HIPPOCAMPUS 11:337–346 (2001)

Medial Temporal and Prefrontal Contributions to Working Memory Tasks With Novel and Familiar Stimuli

Chantal E. Stern,[1,2]* Seth J. Sherman,[1]
Brenda A. Kirchhoff,[1] and Michael E. Hasselmo[1]

[1]*Department of Psychology, Boston University, Boston, Massachusetts*
[2]*Massachusetts General Hospital NMR Center, Charlestown, Massachusetts*

ABSTRACT: Lesions of parahippocampal structures impair performance of delayed matching tasks in nonhuman primates, suggesting a role for these structures in the maintenance of items in working memory and short-term stimulus matching. However, most human functional imaging studies have not shown medial temporal activation during working memory tasks and have primarily focused on functional magnetic resonance imaging (fMRI) signal intensity changes in the prefrontal and posterior parietal cortex. The goal of this study was to test the hypothesis that the difference between the human and nonhuman primate data results from the use of highly familiar stimuli in human working memory studies and trial-unique stimuli in nonhuman primate studies. We used fMRI to examine prefrontal and temporal lobe activation during performance of a working memory (two-back) task, using blocks of novel and highly familiar complex pictures. Performance of the working memory task with novel complex pictures resulted in greater signal change within medial temporal lobe structures than performance of the task with familiar complex pictures. In contrast, the working memory task with highly familiar stimuli resulted in greater prefrontal activation. These results are consistent without hypothesis that the medial temporal lobe is recruited for the short-term maintenance of information that has no prior representation in the brain, whereas the prefrontal cortex is important for monitoring familiar stimuli that have a high degree of interference. A second set of tasks examined stimulus matching. Subjects performed a target-matching task, during which they identified a single target presented in blocks of novel or familiar stimuli. The results provide evidence of hippocampal and parahippocampal recruitment in the target-matching task with familiar stimuli. These results are consistent with prior animal studies and suggest that prefrontal regions may be important for the monitoring and matching of familiar stimuli which have a high potential for interference, whereas medial temporal regions may become proportionally more important for matching and maintenance of novel stimuli. *Hippocampus 2001;11: 337–346.* © 2001 Wiley-Liss, Inc.

KEY WORDS: hippocampus; parahippocampal gyrus; entorhinal cortex; stimulus matching; delayed-match-to-sample

Grant sponsor: Alzheimer's Association; Grant sponsor: National Science Foundation; Grant sponsor: National Institute of Health; Grant Number: R01 NS41636.
*Correspondence to: Chantal Stern, Department of Psychology, Boston University, 64 Cummington St., Boston, MA 02215.
E-mail: chantal@bu.edu
Accepted for publication 16 May 2001

INTRODUCTION

Numerous studies of nonhuman primates have demonstrated that lesions of the medial temporal lobe (MTL) cause impairments of performance on delayed match-to-sample (DMS) tasks (Gaffan, 1974; Gaffan and Murray, 1992) and delayed nonmatch-to-sample (DNMS) tasks (Zola-Morgan et al., 1989, 1993; Alvarez et al., 1994). These impairments appear at long delays (e.g., 1 min, 10 min) but not short delays (0.5, 1, or 3 s) (Gaffan and Murray, 1992; Alvarez et al., 1994). These results are consistent with the notion that the entorhinal cortex and perirhinal cortex are important for maintaining memory for trial-unique stimuli across delays lasting more than a few seconds. Lesions of the entorhinal cortex have also been shown to impair continuous delayed nonmatch-to-sample tasks in rats (Otto and Eichenbaum, 1992a).

Despite these findings, the majority of functional neuroimaging tasks in humans have not reported medial temporal lobe activation during performance of two-back working memory tasks, which require short-term stimulus matching. This discrepancy between the human and nonhuman primate findings may be based on the fact that while animal studies have used trial-unique stimuli, the majority of neuroimaging studies using the two-back task have concentrated on simple, highly familiar stimuli, such as letters, which have a clear prior representation in the brain (Cohen et al., 1997; Owen et al., 1998; Postle et al., 2000; Stern et al., 2000). In contrast with studies using trial-unique stimuli (Zola-Morgan et al., 1989; Alvarez et al., 1994), the use of repeated presentations of small numbers of stimuli in DNMS tasks causes significantly slower learning and poorer performance in nonhuman primates, suggesting that familiar stimuli place very different demands on cognitive processes (Mishkin and Delacour, 1975). In fact, medial temporal lobe lesions in monkeys do not impair performance on delayed-

match-to-sample tasks using 2 or 4 sample stimuli, but result in significant impairments on delayed-match-to-sample tasks with trial-unique stimuli (Eacott et al., 1994). In contrast, lesions of the inferior prefrontal convexity in nonhuman primates do impair performance of matching tasks with small numbers of stimuli (Passingham, 1975; Bachevalier and Mishkin, 1986), which is thought to be primarily a result of an impairment in relearning the matching task irrespective of the delay (Kowalska et al., 1991; Rushworth et al., 1997). Lesions of the mid-dorsolateral prefrontal cortex also cause impairments in tasks which require the avoidance of interference effects with small numbers of familiar stimuli (Petrides, 2000). In rats, perirhinal cortex lesions cause significant impairments of DNMS tasks with both 8 and 16 odors in a set, but prefrontal cortex lesions only impair performance with the smaller 8-odor set, which has a greater amount of interference (Otto and Eichenbaum, 1992a). These studies suggest that the prefrontal cortex plays a role in maintaining distinct representations of small sets of highly familiar stimuli as well as keeping track of stimulus order and recency to avoid interference effects (Petrides, 1994, 2000; Stern et al., 2000). In contrast, the medial temporal lobe may rapidly form representations of novel stimuli which can be utilized for recognition and short-term maintenance of such stimuli, but does not provide information that is sufficient to avoid interference effects.

In this study, we used novel and familiar complex visual pictures as stimuli in a two-back working memory (short-term matching) task. We predicted that when subjects were shown stimuli for which they had no prior long-term representation (two-back task with novel stimuli), medial temporal lobe structures would be recruited in addition to the network of dorsolateral prefrontal, premotor, and posterior parietal regions shown to be activated in previous studies using two-back tasks with simple, familiar stimuli (Cohen et al., 1997; Smith and Jonides, 1999; Owen et al., 1998; Owen, 2000). A second set of control tasks was used to examine long-term target matching.

METHODS

Subjects

Eight right-handed native English-speaking volunteers (6 male, 2 female; age range, 18–25) participated in this study. Informed consent was obtained in a manner approved by the Human Studies Committee of Massachusetts General Hospital and the Boston University Institutional Review Board.

Stimuli

The stimuli for this experiment consisted of indoor and outdoor color visual scenes similar to those used in our previous studies of long-term encoding (Stern et al., 1996; Kirchhoff et al., 2000). We used two types of stimuli in the study: novel pictures and highly familiar pictures. Approximately 1 hour prior to scanning, subjects viewed the familiar picture set, and the task instructions were explained. The familiar set of stimuli was composed of 12 distinct pictures. Each subject viewed these pictures 14 times during pretraining prior to scanning. The novel pictures were each shown once during the scanning session unless they were repeated in the context of a two-back match, in which case they were shown twice. Each stimulus was presented for 2 seconds.

Behavioral Tasks

There were four experimental conditions in this blocked-design functional magnetic resonance imaging (fMRI) study: a working memory two-back task with novel stimuli (N2B), a working memory two-back task with familiar stimuli (F2B), a long-term target-matching task with novel stimuli (NX), and a long-term target-matching task with familiar stimuli (FX). The four tasks are shown in Figure 1. The first two tasks were variants of the two-back working memory task that has been used extensively in fMRI studies (Braver et al., 1997; Cohen et al., 1997; Owen et al., 1998). However, previous studies used simple letters and words as stimuli, while this study used complex color scenes. Both of the two-back task conditions required a short-term match between a visual scene and the scene shown two stimuli prior to it in the sequence. The second two tasks, NX and FX, were variants of a control target-matching condition used previously in two-back tasks. In previous two-back tasks with letter stimuli, the control condition required that subjects decide whether the current letter matches a single target letter, the letter X (Braver et al., 1997; Cohen et al., 1997). In this study, the target stimulus was a predefined target scene (Fig. 1). Thus the second two tasks, NX and FX, required matching each visual scene with a long-term representation of the target scene.

Two-back working memory tasks with novel and familiar stimuli (N2B and F2B)

In the two-back working memory tasks with novel or familiar stimuli, subjects were required to assess whether a stimulus was repeatedly presented with one intervening stimulus (Fig. 1). Subjects were required to indicate whether each stimulus was a match or nonmatch by pressing one of two keys on a button-box placed in their left hand. There was a total of five matches randomly assigned throughout every two-back condition. For the two-back task with novel stimuli (N2B), all the stimuli were presented once throughout the entire experiment. The match stimuli were presented twice: once as a novel stimulus, and once as a match stimulus. The two-back task with familiar stimuli (F2B) condition was similar to the N2B condition, except that all the stimuli presented in the block were highly familiar.

Target-matching tasks (NX and FX)

The target-matching tasks with novel and familiar stimuli involved the detection of a single target stimulus, which was shown to subjects prior to scanning (Fig. 1). Subjects indicated whether or not the current stimulus was the target stimulus by pressing one of

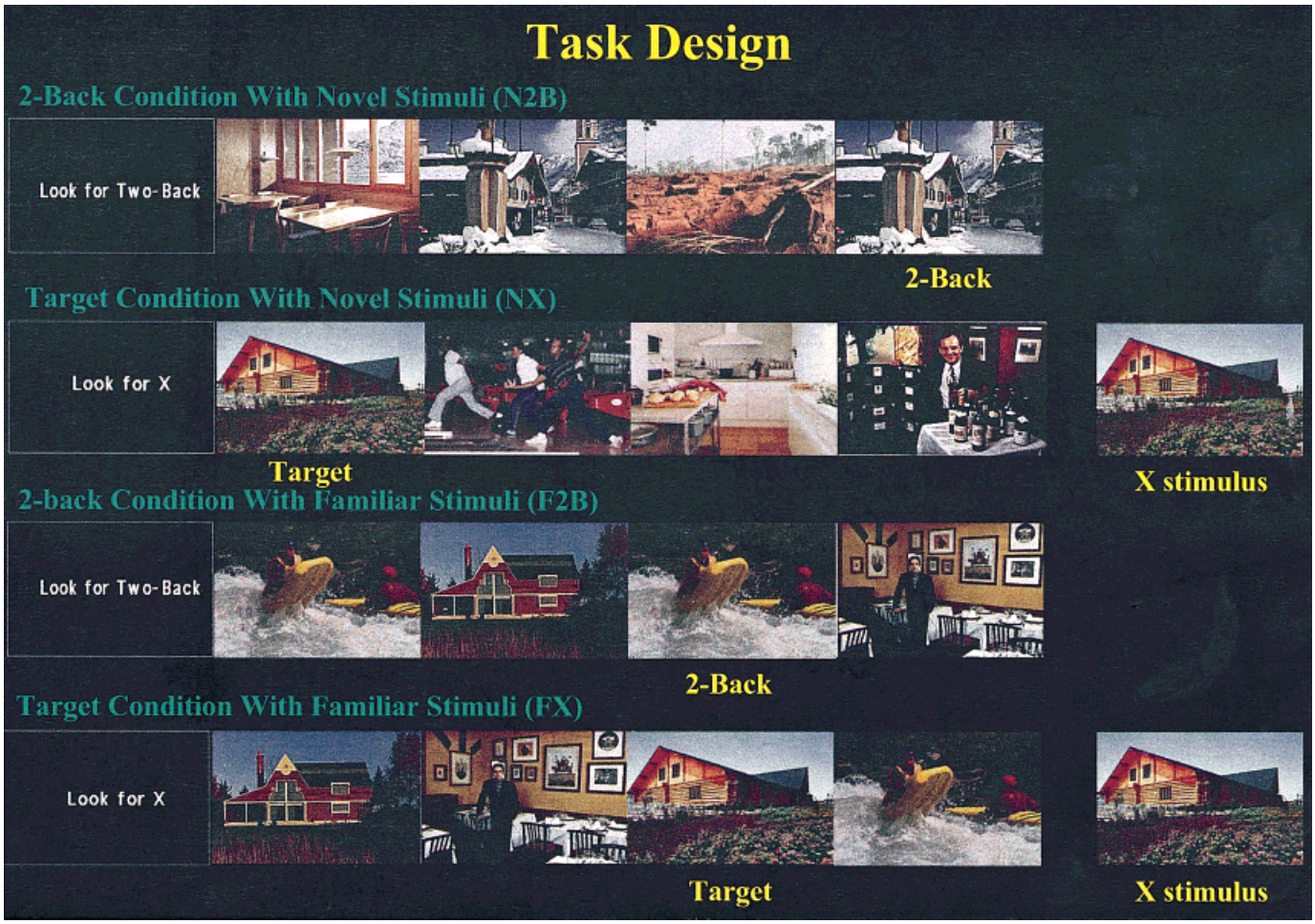

FIGURE 1. Each row shows examples of images from individual tasks. Top row: Two-back condition with novel stimuli (N2B). In this condition, subjects were shown a sequence of novel complex images, and had to respond when an image reappeared after one intervening stimulus (image labeled "2-Back"). Second row: Target condition with novel stimuli (NX). In this condition, subjects viewed novel complex images and responded when an image matched the target image (labeled "Target"). Third row: Two-back condition with familiar stimuli (F2B). Subjects were shown a sequence of familiar complex images, and responded when an image reappeared after one intervening stimulus (image labeled "2-Back"). Bottom row: Target condition with familiar stimuli (FX). Subjects viewed familiar complex images and responded when an image matched the target image ("Target"). The same target picture was used for both the NX and FX conditions.

two keys on a button-box. The same target stimulus was used in both the target-matching tasks. In the target-matching task with novel stimuli (NX), the target stimulus would appear in a sequence of novel stimuli. In the target-matching condition with familiar stimuli (FX), the target stimulus would appear in a sequence of highly familiar stimuli. There was a total of five presentations of the target that appeared randomly throughout each condition.

Recognition test

A surprise recognition test was given immediately following the scanning session outside of the scanner. On a computer monitor, subjects were shown a series of pictures presented one at a time in random order. The set included the 150 novel pictures and the 12 highly familiar pictures from the scan session, and 150 new pictures. Subjects were asked to judge their confidence in recognition of each picture by responding either "high confidence," "low confidence," or "new" with a button press.

fMRI Methods

fMRI data acquisition

Anatomical and functional MR data were acquired on a 3.0T GE Signa scanner with an ANMR upgrade. Structural data were acquired using a T1-weighted rf-spoiled GRASS sequence. Functional data were acquired using a whole-brain echoplanar T2*-weighted gradient echo sequence (TR = 2, TE = 30 ms, flip angle = 60°, 16 AC-PC axial slices with 1-mm skip, 3.125 × 3.125 × 7 mm resolution, 120 images per slice). During training and structural scanning, the subjects practiced the two types of tasks with the familiar stimuli. There was a total of eight functional

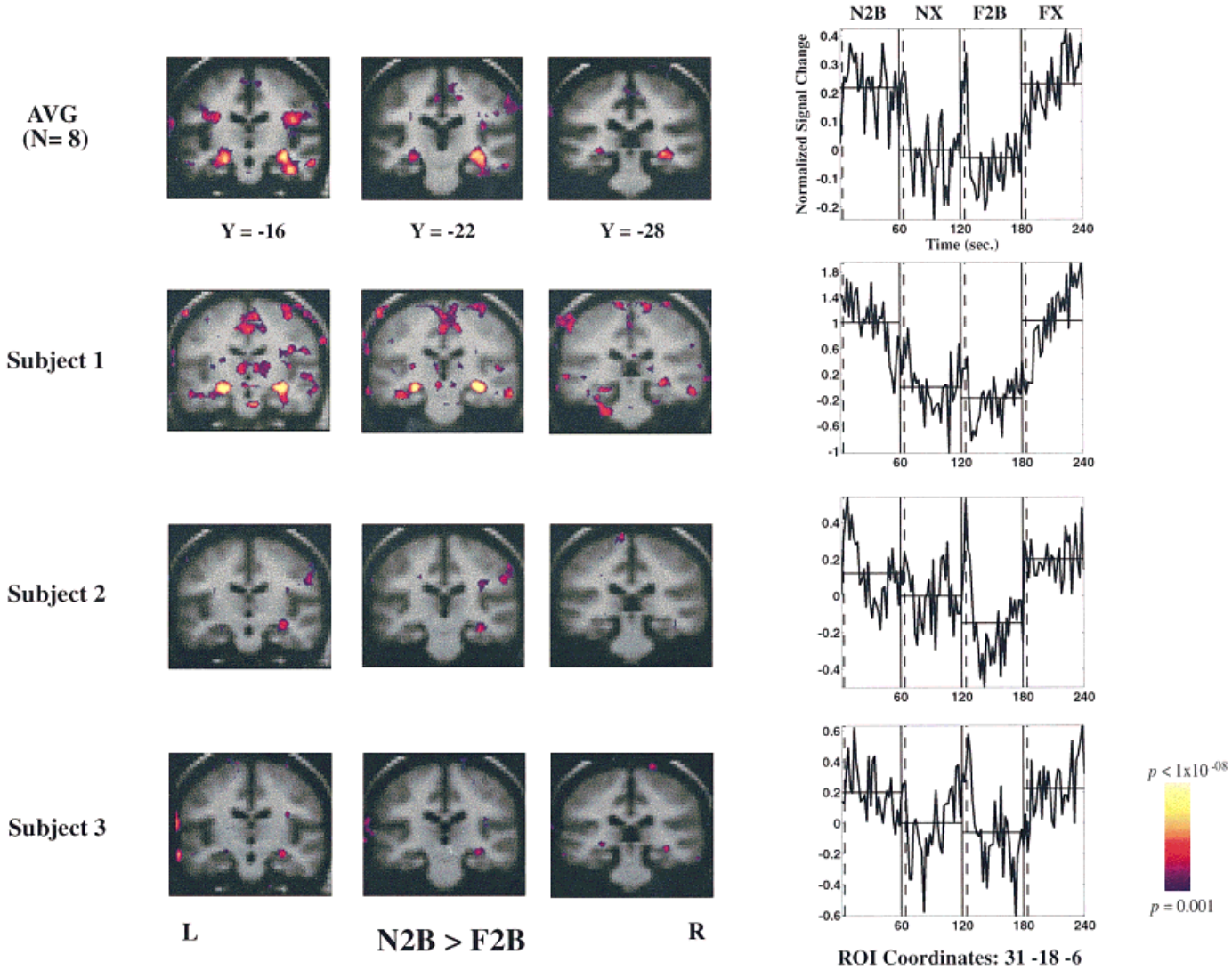

FIGURE 2. Hippocampal activation was found bilaterally in averaged functional data during performance of the novel two-back task (N2B) when compared to the familiar two-back task (F2B) condition. Bilateral hippocampal activation was also greater during the N2B condition compared to the novel matching condition (NX), but was similar to activation in the familiar target condition (FX). Statistical activation map and time-course data are shown for the 8-subject average and for 3 individual subjects. Dashed lines indicates termination of the 4-s instruction period preceding each condition.

runs for each subject. Each of the eight functional runs lasted a total of 4 min. Each condition (N2B, NX, F2B, or FX) was 56 s long and was preceded by a 4-s instructional prompt. A total of 224 time points per condition were collected for averaging within subjects, and 1,792 time points per condition were used for across subject averaging.

Data analysis

Functional data for each subject were first normalized to remove whole-brain intensity changes and detrended to remove potential signal drift. Motion correction was then performed on each run, using Statistical Parametric Mapping software (SPM95) (Friston et al., 1989). The data were transformed into Talairach space (Talairach and Tournoux, 1988). The eight functional runs were subsequently averaged together for each subject and analyzed on an individual-subject basis, as shown in Figure 2. In addition, data were averaged across the eight subjects. Functional maps based on Kolmogorov-Smirnoff statistics were created using MGH-NMR Center analysis software and published methodology (Stern et al., 1996, 2000; Owen et al., 1998). The statistical threshold was set at $P < 0.001$. Percent signal change time-courses were examined for prefrontal, medial temporal, and posterior parietal regions of interest (ROIs). An automated region-defining algorithm was used to identify the Talairach coordinates of the activation peaks of ROIs. These ROIs were defined from the N2B with F2B. The average percent signal change data from four voxels, centered

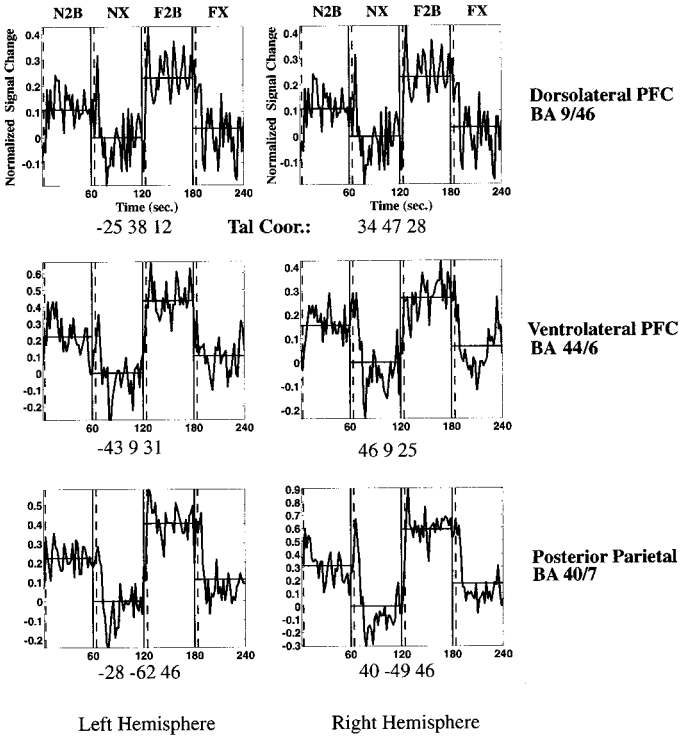

FIGURE 3. Average time-course data demonstrating different patterns of activation for Brodmann's areas 9/46 and 44/6 in prefrontal cortex (PFC) and Brodmann's areas 40/7 in posterior parietal cortex (PP). Both PFC and PP show stronger activation during the familiar two-back condition (F2B) than during the novel two-back condition (N2B). Dashed lines represent termination of 4-s instruction period preceding each condition.

around the Talairach coordinates of the activation peaks of the ROIs, were used to construct percent signal change time-courses.

RESULTS

Behavioral Results

A repeated-measures ANOVA revealed that subjects performed at equivalent levels for both the two-back task with novel stimuli (N2B) and the two-back task with familiar stimuli (F2B). The mean accuracy scores on the N2B and F2B conditions were 91.6% ± 4.23% standard deviation (SD) and 88.6% ± 5.64% SD, respectively. Reaction time data also were not significantly different between the N2B (618 ms ± 70 SD) and F2B (673 ms ± 138 SD) conditions ($P > 0.05$). The mean accuracy score on the NX task was 96.8% ± 3.3% (SD), and the mean accuracy score on the FX task was 97.3% ± 3.1% (SD). There was no significant difference between the means. Reaction time data also did not significantly differ between the NX (521 ms ± 73 ms SD) and FX (526 ms ± 76 ms SD) conditions.

Postscan Recognition

A postscan recognition test containing the familiar and novel sets of stimuli as well as new stimuli was used to assess subject familiarity with the presented stimuli. A repeated-measures ANOVA revealed that subjects correctly recognized familiar stimuli at a significantly higher rate than novel stimuli (familiar, 97.93%; novel, 47.25%; false-alarm rate for new pictures, 22%) ($F(1,4) = 63.3$, $P < 0.05$).

fMRI Results

Data were examined by comparing the two working memory tasks, N2B and F2B, with their respective control conditions, NX and FX, and by directly comparing the novel and familiar working memory tasks (N2B vs. F2B). In addition, the NX and FX tasks were directly compared. Both positive and negative activation patterns were examined and are reported here.

Overall, the results of both two-back tasks support the findings of previous fMRI studies of working memory using two-back tasks. fMRI signal changes were noted in multiple regions including the dorsolateral and ventrolateral prefrontal cortex, lateral and medial premotor cortex, posterior parietal cortex, and medial temporal regions. Here we focused our analysis specifically on ROIs within the prefrontal, posterior parietal, and medial temporal regions.

Working memory tasks with novel and familiar stimuli compared with target control tasks

Comparison of both two-back tasks with target control tasks (i.e., comparison of N2B with NX and comparison of F2B with FX) demonstrated fMRI signal intensity changes in the prefrontal cortex, posterior parietal cortex, and medial and lateral premotor regions, consistent with previous studies. During performance of the novel two-back task (comparison of N2B with NX), the hippocampus showed significant signal change bilaterally. This bilateral signal change in the hippocampus did not occur for the familiar two-back task (comparison of F2B with FX). This result is demonstrated in the time-course data shown in Figure 2. The time-course data demonstrate that activation during the N2B task was high relative to both the F2B and NX conditions, and activation during the F2B task was low relative to the FX condition.

Novel two-back task compared with familiar two-back task

A direct comparison of the novel two-back and familiar two-back tasks was also performed. Clear bilateral activation of medial temporal lobe structures, including the hippocampus, was observed during performance of the novel two-back task relative to performance of the familiar two-back task (comparison of N2B with F2B), as shown in Figure 2. The average and individual time-courses from a right hippocampal ROI are also shown in Figure 2.

Comparison of the F2B and N2B tasks revealed increased bilateral dorsolateral and ventrolateral prefrontal and bilateral posterior

parietal activity in the working memory task with familiar stimuli. Figure 3 presents time-courses from the group average data demonstrating that the signal intensity changes in the dorsolateral and ventrolateral prefrontal cortex (BA 9/46 and 44/6) and posterior parietal cortex (BA 40/7) were significantly higher in the F2B condition than in the N2B, FX, or NX conditions.

Familiar target-matching task compared with novel target-matching task

fMRI signal intensity increases were noted in the medial temporal lobe structures during performance of the target task with familiar stimuli (FX), relative to both the target-matching task with novel stimuli (NX) and the two-back task with familiar stimuli (F2B). Activation in the FX condition was localized bilaterally in the hippocampus, in the same region identified in the N2B task. As can be seen from the individual and group average time-course data shown in Figure 2, the average signal intensity changes observed during the FX and N2B tasks were similar in magnitude in the bilateral hippocampal ROIs. As is shown in Figures 2 and 3, there is a dissociation between the patterns of activation seen in the hippocampal ROIs and the prefrontal and posterior parietal lobe ROIs with regards to the FX and NX target-matching conditions. While both prefrontal and posterior parietal regions (Fig. 3) were active in the two working memory conditions (N2B and F2B), both regions showed much less activation during performance of the target-matching tasks (NX and FX). In contrast, the hippocampal ROIs (Fig. 2) showed significant activity during both short-term working memory tasks with novel stimuli (N2B) and during the long-term target matching task with familiar stimuli (FX). The comparison between the NX and FX tasks within the hippocampal ROIs further suggests that novelty alone does not cause a significant difference in activation level of the hippocampus.

DISCUSSION

Differential Activation During Novel and Familiar Working Memory Tasks

Performance of the two-back task with novel stimuli resulted in greater activation of the medial temporal lobe than performance of the two-back task with familiar stimuli in this study. This suggests a stronger role for the medial temporal lobe in working memory for complex, novel, trial-unique stimuli, relative to working memory for familiar stimuli. In the N2B condition, subjects were required to maintain a previously presented novel stimulus in working memory to assess its match with a current novel stimulus. This contrasted with the F2B task, which had similar task requirements but utilized familiar stimuli, and with the NX condition, which had similar novel stimuli, but lacked the working memory task requirements. The activation in the medial temporal lobe during the N2B condition suggests a specific role for this region in working memory for novel stimuli. In contrast, activation in the prefrontal and posterior parietal cortex during performance of the F2B task suggests that the prefrontal and parietal cortex play a stronger role in working memory for familiar stimuli. We suggest that these differences reflect the engagement of medial temporal lobe regions in tasks that require the formation and maintenance of new short-term representations, whereas the prefrontal cortex is preferentially engaged when prior representations already exist in the brain but must be selectively updated and monitored to avoid interference effects.

Relation of Novel vs. Familiar Working Memory to Previous Studies of Medial Temporal Lobe and Prefrontal Cortex

The prefrontal and posterior parietal lobe activation observed during the F2B task is consistent with extensive studies showing prefrontal and parietal activation during performance of working memory tasks with familiar stimuli (Cohen et al., 1997; Owen et al., 1998; Smith and Jonides, 1999). In addition, a recent fMRI study of working memory showed that whereas prefrontal regions are capable of maintaining consistent responses to repeated presentations of face stimuli, ventral temporal regions show a consistent decrease in response to repeated presentations of both target and distractor stimuli (Jiang et al., 2000). A number of fMRI studies of long-term encoding using novel complex visual scenes as stimuli have demonstrated differences in medial temporal lobe activation when novel stimuli are compared with repeated stimuli (Stern et al., 1996; Gabrieli et al., 1997; Kirchhoff et al., 2000). Although the task demands between the current study and these previous studies differ considerably, one suggestion is that the results of this study and previous studies reflect a common factor, such as novelty. However, two lines of evidence suggest that this is not the case. First, if the response simply reflected novelty, then the target condition with novel stimuli (NX) would produce a similar pattern of activation to the working memory condition (N2B). Secondly, the primary locus of activation within the medial temporal lobe in this study is centered in the hippocampus, and is further anterior than medial temporal lobe activations found in studies of novelty and encoding. Previous studies of the encoding of novel stimuli reported activation in more posterior regions of the medial temporal lobe, primarily localized within the parahippocampal and fusiform gyri along the banks of the collateral sulcus and extending into the posterior portion of the hippocampus (Stern et al., 1996; Kirchhoff et al., 2000).

In contrast to the signal intensity changes in the prefrontal and posterior parietal lobe observed during both the F2B and N2B tasks, hippocampal activation was greater during the N2B task than during the F2B task. These results are consistent with previous nonhuman primate studies showing that medial temporal lesions impair delayed match and nonmatch-to-sample performance with trial-unique stimuli (Zola-Morgan and Squire, 1986; Zola-Morgan et al., 1989; Gaffan and Murray, 1992; Alvarez et al., 1994, 1995). Thus, the essential difference between the human and nonhuman results appears to lie in the use of novel, trial-

unique stimuli vs. highly familiar stimuli, with working memory for novel stimuli requiring activation of medial temporal lobe structures, and working memory for familiar stimuli resulting in activation of prefrontal and parietal structures. This is consistent with previous data showing that medial temporal lesions in monkeys cause stronger impairments of performance on tasks with trial-unique stimuli than on tasks with 2 or 4 sample stimuli (Eacott et al., 1994). The data are also consistent with the finding that prefrontal lesions in the rat cause impairments on DNMS with a small set of 8 odors, but not with a larger set of 16 odors (Otto and Eichenbaum, 1992a). Together, these results suggest different roles for the medial temporal lobe and prefrontal cortex in the representation and retention of novel and familiar stimuli. The results suggest that medial temporal lobe structures can retain information about the sensory features of novel stimuli, whereas prefrontal structures become more important for avoiding interference effects between active working memory representations during retention of smaller numbers of highly familiar stimuli. Consistent with this, lesions of the ventral prefrontal cortex cause strong impairments in relearning matching tasks with recurrent use of the same two visual stimuli (Passingham, 1975; Bachevalier and Mishkin, 1986; Petrides, 1994). A more recent study of ventral prefrontal lesions using delayed and simultaneous matching-to-sample tasks suggested that the delay component is not critical, but that stimulus selection is (Petrides, 1996; Rushworth et al., 1997). Lesions of the mid-dorsolateral prefrontal cortex also impair tasks that require the maintenance and continuous updating of information from small stimulus sets (Petrides, 2000).

Relation to Extracellular Recording of Action Potentials During Behavioral Tasks

In recordings from single neurons in the hippocampal formation, activity patterns have been demonstrated which could contribute to the activation differences observed in these tasks. In particular, in recordings from hippocampal region CA1, a number of neurons showed differential responses dependent on whether the current odor matched with the previously presented odor, and almost all of these neurons responded more strongly to a nonmatch than to a match (Otto and Eichenbaum, 1992b). This type of nonmatch enhancement could result in an overall increase in activity for nonmatching (novel) stimuli in the N2B task. In other recordings in monkeys, preferential responses to novel stimuli were observed for object-place combinations (Cahusac et al., 1989), which may more strongly resemble the stimulus features of the complex visual scenes used in this study. In neuronal recordings from the human hippocampus, responses to visual stimuli were shown to differ, depending on the novelty or familiarity of the stimulus in a recognition memory task (Fried et al., 1997). The presence of this nonmatch enhancement in N2B but not NX might result from the requirement for short-term maintenance of stimuli in N2B but not NX. This could result in the release of neuromodulators associated with maintenance of stimuli, which increase cellular mechanisms for sustained activity and match enhancement (Fransen et al., 1999; Hasselmo et al., 2000). In some delayed matching tasks, hippocampal neurons have been shown to demonstrate sustained activity during task delays (Hampson et al., 1993), but these responses have not been compared for novel vs. familiar conditions.

Passive decreases across multiple presentations of a stimulus with intervening distractors were not observed in hippocampal units in rats or monkeys (Brown et al., 1987; Otto and Eichenbaum, 1992b). However, in single-unit recordings from monkeys, entorhinal neurons have been shown to decrease their responses to familiar stimuli (Brown et al., 1987; Fahy et al., 1993), similar to the suppression of response-to-repeated (match) stimuli observed in the inferotemporal cortex (Miller et al., 1993; Miller and Desimone, 1994) and rhinal cortex (Li et al., 1993). This decrease in entorhinal response to familiar stimuli could contribute to the difference between the N2B and F2B task activation found here, as it would result in a decrease in the magnitude of afferent input from the entorhinal cortex to the hippocampus during viewing of familiar stimuli. This property of single-unit responses in ventral temporal regions appears to be mirrored by the decrease in response to repeated stimuli observed in previous fMRI studies in human parahippocampal and fusiform regions (Stern et al., 1996; Gabrieli et al., 1997; Jiang et al., 2000; Kirchhoff et al., 2000). This match suppression may be an automatic process for any repeated stimulus, whereas match enhancement may be an active process occurring only for a match with the stimulus seen as a sample (Otto and Eichenbaum, 1992b; Miller and Desimone, 1994). In fact, sample stimuli (which must be maintained) often do not show suppression effects (Miller and Desimone, 1994). Both these properties could result from cholinergic modulation during the presentation of the sample stimulus (Sohal and Hasselmo, 2000). The selective release of acetylcholine during presentation of stimuli in N2B could cause greater parahippocampal activity in this task relative to NX, whereas the absence of maintenance requirements in NX might result in an absence of neuromodulation by acetylcholine and a lack of enhancement relative to FX. The general tendency toward match suppression would result in an overall decrease in activity levels with familiar stimuli, which is not offset by match enhancement during presentation of the single-target stimulus. Recent studies showed sustained activity of entorhinal neurons during the delay period of a delayed-nonmatch-to-sample task in rats (Young et al., 1997) and during the delay period of a delayed-match-to-sample task in monkeys (Suzuki et al., 1997), but differences between novel and familiar stimuli were not analyzed in those tasks.

In the standard DNMS task, a monkey must respond to a stimulus based on whether or not he recognizes it. In effect, his response is based on relative familiarity of one stimulus in comparison with another. Monkeys with medial temporal lobe damage are impaired in this task (Zola-Morgan et al., 1989, 1993; Alvarez et al., 1994). Similarly, the novel two-back task described here can also be performed on the basis of relative novelty and familiarity, which may in turn contribute to the greater medial temporal activation in this task. The study presented here does not include presentation of repeated nonmatch stimuli, as utilized in some of the unit recordings from nonhuman primates (Miller and Desimone, 1994; Su-

zuki et al., 1997). This possibility can be tested in future event-related fMRI studies by including one-back repeated stimuli, which would not require a response, but would place stronger demands on working memory for the specific time of stimulus presentations. Such a control might result in greater prefrontal activation during the novel two-back task. However, it should be noted that previous fMRI studies looking at medial temporal lobe responses to novel and familiar stimuli reported activations that are more posterior and parahippocampal to those reported in this study (Stern et al., 1996; Kirchhoff et al., 2000).

Relation to Cellular Properties of Cortical Structures

For a region to maintain working memory for novel stimuli, the neuronal populations must be capable of retaining activity representing a specific sensory stimulus without repeated presentation of these stimuli. The maintenance of novel stimuli is not consistent with mechanisms of working memory, which require modification of excitatory recurrent connectivity during previous exposure (Camperi and Wang, 1998). However, it is consistent with intrinsic mechanisms in neurons that allow a subset of neurons activated by a sensory stimulus to maintain that activity without further synaptic input (Lisman and Idiart, 1995; Jensen and Lisman, 1996). The latter mechanism has been described using cellular recordings in brain slice preparations of entorhinal cortex (Klink and Alonso, 1997a,b; Fransen et al., 1999; Hasselmo et al., 2000). In slice preparations, muscarinic cholinergic receptors activate a calcium-sensitive nonselective cation current that allows a subset of neurons to show sustained spiking activity once they have been activated. In this mechanism, during cholinergic modulation, all neurons will show some depolarization due to activation of this current, but only those neurons that spike in response to afferent input will have the calcium influx necessary to cause regenerative activation of this current. Thus, only the subset of neurons that are activated by sensory input will show sustained activity. This provides an ideal mechanism for sustaining information about a novel stimulus during a delay period, and could drive hippocampal activity via perforant path input from the entorhinal cortex.

Differential Activation During Target-Matching

In addition to the clear differences seen between the N2B and F2B tasks described above, there were also differences observed between the FX and NX matching tasks. In particular, medial temporal regions showed greater activation during the matching of a target stimulus presented in a series of familiar stimuli (FX) than during the matching of a target stimulus presented in a series of novel stimuli (NX). The activation during the matching task with familiar stimuli (FX) was similar in magnitude to the activity observed during N2B. The strong response to the FX task suggests that a possible reason that medial temporal activation has not been shown in other two-back working memory imaging studies may result from the use of the long-term target-matching tasks as a baseline condition.

The activation reported here for the FX task suggests an important role for the medial temporal lobe in holding a stimulus for comparison, and in comparing input stimuli with this single target. The requirement to hold a stimulus for an extended period over multiple distractors could place greater demands on mechanisms that do not involve sustained activity, drawing instead on synaptic mechanisms mediating intermediate-term storage in the hippocampus and adjacent structures. In fact, it has been shown that greater fMRI activation occurs within the hippocampus even in simple DNMS tasks when the delay is long (15 s), as compared to a shorter delay (5 s) (Elliott and Dolan, 1999). Thus, the simple requirement of holding information beyond a certain minimum time period appears to recruit medial temporal structures. Hippocampal structures may also be specifically important for performing a comparison or matching process between an internal representation of a target stimulus and a current stimulus. In the NX condition, the match between the current stimulus and the internal target representation can be made using a simple sense of familiarity. In contrast, in the FX condition, all the stimuli matched stored representations (i.e., they are all familiar), and what is required is a specific match between the current stimulus and the internal target representation. This requirement for specific matching may preferentially engage the hippocampus and would be reflected here as greater activity during the FX condition than during NX. The connectivity of the hippocampal formation was previously described as providing a comparison function in region CA1 between the retrieval from region CA3 with the new afferent input from the entorhinal cortex (Gray, 1982; Eichenbaum and Buckingham, 1990; Hasselmo and Schnell, 1994; Hasselmo and Wyble, 1997).

The difference in medial temporal activation during the FX and NX tasks can also be discussed in terms of electrophysiological data on unit responses during performance of delayed matching tasks. In particular, electrophysiological data argue against the notion that the difference between the N2B and F2B tasks described above results simply from a passive decrease in response to familiar stimuli. Instead, it suggests the importance of changes in neuronal activity associated with the matching of individual stimuli. Studies of neuronal activity in the entorhinal cortex have shown match enhancement in addition to match suppression during performance of delayed matching tasks in rats (Young et al., 1997) and monkeys (Suzuki et al., 1997). In recordings from single neurons, enhancement of response to matching stimuli has been demonstrated within hippocampal region CA1 (Otto and Eichenbaum, 1992b), and hippocampal neurons have been shown to demonstrate sustained activity during task delays (Hampson et al., 1993). In human imaging studies, there is an enhancement of response to the first match of a target stimulus, in contrast to the decreased response to repeated presentations (Jiang et al., 2000). These types of changes could contribute to the differential activity observed during the FX task, particularly if the stronger task demands for recollection specifically require recruitment of hippocampal circuits during performance of the FX task.

In summary, these results provide evidence suggesting that prefrontal and posterior parietal regions may be important for work-

ing memory tasks with familiar stimuli that have a high potential for interference effects. In contrast, medial temporal regions may become increasingly important for working memory with novel stimuli and for long-term stimulus-matching. The results presented here provide evidence that the difference in medial temporal lobe recruitment in human neuroimaging studies and nonhuman primate studies may reflect the use of trial-unique stimuli in nonhuman studies and highly familiar stimuli in human imaging studies. Further studies using event-related fMRI are necessary to study the separate contributions of these regions to stimulus maintenance over delay periods and stimulus-matching functions.

REFERENCES

Alvarez P, Zola-Morgan S, Squire LR. 1994. The animal model of human amnesia: long-term memory impaired and short-term memory intact. Proc Natl Acad Sci USA 91:5637–5641.

Alvarez P, Zola-Morgan S, Squire LR. 1995. Damage limited to the hippocampal region produces long-lasting memory impairment in monkeys. J Neurosci 15:3796–3807.

Bachevalier J, Mishkin M. 1986. Visual recognition impairment follows ventromedial but not dorsolateral prefrontal lesions in monkeys. Behav Brain Res 20:249–261.

Braver TS, Cohen JD, Nystrom LE, Jonides J, Smith EE, Noll DC. 1997. A parametric study of prefrontal cortex involvement in human working memory. Neuroimage 5:49–62.

Brown MW, Wilson FA, Riches IP. 1987. Neuronal evidence that inferomedial temporal cortex is more important than hippocampus in certain processes underlying recognition memory. Brain Res 409:158–162.

Cahusac PM, Miyashita Y, Rolls ET. 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.

Camperi M, Wang XJ. 1998. A model of visuospatial working memory in prefrontal cortex: recurrent network and cellular bistability. J Comput Neurosci 5:383–405.

Cohen JD, Perlstein WM, Braver TS, Nystrom LE, Noll DC, Jonides J, Smith EE. 1997. Temporal dynamics of brain activation during a working memory task. Nature 386:604–608.

Eacott MJ, Gaffan D, Murray EA. 1994. Preserved recognition memory for small sets, and impaired stimulus identification for large sets, following rhinal cortex ablations in monkeys. Eur J Neurosci 6:1466–1478.

Eichenbaum H, Buckingham J. 1990. Studies on hippocampal processing: experiment, theory and model. In: Gabriel M, Moore J, editors. Learning and computational neuroscience: foundation of adaptive networks. Cambridge, MA: MIT Press. p 171–231.

Elliott R, Dolan RJ. 1999. Differential neural responses during performance of matching and nonmatching to sample tasks at two delay intervals. J Neurosci 19:5066–5073.

Fahy FL, Riches IP, Brown MW. 1993. Neuronal activity related to visual recognition memory: long-term memory and the encoding of recency and familiarity information in the primate anterior and medial inferior temporal and rhinal cortex. Exp Brain Res 96:457–472.

Fransen E, Alonzo A, Hesselmo ME. 1999. Intrinsic properties of rat entorhinal cells relevant to working memory. Soc Neurosci Abst:25: 725–726.

Fried I, MacDonald KA, Wilson CL. 1997. Single neuron activity in human hippocampus and amygdala during recognition of faces and objects. Neuron 18:753–765.

Friston KJ, Passingham RE, Nutt JG, Heather JD, Sawle GV, Frackowiak RS. 1989. Localisation in PET images: direct fitting of the intercommissural (AC-PC) line. J Cereb Blood Flow Metab 9:690–695.

Gabrieli JD, Brewer JB, Desmond JE, Glover GH. 1997. Separate neural bases of two fundamental memory processes in the human medial temporal lobe. Science 276:264–266.

Gaffan D. 1974. Recognition impaired and association intact in the memory of monkeys after transection of the fornix. J Comp Physiol Psychol 86:1100–1109.

Gaffan D, Murray EA. 1992. Monkeys (*Macaca fascicularis*) with rhinal cortex ablations succeed in object discrimination learning despite 24-hr intertrial intervals and fail at matching to sample despite double sample presentations. Behav Neurosci 106:30–38.

Gray JA. 1982. Neuropsychology of anxiety. Oxford: Oxford University Press. 548 p.

Hampson RE, Heyser CJ, Deadwyler SA. 1993. Hippocampal cell firing correlates of delayed-match-to-sample performance in the rat. Behav Neurosci 107:715–739.

Hasselmo ME, Schnell E. 1994. Laminar selectivity of the cholinergic suppression of synaptic transmission in rat hippocampal region CA1: computational modeling and brain slice physiology. J Neurosci 14: 3898–914.

Hasselmo ME, Wyble BP. 1997. Free recall and recognition in a network model of the hippocampus: simulating effects of scopolamine on human memory function. Behav Brain Res 89:1–34.

Hasselmo ME, Fransen E, Dickson C, Alonso AA. 2000. Computational modeling of entorhinal cortex. Ann NY Acad Sci 911:418–446.

Jensen O, Lisman JE. 1996. Theta/gamma networks with slow NMDA channels learn sequences and encode episodic memory: role of NMDA channels in recall. Learn Mem 3:264–278.

Jiang Y, Haxby JV, Martin A, Ungerleider LG, Parasuraman R. 2000. Complementary neural mechanisms for tracking items in human working memory. Science 287:643–646.

Kirchhoff BA, Wagner AD, Maril A, Stern CE. 2000. Prefrontal-temporal circuitry for episodic encoding and subsequent memory. J Neurosci 20:6173–6180.

Klink R, Alonso A. 1997a. Ionic mechanisms of muscarinic depolarization in entorhinal cortex layer II neurons. J Neurophysiol 77:1829–1843.

Klink R, Alonso A. 1997b. Muscarinic modulation of the oscillatory and repetitive firing properties of entorhinal cortex layer II neurons. J Neurophysiol 77:1813–1828.

Kowalska DM, Bachevalier J, Mishkin M. 1991. The role of the inferior prefrontal convexity in performance of delayed nonmatching-to-sample. Neuropsychologia 29:583–600.

Li L, Miller EK, Desimone R. 1993. The representation of stimulus familiarity in anterior inferior temporal cortex. J Neurophysiol 69:1918–1929.

Lisman JE, Idiart MA. 1995. Storage of 7 +/− 2 short-term memories in oscillatory subcycles. Science 267:1512–1515.

Miller EK, Desimone R. 1994. Parallel neuronal mechanisms for short-term memory. Science 263:520–522.

Miller EK, Li L, Desimone R. 1993. Activity of neurons in anterior inferior temporal cortex during a short-term memory task. J Neurosci 13:1460–1478.

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

Otto T, Eichenbaum H. 1992a. Complementary roles of the orbital prefrontal cortex and the perirhinal-entorhinal cortices in an odor-guided delayed-nonmatching-to-sample task. Behav Neurosci 106:762–775.

Otto T, Eichenbaum H. 1992b. Neuronal activity in the hippocampus during delayed non-match to sample performance in rats: evidence for hippocampal processing in recognition memory. Hippocampus 2:323–334.

Owen AM. 2000. The role of the lateral frontal cortex in mnemonic processing: the contribution of functional neuroimaging. Exp Brain Res 133:33–43.

Owen AM, Stern CE, Look RB, Tracey I, Rosen BR, Petrides M. 1998. Functional organization of spatial and nonspatial working memory processing within the human lateral frontal cortex. Proc Natl Acad Sci USA 95:7721–7726.

Passingham R. 1975. Delayed matching after selective prefrontal lesions in monkeys (*Macaca mulatta*). Brain Res 92:89–102.

Petrides M. 1994. Frontal lobes and behaviour. Curr Opin Neurobiol 4:207–211.

Petrides M. 1996. Specialized systems for the processing of mnemonic information within the primate frontal cortex. Philos Trans R Soc Lond [Biol] 351:1455–1462.

Petrides M. 2000. Dissociable roles of mid-dorsolateral prefrontal and anterior inferotemporal cortex in visual working memory. J Neurosci 20:7496–7503.

Postle BR, Stern CE, Rosen BR, Corkin S. 2000. An fMRI investigation of cortical contributions to spatial and nonspatial visual working memory. Neuroimage 11:409–423.

Rushworth MF, Nixon PD, Eacott MJ, Passingham RE. 1997. Ventral prefrontal cortex is not essential for working memory. J Neurosci 17:4829–4838.

Smith EE, Jonides J. 1999. Storage and executive processes in the frontal lobes. Science 283:1657–1661.

Sohal VS, Hasselmo ME. 2000. A model for experience-dependent changes in the responses of inferotemporal neurons. Network 11:169–190.

Stern CE, Corkin S, Gonzalez RG, Guimaraes AR, Baker JR, Jennings PJ, Carr CA, Sugiura RM, Vedantham V, Rosen BR. 1996. The hippocampal formation participates in novel picture encoding: evidence from functional magnetic resonance imaging. Proc Natl Acad Sci USA 93:8660–8665.

Stern CE, Owen AM, Tracey I, Look RB, Rosen BR, Petrides M. 2000. Activity in ventrolateral and mid-dorsolateral prefrontal cortex during nonspatial visual working memory processing: evidence from functional magnetic resonance imaging. Neuroimage 11:392–399.

Suzuki WA, Miller EK, Desimone R. 1997. Object and place memory in the macaque entorhinal cortex. J Neurophysiol 78:1062–1081.

Talairach J, Tournoux P. 1988. Co-planar stereotaxic atlas of the human brain. Stuttgart: Thieme Medical Publishers, Inc. 122 p.

Young BJ, Otto T, Fox GD, Eichenbaum H. 1997. Memory representation within the parahippocampal region. J Neurosci 17:5183–195.

Zola-Morgan S, Squire LR. 1986. Memory impairment in monkeys following lesions limited to the hippocampus. Behav Neurosci 100:155–160.

Zola-Morgan S, Squire LR, Amaral DG, Suzuki WA. 1989. Lesions of perirhinal and parahippocampal cortex that spare the amygdala and hippocampal formation produce severe memory impairment. J Neurosci 9:4355–4370.

Zola-Morgan S, Squire LR, Clower RP, Rempel NL. 1993. Damage to the perirhinal cortex exacerbates memory impairment following lesions to the hippocampal formation. J Neurosci 13:251–165.