

Medial Temporal Lobe Activation During Episodic Encoding and Retrieval: A PET Study

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ABSTRACT: Recent neuroimaging studies have obtained evidence of activation in the medial temporal lobe (MTL) during episodic encoding and retrieval. On the basis of a meta-analysis of MTL activations in studies that used positron emission tomography (PET), Lepage et al. (*Hippocampus* 1998;8:313–322) suggested that episodic encoding tends to involve the anterior MTL, whereas episodic retrieval tends to involve the posterior MTL. In a meta-analysis of studies that used PET and functional magnetic resonance imaging, Schacter and Wagner (*Hippocampus* 1999;9:7–24) reported weaker evidence for such a rostrocaudal distribution of encoding and retrieval activations. However, these meta-analyses were based largely on studies that examined encoding or retrieval separately. Here, we report a direct, within-subjects comparison of MTL activation during episodic encoding and retrieval by using PET. Results indicated that both encoding and retrieval were associated with blood flow increases in similar MTL regions with little indication that encoding and retrieval are preferentially associated with activity in the anterior versus the posterior MTL. Direct comparisons revealed greater blood flow increases in posterior MTL during encoding than retrieval. *Hippocampus* 1999;9:575–581. © 1999 Wiley-Liss, Inc.

KEY WORDS: functional neuroimaging; PET; encoding; retrieval; medial temporal lobes

INTRODUCTION

Neuropsychological studies of patients with brain injuries have established that damage to the medial temporal lobes (MTL) produces an

amnesic syndrome, thereby implicating the MTL in episodic or declarative memory (e.g., Squire, 1992). Early neuroimaging studies that used positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) sometimes failed to report evidence of MTL activation during episodic encoding and retrieval (e.g., Shallice et al., 1994; Tulving et al., 1994). However, a variety of more recent studies have demonstrated that MTL activation can be reliably observed during both episodic encoding and retrieval (for reviews, see Lepage et al., 1998; Schacter and Wagner, 1999).

In a meta-analysis of PET studies that reported evidence of MTL activation, Lepage et al. (1998) noted an asymmetry in the rostrocaudal distribution of activation foci during encoding and retrieval. For heuristic purposes, Lepage et al. (1998) suggested the use of a coronal plane 26 mm posterior to the anterior commissure in the brain atlas of Talairach and Tournoux (1988) to distinguish between rostral and caudal activations (i.e., they compared activations rostral to $y = -26$ mm with those caudal to this point). Encoding activations were observed almost exclusively in rostral MTL (i.e., hippocampus proper, anterior to $y = -26$), whereas retrieval activations were observed almost exclusively in the caudal MTL (i.e., posterior hippocampus and parahippocampal gyrus, posterior to $y = -26$). By contrast, Schacter and Wagner (1999) reviewed fMRI studies indicating that encoding activations are observed almost exclusively in posterior (i.e., caudal) MTL, the exact opposite of what Lepage et al. (1998) reported for PET studies (although there were too few fMRI retrieval

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activations in the MTL to warrant conclusions about their rostrocaudal location).

Schacter and Wagner (1999) reanalyzed the PET studies, and also included additional activation foci from studies that had not been included in the meta-analysis by Lepage et al. (1998). On the basis of this revised meta-analysis, Schacter and Wagner concluded that PET studies of encoding have yielded activation in both anterior and posterior MTL, thereby removing the apparent contradiction with the fMRI results (see also, Fernandez et al., 1999). Consistent with Lepage et al., Schacter and Wagner also noted that MTL retrieval activations in PET studies tend to fall in the posterior MTL, but the tendency is less pronounced in the revised meta-analysis by Schacter and Wagner than that reported previously by Lepage et al. (1998).

Almost all of the studies reviewed by Lepage et al. (1998) and Schacter and Wagner (1999) share a common feature, i.e., they examined encoding or retrieval separately. Thus, conclusions about the relative locations of MTL encoding and retrieval activations have been based largely on cross-experiment comparisons. Several studies have reported within-experiment comparisons of MTL encoding and retrieval activations, but the results have been mixed. In a PET study, Roland and Gulyás (1995) reported anterior MTL activation during encoding of visual patterns compared with a passive fixation control, and reported posterior MTL activation during retrieval of these patterns compared with the fixation control. For the encoding foci, Roland and Gulyás reported a direct comparison with the retrieval conditions, but it yielded no evidence of MTL activation. By using fMRI, Gabrieli et al. (1997) reported posterior MTL activation during encoding of novel compared with familiar pictures of outdoor scenes, and anterior MTL (subiculum) activation during retrieval of previously studied line drawings in response to word cues. However, this comparison is potentially problematic because different materials were used for the encoding and retrieval tasks (Dolan and Fletcher, 1999). In a follow-up experiment with two subjects, encoding scans were performed while subjects viewed drawings; retrieval scans were performed while subjects viewed the drawings and indicated whether each one corresponded to a previously studied word. Gabrieli et al. (1997) again reported posterior MTL activation during encoding and anterior MTL activation during retrieval. Nonetheless, Gabrieli et al. did not report a direct, within-subjects comparison between encoding and retrieval scans in either experiment.

In a more recent fMRI study, Dolan and Fletcher (1999) used a paradigm in which subjects were presented with strings of letters generated by a finite-state grammar rule system. The same strings were presented repeatedly, and subjects were asked to judge whether the string was grammatical (e.g., JMQH) or ungrammatical (e.g., JQLD). Left anterior MTL (i.e., hippocampal) activation was observed during responses to novel strings, which were assumed to reflect encoding processes. Left posterior MTL (i.e., parahippocampal gyrus) activation was observed during responses to familiar strings, which were assumed to reflect retrieval processes (for similar patterns of results, see Strange et al., 1999). However, it is difficult to compare the latter result with other findings concerning MTL retrieval activations reviewed by Lepage

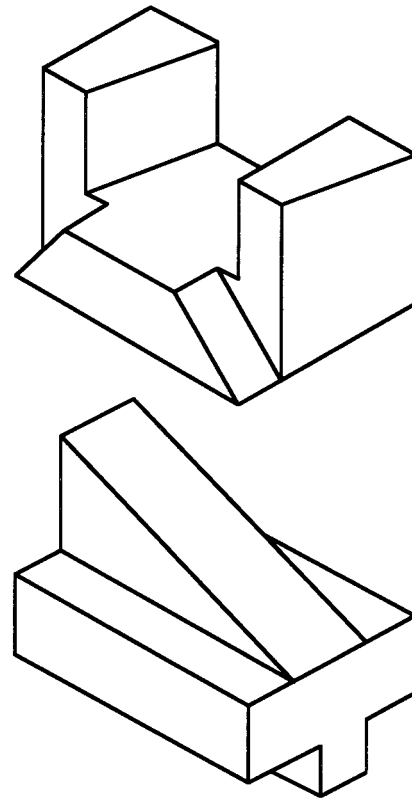


FIGURE 1. Examples of novel three-dimensional objects used in the experiment.

et al. (1998) and Schacter and Wagner (1999). Subjects in the study by Dolan and Fletcher (and also that of Strange et al., 1999) were not specifically required to engage in episodic retrieval of previously presented items. Rather, they were required to make grammaticality judgments throughout to increasingly familiar stimuli. By contrast, participants in the studies reviewed by Lepage et al. (1998) and Schacter and Wagner (1999) were specifically required to engage in episodic retrieval (i.e., to try to remember previously presented target items).

To further explore the relation between MTL encoding and retrieval activations, we used an experimental paradigm that allows a direct comparison between episodic encoding and episodic retrieval, while at the same time holding constant such potentially confounding factors as differences in materials, presentation times, and so forth. The paradigm has previously produced evidence of increased regional cerebral blood flow (rCBF) in the MTL during episodic retrieval (Schacter et al., 1995, 1997; Uecker et al., 1997). In this paradigm, participants first study a series of novel, three-dimensional objects (Fig. 1) and then undergo PET rCBF scans while making old/new recognition judgments about previously studied objects or new objects. Compared with a control condition in which subjects passively view new objects, we found significant rCBF increases, mainly in posterior MTL (hippocampus and parahippocampal gyrus), during recognition judgments about both old and new objects (Schacter et al., 1995, 1997; Uecker et al., 1997). In the present experiment, we extended this paradigm to allow a direct compari-

son of rCBF changes during encoding of old and new objects with rCBF changes during retrieval of old and new objects.

Twelve subjects completed two study-test phases, each beginning with visual presentation of a study list, before the initiation of PET scans, that contained line drawings of novel three-dimensional objects such as those shown in Figure 1. During each of eight subsequent scans (four after each of the study lists), subjects made either old/new recognition judgments about previously studied objects (retrieval-old) or new objects (retrieval-new), or were instructed to study for a future test previously studied objects (encoding-old) or new objects (encoding-new). Additional scans involved passive viewing of nonstudied objects or fixation on a crosshair.

RESULTS AND DISCUSSION

Analysis of behavioral data obtained from the retrieval-old and retrieval-new scans indicated that the accuracy of old/new recognition judgments was high. The hit rate (i.e., “old” judgments to objects in the retrieval/old scans) was 84%, whereas the false-alarm rate (i.e., “old” judgments to objects in the retrieval/new scans) was 27%.

By using statistical parametric mapping (SPM), we first compared rCBF from the retrieval scans and encoding scans, respectively, with the passive viewing and fixation scans. We then carried out a direct within-subject comparison between encoding scans and retrieval scans. Replicating previous results, comparisons of retrieval-old and retrieval-new scans, separately and together, to the passive viewing scan revealed significant ($P < .005$, uncorrected for multiple comparisons) rCBF increases in the left hippocampal formation (Table 1; Fig. 2). A similar pattern was observed when these conditions were compared with the crosshair fixation control, except that the rCBF increases were observed bilaterally and included parahippocampal gyrus.

Surprisingly, there was also significantly greater rCBF in the retrieval-new than the retrieval-old scan ($-34 - 40 -4$; $z = 3.63$). Schacter et al. (1995, 1997) reported conditions in which rCBF increases are observed in retrieval-old compared with retrieval-new. However, there are differences between the present paradigm and these earlier studies: Schacter et al. (1995, 1997) used one study exposure whereas our experiment used two study exposures, the retention interval was slightly longer in experiments by Schacter et al. (1995, 1997) than in ours, and the object set used in our experiment differed from the object sets used in the earlier experiments. Related to these procedural differences, accuracy of recognition performance was somewhat higher in the present study (hits minus false alarms = 57%) than in Schacter et al. (1995) (hits minus false alarms = 49%) and considerably higher than in Schacter et al. (1997) (hits minus false alarms = 32%). A more recent experiment (conducted at the Massachusetts General Hospital PET laboratory; S. Heckers et al., unpublished observations) also examined recognition memory for novel objects. The paradigm was similar to the one used in the present experiment

TABLE 1. *MTL Blood Flow Increases in Critical Comparisons**

Comparison	Region	x	y	z	z-score
Retrieval increases					
Retrieval new—	PHG	18	-32	0	3.15
Fixation	PHG/FG	-28	-42	-8	2.70
Retrieval old—	HF	-16	-26	-4	3.02
Fixation					
Retrieval new & old—	HF	16	-32	-4	3.09
Fixation					
Retrieval new—	HF	-30	-34	-4	3.52
Passive viewing					
Retrieval old—	HF	-20	-26	-4	2.67
Passive viewing					
Retrieval new & old—	HF	-26	-30	-4	2.95
Passive viewing					
Encoding increases					
Encoding new—	PHG	16	-48	4	2.83
Fixation					
Encoding old—	PHG	18	-40	0	2.72
Fixation	HF/PHG	-18	-32	-8	2.75
Encoding new & old—	PHG	16	-48	4	3.16
Fixation		30	-24	-20	2.93
Encoding new—	HF	-28	-34	-4	2.77
Passive viewing					
Encoding old—	HF	30	-24	-16	2.88
Passive viewing					
Encoding new & old—	PHG	34	-26	-20	3.33
Passive viewing	HF	-26	-32	-8	2.87
Encoding vs. retrieval					
Encoding new—	PHG/FG	38	-34	-12	3.13
Retrieval old	PHG/FG	-36	-42	-8	3.17
Encoding old—	PHG/FG	38	-30	-16	2.83
Retrieval old					
Encoding new & old—	PHG/FG	38	-28	-16	3.45
Retrieval new & old					

*Location and magnitude of significant blood flow increases for each of the comparisons noted in the table; significant changes were also observed in additional regions outside the medial temporal lobe that are not reported here. The location of maximal z-scores was defined according to the brain atlas of Talairach and Tournoux (1988), such that x is the distance in millimeters to the right (+) or left (-) of midline, y is the distance in millimeters anterior (+) or posterior (-) to the anterior commissure, and z is the distance in millimeters superior (+) or inferior (-) to a horizontal plane through the anterior and posterior commissures. HF, hippocampal formation; PHG, parahippocampal gyrus; FG, fusiform gyrus.

with respect to the above-noted procedural features. There was again a retrieval new > retrieval old activation in posterior MTL, and the performance level was again quite high (hits minus false alarms = 69%). Future studies that elucidate the theoretical significance of these differences would be highly desirable.

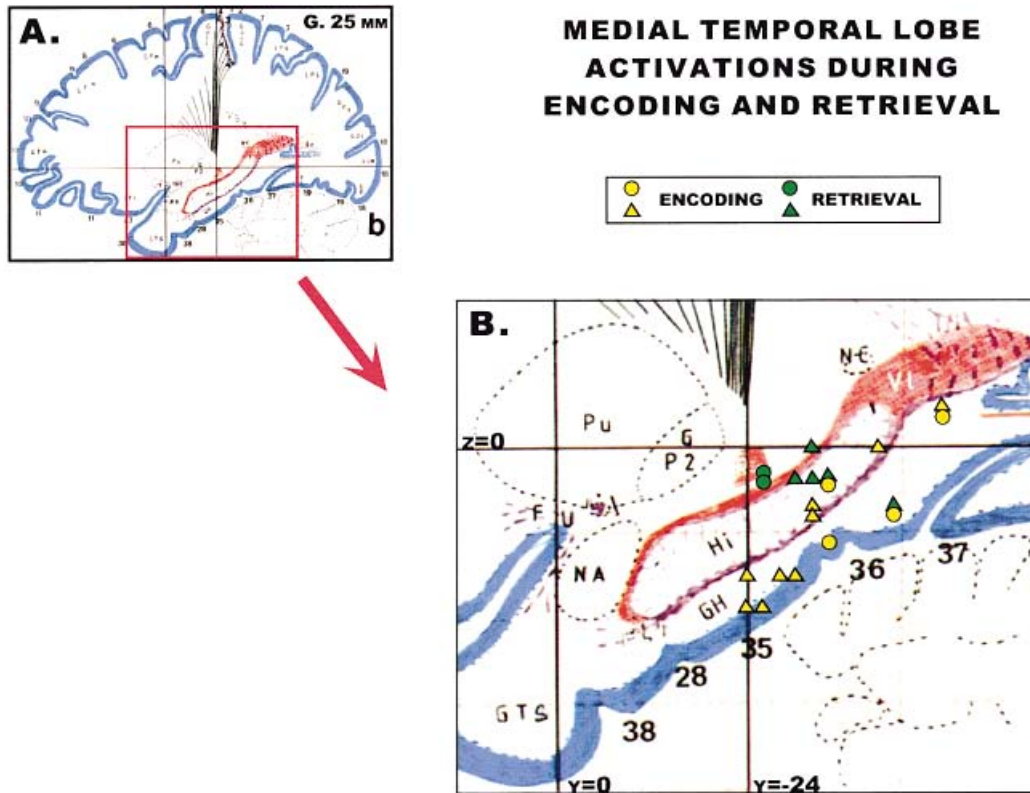


FIGURE 2.

FIGURE 2. Schematic renderings of PET encoding and retrieval activations. Each point corresponds to an activation from one of the comparisons presented in Table 1. Circles indicate activation foci from our encoding-new and retrieval-old conditions, which meet the inclusion criteria used in the meta-analyses reported by Lepage et al. (1998) and Schacter and Wagner (1999; see text for discussion) and, therefore, are most directly relevant to those meta-analyses; triangles

indicate activation foci from the other comparisons in Table 1 involving encoding-old or retrieval-new conditions. Foci from both the left and right hemispheres are shown on a single sagittal plane taken from the Talairach and Tournoux (1988) atlas (25 mm lateral to the midline). Overlapping activations were offset slightly. Atlas coordinates corresponding to each of the foci in the figure are presented in Table 1.

Focusing on the rostrocaudal location of the retrieval activations, they tended to cluster in the mid- to posterior MTL extending into fusiform gyrus, ranging from $y = -26$ to $y = -42$. A generally similar pattern of rCBF increases in the posterior MTL was observed when we compared encoding scans for old or new objects, or both old and new objects, with passive viewing or fixation baseline scans (Table 1; Fig. 2). Perhaps most important, the rostrocaudal distribution of rCBF increases during encoding closely resembled that observed for retrieval increases, ranging from $y = -24$ to $y = -48$.

Direct within-subject comparisons of retrieval and encoding scans revealed that a region of posterior MTL involving parahippocampal gyrus and fusiform gyrus showed significantly greater rCBF in the comparisons of encoding-new vs. retrieval-old and encoding-old vs. retrieval-old (Table 1; Fig. 3). A similar region showed a significant increase in the combined comparison of encoding old&new vs. retrieval old&new (Table 1). By contrast, no regions within the MTL showed significantly greater rCBF during retrieval scans than encoding scans.

The overall pattern of rCBF effects in the MTL does not indicate a rostrocaudal distribution of encoding and retrieval activations of the kind described by Lepage et al. (1998), in which encoding is preferentially associated with anterior MTL activation, and retrieval is preferentially associated with posterior MTL activation. Instead, both encoding and retrieval conditions produced similar rostrocaudal distributions of rCBF increases, involving mainly posterior hippocampus, parahippocampal gyrus, and fusiform gyrus. The fact that posterior MTL (parahippocampal/fusiform gyri) showed greater rCBF during encoding fits well with fMRI studies of encoding (e.g., Brewer et al., 1998; Kelley et al., 1998; Wagner et al., 1998) and also with a number of PET studies reviewed by Schacter and Wagner (1999), including Bookheimer et al. (1995), Kapur et al. (1995), and Wiggs et al. (1999).

Lepage et al. (1998) included only conditions analogous to our "retrieval-old" condition in their meta-analysis. They were careful to exclude from consideration conditions analogous to our "retrieval-new" condition, arguing that activation in such conditions could reflect either attempted retrieval of novel items or

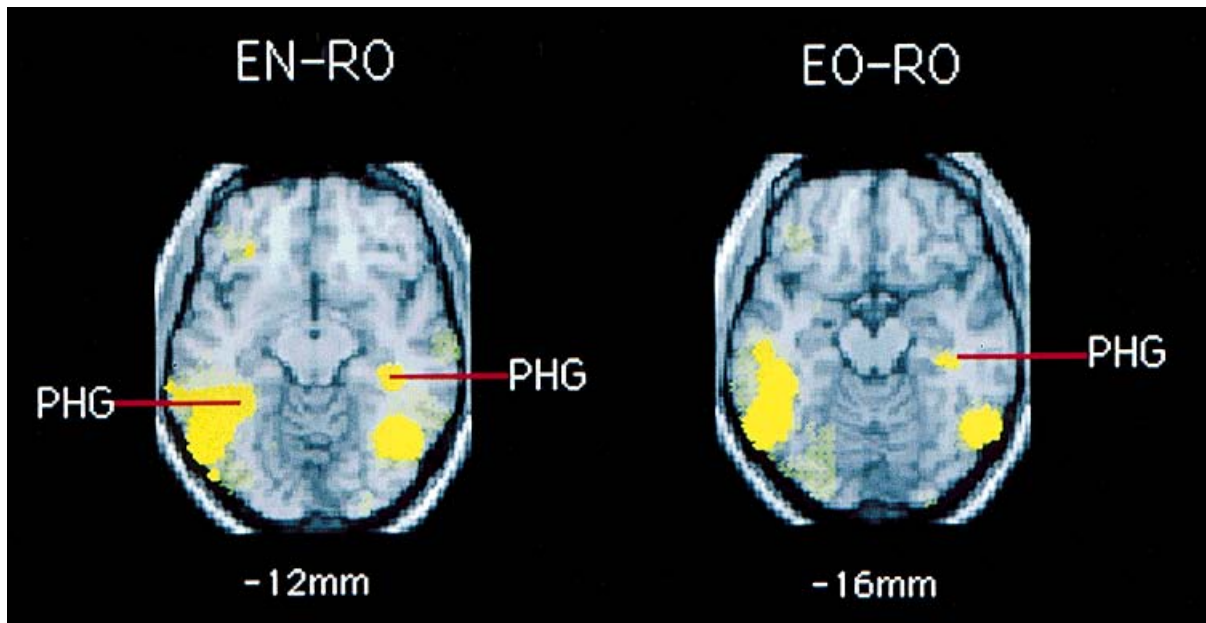


FIGURE 3. Significant increases in parahippocampal blood flow in two “Encoding minus Retrieval” subtractions. In each case, a statistical map of significant increases in regional cerebral blood flow ($P < .005$, uncorrected for multiple comparisons, in yellow) was superimposed onto a spatially standardized magnetic resonance image of the brain; the left side of each image corresponds to the left side of the brain. As indicated in a horizontal section 12 mm inferior to a plane through the anterior and posterior commissures, encoding new minus retrieval old (EN-RO) was associated with significantly

increased blood flow in the left and right parahippocampal gyri (PHG). (Additional increases [not labeled] were observed in the left and right middle temporal and fusiform gyri.) As indicated in a horizontal section 16 mm inferior to a plane through the anterior and posterior commissures, EO-RO was associated with significantly increased blood flow in the right PHG. (Additional increases [not labeled] were observed in the left and right inferior temporal and fusiform gyri.)

initial encoding of those items into memory. Reasoning along similar lines, our “encoding-old” condition could be problematic, because when presented with previously studied items and asked to study them for a future test, subjects may retrieve information about their prior occurrence.

In view of these considerations, the “purest” conditions in our experiment are encoding-new and retrieval-old. As indicated by the data in Table 1 and Figure 2, the encoding-new and retrieval-old conditions yielded rCBF increases that were roughly similar to those seen in encoding-old and retrieval-new conditions. Indeed, there is a tendency for the peak foci in encoding-new increases, relative to baseline, to be located posterior to the retrieval-old increases, the opposite of what would be expected from the pattern described by Lepage et al. (1998). Similarly, direct comparison between encoding-new and retrieval-old revealed encoding-related increases in posterior MTL.

If encoding and retrieval both produce posterior MTL activation in the present study, then what accounts for the anterior MTL activation observed in PET studies reviewed by Lepage et al. (1998) and Schacter and Wagner (1999)? Schacter and Wagner (1999) noted that PET studies that produced evidence of anterior MTL encoding activation tended to require subjects encode multiple stimuli (e.g., word pairs or object pairs). Consistent with previous accounts of hippocampal function that have emphasized relational encoding processes (e.g., Squire, 1992; Cohen and Eichenbaum, 1993; Rudy and Sutherland, 1994), Schacter and

Wagner (1999) suggested that anterior MTL activation will tend to be observed under encoding conditions that emphasize relational processing of multiple stimuli. Note that this account is also consistent with the study described earlier by Dolan and Fletcher (1999; see also Strange et al., 1999), in which anterior MTL encoding activation was observed when subjects made grammaticality judgments about novel letter strings. To make such judgments, subjects presumably had to focus on and encode relations among the letters that constitute each string. However, as the items became increasingly familiar with repetition, they may have eventually assumed the status of functional units that no longer required relational encoding, which could be one reason why posterior MTL activation was observed for familiar strings. Indeed, computational modeling suggests that artificial grammar learning may proceed through a process in which individual letters become chunked into higher-order representations (Servan-Schreiber and Anderson, 1990).

In contrast, there is no requirement for relational encoding in the present paradigm, hence, encoding activation was observed mainly in posterior MTL. The same line of reasoning can be applied to retrieval. Recognition judgments in the present paradigm do not specifically require relational processing. As Schacter and Wagner (1999) suggested, it is possible that episodic retrieval will be associated with anterior MTL activation when relational processing is required, and with posterior MTL activation when it is not. This account still leaves open the issue of exactly what kinds

of nonrelational encoding and retrieval processes are supported by posterior MTL structures and how they are similar to and different from one another.

Further investigation of the issue could be informed by the distinction recently drawn by Tulving et al. (1999) between “how” regions (i.e., regions whose activity is associated with how well a given task is carried out) and “what” regions (i.e., regions that distinguish between the presence/absence of a particular process). Tulving et al. characterized posterior MTL as a “how” region; its activities should vary in relation to level of task performance. This distinction might also be relevant to the contrasting patterns of posterior MTL retrieval activation discussed earlier: retrieval new > retrieval old in the present study and that of Heckers et al. (unpublished observations), compared with retrieval old > retrieval new reported in the earlier studies of Schacter et al. (1995, 1997). As we pointed out, recognition accuracy was higher in the present experiment and that of Heckers et al. than it was in the previous ones. Although the precise theoretical relevance of these differences to the contrasting patterns of results is not known, performance-related differences would be expected in “how” regions. Future studies that systematically manipulate performance levels in the present recognition memory paradigm could provide useful clues concerning the kinds of retrieval and encoding operations that are associated with the posterior MTL.

DETAILED METHODS

Subjects

Twelve healthy, unmedicated right-handed females (mean, \pm SD; age, 30 ± 6.2 years) participated in the experiment. All subjects had a normal neurologic examination and no evidence of psychiatric disorders determined by a structured psychiatric interview. None of the subjects had participated in our previous experiments (Schacter et al., 1995, 1997; Uecker et al., 1997) involving the novel object set used in the present experiment.

Materials

The stimuli were 160 line-drawings (300×300 pixels) of novel three-dimensional objects (“possible objects” from Schacter et al., 1991; Williams and Tarr, 1997). A plus-sign was used in the fixation condition.

Design and Procedure

The two primary, within-subject independent variables were task (encoding, retrieval) and memory status (old, new). The two baseline conditions were passive object viewing (new objects) and passive fixation viewing. All conditions were replicated in two study-test phases.

Each study-test phase began with a study list of 34 objects (not scanned). The first and last objects on the list were buffer items that did not appear on the subsequent test. The study list was presented twice in different random orders. Each object was

displayed for 4.5 seconds with a 0.5-second interstimulus interval. As an encoding task, subjects decided whether each object would be best used as a tool (e.g., scooping, cutting, or pounding) or for support (e.g., stepping, sitting, or leaning on it), and indicated their choice by pressing one of two keys. A 10-minute retention interval followed each study list.

Each study list was followed by six scanned conditions: encoding/new, encoding/old, retrieval/new, retrieval/old, passive objects, passive fixation. Each block contained 16 stimuli that were each presented for 3.5 seconds with a 0.25-second interstimulus interval. In the retrieval conditions, subjects were asked to perform a recognition task, i.e., pressing one key for previously studied (old) objects and another key for new objects. In the encoding conditions, subjects were told to carefully study each object, so they would remember it later, but no overt response was required. In the passive conditions, subjects passively view each stimulus (objects or fixation). In the passive object condition, subjects were specifically told not to memorize the objects because memory for them would not be tested. The two encoding and retrieval conditions always occurred consecutively in either scans 1 and 2 or scans 4 and 5. The condition order was counterbalanced so that a subject who was required to retrieve in scans 1 and 2 would be required to encode in scans 7 and 8 (the first and second scans of study-test phase 2). The two passive conditions always occurred in scans 3 and 6, and the order in phase 2 was the opposite of the phase 1 order. Counterbalancing across all subjects ensured that each object appeared in each condition two or three times, each experimental condition occurred in each scan position (scan 1, 2, 4, 5, 7, 8, 10, or 11) three times, and each passive baseline condition occurred in each scan position (scan 3, 6, 9, or 12) six times.

PET Methods

Twelve 31-slice PET images of regional cerebral blood flow were obtained by using the ECAT 951/31 scanner (Siemens, Knoxville, TN), 45 mCi intravenous bolus injections of [^{15}O] water, and 60-second scans separated by 10–15 minutes between scans. PET images were reconstructed with an in-plane resolution of about 10 mm full-width at half-maximum (FWHM) and a slice thickness of about 5 mm FWHM. For data analysis, a Gaussian filter yielded an in-plane resolution of about 20 mm FWHM and a slice thickness of about 10 mm FWHM.

Automated algorithms were used to align the sequential PET images from each subject, spatially transform them into the coordinates of a standard brain atlas, control for variations in whole brain measurements, compute z-score maps of significant increases in regional blood flow for each comparison (z-score > 2.58, $P < .005$, uncorrected for multiple comparisons; for detailed discussion of statistical basis for this threshold, see Reiman et al., 1997), and superimpose the maps onto an average of 12 spatially standardized brain MRIs (Talairach and Tournoux, 1988; Friston et al., 1991; Woods et al., 1992; Collins et al., 1994). Here, we report only the results of hypothesis testing comparisons regarding MTL activations; significant rCBF changes

in additional brain regions were also observed during encoding and retrieval.

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