal and posterior cortical regions (Chafee and Goldman-Rakic, 1998; Fuster, 1997, 1995; O'Reilly et al., 1999; Suzuki et al., 1997), and our results further suggest that when novel information must be held in the active state, the hippocampus will be recruited.

Experimental Procedures

Subjects

Eight right-handed volunteers participated in Experiments 1A and 1B, and seven right-handed volunteers participated in Experiment 2. All volunteers were recruited from the University of Pennsylvania student community.

Procedure

In experiment 1, participants performed alternating runs of a WM task, a LTM encoding task, and a LTM retrieval task, schematically depicted in Figure 1. On each WM trial, a face was shown for 1 s, followed by a fixation cross for 7 s, followed by a probe face for 1 s. A fixation cross was shown on the screen during the 13 s intertrial interval (ITI). Participants were instructed to pay careful attention to the first face in each trial and maintain a mental image of that face throughout the delay period. The length of this delay period was chosen to be comparable to other studies that have reported sustained activity related to WM maintenance (Courtney et al., 1998, 1997; Postle and D'Esposito, 1999; Postle et al., 2000). Participants made a keypress with the left index finger if the second face matched the first (50%) and the right index finger if it did not (50%). On each LTM encoding trial, participants were shown a face for 1 s and instructed to pay attention to it in order to remember it for a later test. A fixation cross was shown on the screen during the 21 s ITI. The unfilled delay between LTM encoding and retrieval runs lasted $\sim$5–10 min. On each LTM retrieval trial, participants were cued with a red fixation cross for 1 s, marking the beginning of a trial, followed by a fixation cross for 7 s, followed by a probe face for 1 s. Thus, in the LTM retrieval task, as in the WM task, participants anticipated an upcoming probe face during the delay period. But because the number of faces presented during encoding runs exceeded the span of working memory, it was unlikely that participants would actively maintain faces during the LTM delay period. Participants made a keypress with the left index finger if the probe face was studied in the previous scanning run (50%) and the right index finger if it did not (50%). Participants performed three runs of each task, for a total of 54 WM and LTM retrieval trials and 27 LTM encoding trials. In experiment 2, seven participants performed eight runs of the WM task used in experiment 1A for a total of 72 novel and 72 repeated face trials. In addition to performing these tasks, participants in both experiments performed a visuomotor response task used to derive an estimated hemodynamic response function (Aguirre et al., 1998) and a passive viewing task to identify face-sensitive regions of extrastriate cortex (Kanwisher et al., 1997).

MRI Acquisition and Processing

Functional images were acquired with a gradient echo echoplanar sequence (TR = 2000 ms, TE = 50 ms, matrix size = 64 $\times$ 64, FOV = 24 cm) sensitive to BOLD contrast. Each functional volume consisted of 21 contiguous 5 mm thick axial slices. FMRI data processing included sinc interpolation in time to correct for between-slice timing differences in image acquisition (Aguirre et al., 1998); motion detection and correction using a six-parameter, rigid-body transformation algorithm (Friston et al., 1995); motion compensation using a partial correlation method (Zarahn et al., 1997b); and normalization of the time series of each voxel by its mean signal value to attenuate between-run scaling differences.

Data Analysis

Event-related BOLD responses to each task component in experiments 1 and 2 were analyzed using a modified general linear model (see "Modeling of Within-Trial Activity," below [Worsley and Friston, 1995]). All models incorporated empirically derived estimates of intrinsic temporal autocorrelation (Zarahn et al., 1997a) and filters to remove frequencies above .25 Hz and below 0.01 Hz. Separate statistical parametric maps (SPMs) were made for each subject by computing t values on linear combinations of the covariates modeling the each task period. Each SPM was spatially normalized to the MNI reference brain (Cocosco et al., 1997) using algorithms from Statistical Parametric Mapping (SPM96) software, and smoothed with a 7.5 mm isotropic gaussian kernel to account for remaining between-subject anatomical variability. Coordinates of peak activations were reported using the stereotactic system and nomenclature of Talairach and Tournoux (1988). However, anatomical regions identified by coordinates on the MNI reference brain do not precisely correspond to regions identified by the same coordinates on slices from the atlas of Talairach and Tournoux (1988).

Group random-effects analyses were performed for each contrast of interest to test whether the mean of the individual subjects' t values at each voxel was reliably greater than zero. This analysis method enabled us to generalize results from this sample of subjects to the population from which they were drawn, in contrast to fixed-effects analysis methods, in which the entire sample of subjects is treated as a case study. Accordingly, random-effects analysis methods are less likely to reveal spurious activation when results from one subject diverge markedly from others in the rest of the group (Aguirre and D'Esposito, 1999; Josephs and Henson, 1999; Postle et al., 2000). In experiment 1, areas of significant activation were determined by identifying regions whose peak activation exceeded a mapwise threshold of $p < 0.05$ (corrected for multiple comparisons, given the smoothness of the data). The extent of activation surrounding these peaks, used to delineate ROIs, was defined as contiguous voxels within the same anatomical region whose significance exceeded $p < 0.001$, uncorrected. Because accuracy differed between the WM and LTM tasks in experiment 1, fMRI analyses were repeated using only results from trials on which participants responded correctly. These results were no different than those obtained when all trials from each task were included, as can be expected given the high accuracy rates in both tasks. In experiment 2, statistical analyses were performed on activity averaged within the anterior hippocampal and parahippocampal ROIs that were defined a priori based on results from experiment 1. This allowed us to rigorously test whether results from the identical regions activated in experiment 1 would replicate in experiment 2.

Modeling of Within-Trial Activity

Our methods for analyzing temporal patterns of brain activation within a trial have been described in detail elsewhere (Postle et al., 2000) and are summarized below. Activation during individual epochs of each trial (i.e., cue, delay, and probe) was assessed using multiple regression (Courtney et al., 1998, 1997; Postle et al., 2000; Zarahn et al., 1997b). Analogous to the way activation is operationally defined in single-unit recording studies (Fuster, 1997), covariates (i.e., reference functions) corresponding to each epoch identified changes in BOLD signal relative to baseline activity during the ITI (D'Esposito et al., 1999; Postle et al., 2000; Zarahn et al., 1997b). Each covariate was composed of estimated hemodynamic responses positioned in time to represent BOLD signal changes associated with the onset of each task epoch. A hemodynamic response function (HRF) was individually estimated for each subject based on BOLD responses observed in sensorimotor cortex during a bimanual response task (see Aguirre et al., 1998, for a detailed description of this procedure). Several studies have demonstrated that the shape of the hemodynamic response to a brief period of neural activity differs substantially between individuals but remains relatively stable across successive sessions within the same individual (Aguirre et al., 1998; Miezin et al., 2000). We note that the shape of the average HRF across groups of subjects may exhibit regional variability (Miezin et al., 2000), suggesting that an individual's HRF derived from sensorimotor cortex may differ somewhat from HRFs in other regions. Nonetheless, we have observed that an individually derived sensorimotor HRF is more effective at modeling activations across the brain than canonical response shapes such as γ or poisson functions. Accordingly, modeling BOLD responses with individually estimated HRFs enhanced the sensitivity and specificity of our estimates of activity associated with each trial epoch.

One concern in modeling activity during delay tasks is that neural activity limited to the cue period might produce a hemodynamic response that extends into the subsequent delay period (i.e., due to the sluggishness of the hemodynamic response) leading to activity captured by the delay period covariate that is contaminated by cue period activity. Indeed, simulation results (Postle et al., 2000; Zarahn et al., 1997b) suggest that this might occur if the delay period covariate attempts to model activity too close in time to the cue period covariate (Courtney et al., 1998, 1997). However, we have demon-

strated that spacing the onset of the delay period covariate at least 4 s from the onset of cue and response covariates successfully identifies delay-specific activity, while activity earlier in the trial is modeled by the cue period covariate (D'Esposito et al., 1999; Postle et al., 2000; Zarahn et al., 1997b).

Acknowledgments

We thank C. Curtis, M.K. Johnson, R.T. Knight, P.J. Reber, E. Schumacher, and three anonymous reviewers for their helpful comments on earlier drafts of this manuscript; J. Berger, D. Caggiano, T.J. Druzgal, and A. Taich for their assistance; and N. Kanwisher for sharing her stimuli. C.R. was supported by a National Institutes of Health postdoctoral fellowship and the McDonnell-Pew Program in Cognitive Neuroscience, and M.D. was supported by grants from the NIH and the American Federation for Aging Research.

Received January 23, 2001; revised June 21, 2001.

References

Aggleton, J.P., and Brown, M.W. (1999). Episodic memory, amnesia, and the hippocampal-anterior thalamic axis. Behav. Brain Sci. *22*, 425–444.

Aggleton, J.P., Shaw, C., and Gaffan, E.A. (1992). The performance of postencephalitic amnesic subjects on two behavioural tests of memory: concurrent discrimination learning and delayed matching-to-sample. Cortex *28*, 359–372.

Aguirre, G., and D'Esposito, M. (1999). Experimental design for brain fMRI. In Functional MRI, C.T.W. Moonen and P.A. Bandettini, eds. (Berlin: Springer Verlag), pp. 369–380.

Aguirre, G.K., Zarahn, E., and D'Esposito, M. (1998). The variability of human, BOLD hemodynamic responses. Neuroimage *8*, 360–369.

Baddeley, A. (1986). Working Memory (New York: Oxford University Press).

Baxter, M.G., and Murray, E.A. (2001). Opposite relationship of hippocampal and rhinal cortex damage to delayed nonmatching-to-sample deficits in monkeys. Hippocampus *11*, 61–71.

Buffalo, E.A., Reber, P.J., and Squire, L.R. (1998). The human perirhinal cortex and recognition memory. Hippocampus *8*, 330–339.

Cabeza, R., Rao, S.M., Wagner, A.D., Mayer, A.R., and Schacter, D.L. (2001). Can medial temporal lobe regions distinguish true from false? An event-related functional MRI study of veridical and illusory recognition memory. Proc. Natl. Acad. Sci. USA *98*, 4805–4810.

Cahusac, P.M., Miyashita, Y., and Rolls, E.T. (1989). Responses of hippocampal formation neurons in the monkey related to delayed spatial response and object-place memory tasks. Behav. Brain Res. *33*, 229–240.

Cave, C.B., and Squire, L.R. (1992). Intact verbal and nonverbal short-term memory following damage to the human hippocampus. Hippocampus *2*, 151–163.

Chafee, M.V., and Goldman-Rakic, P.S. (1998). Matching patterns of activity in primate prefrontal area 8a and parietal area 7ip neurons during a spatial working memory task. J. Neurophysiol. *79*, 2919–2940.

Cocosco, C., Kollokian, V., Kwan, R., and Evans, A. (1997). Brainweb: online interface to a 3D MRI simulated brain database. Neuroimage *5*, s425.

Cohen, N.J., Ryan, J., Hunt, C., Romine, L., Wszalek, T., and Nash, C. (1999). Hippocampal system and declarative (relational) memory: Summarizing the data from functional neuroimaging studies. Hippocampus *9*, 83–98.

Courtney, S.M., Ungerleider, L.G., Keil, K., and Haxby, J.V. (1997). Transient and sustained activity in a distributed neural system for human working memory. Nature *386*, 608–611.

Courtney, S.M., Petit, L., Maisog, J.M., Ungerleider, L.G., and Haxby, J.V. (1998). An area specialized for spatial working memory in human frontal cortex. Science *279*, 1347–1351.

Curtis, C.E., Zald, D.H., Lee, J.T., and Pardo, J.V. (2000). Object and spatial alternation tasks with minimal delays activate the right anterior hippocampus proper in humans. Neuroreport *11*, 2203–2207.

D'Esposito, M., Zarahn, E., and Aguirre, G.K. (1999). Event-related functional MRI: implications for cognitive psychology. Psychol. Bull. *125*, 155–164.

D'Esposito, M., Postle, B.R., and Rypma, B. (2000). Prefrontal cortical contributions to working memory: evidence from event-related fMRI studies. Exp. Brain Res. *133*, 3–11.

Eichenbaum, H., Dudchenko, P., Wood, E., Shapiro, M., and Tanila, H. (1999). The hippocampus, memory, and place cells: Is it spatial memory or a memory space? Neuron *23*, 209–226.

Eldridge, L.L., Knowlton, B.J., Furmanski, C.S., Bookheimer, S.Y., and Engel, S.A. (2000). Remembering episodes: a selective role for the hippocampus during retrieval. Nat. Neurosci. *3*, 1149–1152.

Eliot, R., and Dolan, R. (1999). Differential neural responses during performance of matching and nonmatching to sample tasks at two delay intervals. J. Neurosci. *19*, 5066–5073.

Fried, I., MacDonald, K.A., and Wilson, C.L. (1997). Single neuron activity in human hippocampus and amygdala during recognition of faces and objects. Neuron *18*, 753–765.

Friedman, H.R., and Goldman-Rakic, P.S. (1988). Activation of the hippocampus and dentate gyrus by working memory: A 2-deoxyglucose study of behaving rhesus monkeys. J. Neurosci. *8*, 4693–4706.

Friston, K.J., Ashburner, J., Frith, C.D., Poline, J.-B., Heather, J.D., and Frackowiak, R.S.J. (1995). Spatial registration and normalization of images. Hum. Brain Map. *2*, 165–189.

Fuster, J.M. (1995). Memory in the Cerebral Cortex (Cambridge: The MIT Press).

Fuster, J. (1997). The Prefrontal Cortex: Anatomy, Physiology, and Neuropsychology of the Frontal Lobes, Third edition (New York: Raven Press).

Fuster, J.M., and Jervey, J.P. (1982). Neuronal firing in the inferotemporal cortex of the monkey in a visual memory task. J. Neurosci. *2*, 361–371.

Gabrieli, J.D.E., Brewer, J.B., Desmond, J.E., and Glover, G.H. (1997). Separate neural bases of two fundamental memory processes in the human medial temporal lobe. Science *276*, 264–266.

Haxby, J.V., Ungerleider, L.G., Horwitz, B., Rapoport, S.I., and Grady, C.L. (1995). Hemispheric differences in neural systems for face working memory: a PET-rCBF study. Hum. Brain Map. *3*, 68–82.

Henson, R.N.A., Rugg, M.D., Shallice, T., Josephs, O., and Dolan, R.J. (1999). Recollection and familiarity in recognition memory: An event-related functional magnetic resonance imaging study. J. Neurosci. *19*, 3962–3972.

Holdstock, J.S., Shaw, C., and Aggleton, J.P. (1995). The performance of amnesic subjects on tests of delayed matching-to-sample and delayed matching-to-position. Neuropsychologia *33*, 1583–1596.

Johnson, M.K., and Chalfonte, B.L. (1994). Binding complex memories: The role of reactivation and the hippocampus. In Memory Systems, D.L. Schacter and E. Tulving, eds. (Cambridge, MA: MIT Press), pp. 311–350.

Josephs, O., and Henson, R.N. (1999). Event-related functional magnetic resonance imaging: modelling, inference and optimization. Philos. Trans. R. Soc. Lond. B. Biol. Sci. *354*, 1215–1228.

Kanwisher, N., McDermott, J., and Chun, M.M. (1997). The fusiform face area: a module in human extrastriate cortex specialized for face perception. J. Neurosci. *17*, 4302–4311.

Kelley, W.M., Miezin, F.M., McDermott, K.B., Buckner, R.L., Raichle, M.E., Cohen, N.J., Ollinger, J.M., Akbudak, E., Conturo, T.E., Snyder, A.Z., and Petersen, S.E. (1998). Hemispheric specialization in human dorsal frontal cortex and medial temporal lobe for verbal and nonverbal memory encoding. Neuron *20*, 927–936.

Kimberg, D.Y., D'Esposito, M., and Farah, M.J. (1997). Cognitive functions in the prefrontal cortex—Working memory and executive control. Current Directions in Psychological Science *6*, 185–192.

Kirchhoff, B.A., Wagner, A.D., Maril, A., and Stern, C.E. (2000). Prefrontal-temporal circuitry for episodic encoding and subsequent memory. J. Neurosci. *20*, 6173–6180.

Knight, R.T. (1996). Contribution of human hippocampal region to novelty detection. Nature *383*, 256–259.

Kreiman, G., Koch, C., and Fried, I. (2000). Imagery neurons in the human brain. Nature *408*, 357–361.

Miezin, F.M., Maccotta, L., Ollinger, J.M., Petersen, S.E., and Buckner, R.L. (2000). Characterizing the hemodynamic response: effects of presentation rate, sampling procedure, and the possibility of ordering brain activity based on relative timing. Neuroimage *11*, 735–759.

Miller, E.K., Li, L., and Desimone, R. (1993). Activity of neurons in anterior inferior temporal cortex during a short-term memory task. J. Neurosci. *13*, 1460–1478.

Milner, B., Squire, L.R., and Kandel, E.R. (1998). Cognitive neuroscience and the study of memory. Neuron *20*, 445–468.

Mishkin, M., and Delacour, J. (1975). An analysis of short-term visual memory in the monkey, J. Exp. Psychol. Anim. Behav. Process. *1*, 326–334.

Mitchell, K.J., Johnson, M.K., Raye, C.L., and D'Esposito, M. (2000). fMRI evidence of age-related hippocampal dysfunction in feature binding in working memory. Brain Res. Cogn. Brain Res. *10*, 197–206.

Miyashita, Y., and Chang, H.S. (1988). Neuronal correlate of pictorial short-term memory in the primate temporal cortex. Nature *331*, 68–70.

Murray, E.A., and Mishkin, M. (1986). Visual recognition in monkeys following rhinal cortical ablations combined with either amygdalectomy or hippocampectomy. J. Neurosci. *6*, 1991–2003.

O'Reilly, R.C., Braver, T.S., and Cohen, J.D. (1999). A biologically based computational model of working memory. In Models of Working Memory: Mechanisms of Active Maintenance of Executive Control, A. Miyake and P. Shah, eds. (Cambridge: Cambridge University Press), pp. 375–411.

Owen, A.M., Sahakian, B.J., Semple, J., Polkey, C.E., and Robbins, T.W. (1995). Visuo-spatial short-term recognition memory and learning after temporal lobe excisions, frontal lobe excisions or amygdalo-hippocampectomy in man. Neuropsychologia *33*, 1–24.

Parker, A., Wilding, E.L., and Akerman, C. (1998). The Von Restorff effect in visual object recognition memory in humans and monkeys. The role of frontal/perirhinal interaction. J. Cogn. Neurosci. *10*, 691–703.

Petrides, M. (1989). Frontal lobes and memory. In Handbook of Neuropsychology, F. Boller and J. Grafman, eds. (The Netherlands: Elsevier), pp. 601–614.

Postle, B.R., and D'Esposito, M. (1999). "What"-Then-Where" in visual working memory: an event-related fMRI study. J. Cogn. Neurosci. *11*, 585–597.

Postle, B.R., and D'Esposito, M. (2000). Evaluating models of the topographical organization of working memory function in frontal cortex with event-related fMRI. Psychobiology *28*, 132–145.

Postle, B.R., Zarahn, E., and D'Esposito, M. (2000). Using event-related fMRI to assess delay-period activity during performance of spatial and nonspatial working memory tasks. Brain Res. Brain Res. Protoc. *5*, 57–66.

Sidman, M., Stoddard, L.T., and Mohr, J.P. (1968). Some additional quantitative observations of immediate memory in a patient with bilateral hippocampal lesions. Neuropsychologia *6*, 245–254.

Squire, L.R., Zola-Morgan, S., and Chen, K.S. (1988). Human amnesia and animal models of amnesia: performance of amnesic patients on tests designed for the monkey. Behav. Neurosci. *102*, 210–221.

Stern, C.E., and Hasselmo, M.E. (1999). Bridging the gap: integrating cellular and functional magnetic resonance imaging studies of the hippocampus. Hippocampus *9*, 45–53.

Stern, C.E., Corkin, S., Gonzalez, R.G., Guimaraes, A.R., Baker, J.R., Jennings, P.J., Carr, C.A., Sugiura, R.M., Vedantham, V., and Rosen, B.R. (1996). The hippocampal formation participates in novel picture encoding: evidence from functional magnetic resonance imaging. Proc. Natl. Acad. Sci. USA *93*, 8660–8665.

Suzuki, W.A., Miller, E.K., and Desimone, R. (1997). Object and place memory in the macaque entorhinal cortex. J. Neurophysiol. *78*, 1062–1081.

Sybirska, E., Davachi, L., and Goldman-Rakic, P.S. (2000). Prominence of direct entorhinal-CA1 pathway activation in sensorimotor and cognitive tasks revealed by 2-DG functional mapping in nonhuman primate. J. Neurosci. *20*, 5827–5834.

Talairach, J., and Tournoux, P. (1988). Co-Planar Stereotaxic Atlas of the Human Brain (New York: Thieme).

Wagner, A.D., Schacter, D.L., Rotte, M., Koutstaal, W., Maril, A., Dale, A.M., Rosen, B.R., and Buckner, R.L. (1998). Building memories: remembering and forgetting of verbal experiences as predicted by brain activity. Science *281*, 1188–1191.

Watanabe, T., and Niki, H. (1985). Hippocampal unit activity and delayed response in the monkey. Brain Res. *325*, 241–254.

Wickelgren, W.A. (1968). Sparing of short-term memory in an amnesic patient: Implications for strength theory of memory. Neuropsychologia *6*, 235–244.

Worsley, K.J., and Friston, K.J. (1995). Analysis of fMRI time-series revisited—again. Neuroimage *2*, 173–182.

Zarahn, E., Aguirre, G.K., and D'Esposito, M. (1997a). Empirical analyses of BOLD fMRI statistics. I. Spatially unsmoothed data collected under null-hypothesis conditions. Neuroimage *5*, 179–197.

Zarahn, E., Aguirre, G.K., and D'Esposito, M. (1997b). A trial-based experimental design for functional MRI. Neuroimage *6*, 122–138.

Zola-Morgan, S., and Squire, L. (1985). Medial temporal lesions on monkeys impair memory in a variety of tasks sensitive to human amnesia. Behav. Neurosci. *99*, 22–34.

Zola-Morgan, S., Squire, L., Amaral, D., and Suzuki, W. (1989). Lesions of perirhinal and parahippocampal cortex that spare the amygdala and the hippocampal formation produce severe memory impairment. J. Neurosci. *9*, 4355–4370.

Zola-Morgan, S., Squire, L.R., Clower, R.P., and Rempel, N.L. (1993). Damage to the perirhinal cortex exacerbates memory impairment following lesions to the hippocampal formation. J. Neurosci. *13*, 251–265.