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
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 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-
together, to the passive viewing scan revealed significant (sons of retrieval-old and retrieval-new scans, separately and scans and retrieval scans. Replicating previous results, compari-
carried out a direct within-subject comparison between encoding
respectively, with the passive viewing and fixation scans. We then
compared rCBF from the retrieval scans and encoding scans,
object recognition rate (i.e., “old” judgments to objects in the retrieval/new
objects in the retrieval/old scans) was 84%, whereas the false-
judgments was high. The hit rate (i.e., “old” judgments to
retrieval-new scans indicated that the accuracy of old/new recogni-
tion judgments was high.

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, compar-
isons 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 observa-
tions) also examined recognition memory for novel objects. The
paradigm was similar to the one used in the present experiment

### RESULTS AND DISCUSSION

Analysis of behavioral data obtained from the retrieval-old and
retrieval-new scans indicated that the accuracy of old/new recogni-
tion 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%.

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paradigm was similar to the one used in the present experiment

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

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Region</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>z-score</th>
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<td></td>
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<td>-32</td>
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<td>-42</td>
<td>-8</td>
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<td>Retrieval old—</td>
<td>HF</td>
<td>-16</td>
<td>-26</td>
<td>-4</td>
<td>3.02</td>
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<td>Fixation</td>
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<td>HF</td>
<td>16</td>
<td>-32</td>
<td>-4</td>
<td>3.09</td>
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<td>Fixation</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Retrieval new—</td>
<td>HF</td>
<td>-30</td>
<td>-34</td>
<td>-4</td>
<td>3.52</td>
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<td>Retrieval old—</td>
<td>HF</td>
<td>-20</td>
<td>-26</td>
<td>-4</td>
<td>2.67</td>
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<td>-26</td>
<td>-30</td>
<td>-4</td>
<td>2.95</td>
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<td>PHG</td>
<td>16</td>
<td>-48</td>
<td>4</td>
<td>2.83</td>
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<td>-32</td>
<td>-8</td>
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<td>Fixation</td>
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<tr>
<td>Encoding new &amp; old—</td>
<td>PHG</td>
<td>16</td>
<td>-48</td>
<td>4</td>
<td>3.16</td>
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<td>Fixation</td>
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<td>HF</td>
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<td>-34</td>
<td>-4</td>
<td>2.77</td>
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<td>Passive viewing</td>
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<td>-16</td>
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<tr>
<td>Encoding new &amp; old—</td>
<td>PHG</td>
<td>34</td>
<td>-26</td>
<td>-20</td>
<td>3.33</td>
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<td>Passive viewing</td>
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<tr>
<td>Encoding vs. retrieval</td>
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<td></td>
</tr>
<tr>
<td>Encoding new—</td>
<td>PHG/FG</td>
<td>38</td>
<td>-34</td>
<td>-12</td>
<td>3.13</td>
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<td>Retrieval old—</td>
<td>PHG/FG</td>
<td>-36</td>
<td>-42</td>
<td>-8</td>
<td>3.17</td>
</tr>
<tr>
<td>Encoding old—</td>
<td>PHG/FG</td>
<td>38</td>
<td>-30</td>
<td>-16</td>
<td>2.83</td>
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<td>PHG/FG</td>
<td>38</td>
<td>-28</td>
<td>-16</td>
<td>3.45</td>
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</table>

*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 commissu-
res. 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.
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 gyr) 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...
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 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) 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, 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

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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 association with retrieval is well-established) 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.

**Subjects**

Twelve healthy, unmedicated right-handed females (mean, ± 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 [15O] 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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REFERENCES


