Introduction
The ability to remember previously learned words relies on a distributed neural network that includes modules in the prefrontal cortex and medial temporal lobe (MTL) (Eichenbaum, 2000; Buckner and Wheeler, 2001). Previous neuroimaging studies of word retrieval in episodic memory tasks have documented several neural substrates underlying simple recognition, cue recall, or free recall of previously studied words (Buckner and Wheeler, 2001). One mechanism common to all three retrieval modes is the activation of anterior [Brodmann area (BA) 10] and posterior (BA 44/6) dorsolateral prefrontal cortex (DLPFC) modules, each of which contributes to distinct aspects of the recollective experience (Buckner and Wheeler, 2001). Activation of MTL structures is correlated with retrieval success (Nyberg et al., 1996) and hippocampal recruitment is linked to the detailed recollection of an episode in contrast to a general sense of familiarity (Eldridge et al., 2000).

We previously demonstrated that word-stem cued recall after deep, semantic encoding was associated with MTL activation, while retrieval following shallow, perceptual encoding was associated with bilateral prefrontal cortex activation (Schacter et al., 1996a,b; Heckers et al., 1998). In these previous studies, word-stem cued recall followed one of two encoding conditions: semantic encoding of words presented repeatedly, or perceptual encoding of a word presented once. This design allowed us to study the association of recall accuracy with hippocampal blood flow changes, but it did not allow us to disentangle the effects of word repetition and encoding task during study on subsequent cued recall. Previously observed changes in hippocampal blood flow during cued recall could be attributable to increased recall accuracy due to semantic encoding, repetition, or the combined effect of these two influences. Therefore, we used a 2 × 2 factorial design to study the main effects of word repetition (4× versus 1× presentation) and encoding task (semantic versus perceptual) on subsequent word-stem cued recall. We hypothesized that both encoding task and stimulus repetition would affect recall accuracy and that increases in recall accuracy would be associated with hippocampal recruitment.

Materials and Methods
Subjects
We studied 12 healthy male volunteers (mean age 48.8 ± 10.5 years), who provided written informed consent. Subjects were excluded if they had a history of neurological or medical illness, current substance abuse, or lifetime substance dependence. Furthermore, the subjects had no history of a psychiatric disorder, as assessed by the Structured Clinical Interview for DSM-III-R (SCID) (Spitzer et al., 1991). The study was approved by the Human Research Committee of the Massachusetts General Hospital and the Central Office Research Review Committee of the Commonwealth of Massachusetts, Department of Mental Health.

Experimental Paradigm
The experiment consisted of two study–test units. During the study period, subjects viewed a randomized list of 100 target words: one set of 20 words presented once and one set of 20 words presented four times. Words were presented on an Apple G3 Powerbook computer, in 72 point Geneva font, for 5 s each. The subjects were instructed to answer one of two questions while viewing each study word: ‘How many T-junctions does this word have?’ (perceptual encoding task) or ‘How many T-junctions does this word have?’ (semantic encoding task). T-junctions were defined as crossing perpendicular lines in each letter of the study words. All subjects successfully completed an offline practice trial to ensure that they were able to follow the instructions. Each subject studied four sets of words during the two study blocks, which resulted in four encoding conditions: semantic × 1, semantic × 4, perceptual × 1, perceptual × 4. Word lists were rotated amongst the four encoding conditions in a counterbalanced fashion.

Subjects were scanned during two test periods, which followed each of the two study periods with delays of 10 and 30 min, respectively. Subjects viewed three-letter stems of the study words and were asked to complete them with the target word. Word stems were presented for 5 s in blocks that represented the four encoding conditions described above. The order of the blocks during test was counterbalanced across the 12 subjects, with the only constraint that two blocks were always paired (either semantic × 1 + perceptual × 4 or semantic × 4 + perceptual × 1) for each study–test unit.

Before and after the two study–test units, subjects were scanned while they were presented with 20 three-letter stems of unstudied words,
with the instruction to complete these stems with the first word that came to mind (lexical retrieval).

**Positron Emission Tomography (PET) Data Acquisition**

PET data were acquired with a General Electric Scanditronix PC4096 15 slice whole body tomograph. The slice geometry consisted of contiguous slices with center-to-center distance of 6.5 mm (axial field = 97.5 mm) and axial resolution of 6.0 mm full-width half-maximum (FWHM). Images were reconstructed using a computed attenuation correction and a Hanning-weighted reconstruction filter set to yield 8.0 mm in-plane spatial resolution FWHM. Additional corrections were made to account for photon absorption, scatter and dead-time effects.

Subjects were positioned in the scanner with an individually molded thermoplastic mask to minimize head motion. Head alignment was made relative to the canthomeatal line to ensure maximal coverage of prefrontal areas and complete coverage of the medial temporal lobes. Transmission measurements were made using an orbiting pin source. Subjects underwent six 1 min scans and inhaled $^{15}$O$\text{CO}_2$ gas beginning 30 s after the initiation of the task. Each scan was followed by a 10 min wash-out period.

**Data Analysis**

**Behavioral Data**

We analyzed the effects of repetition ($\times 1$ or $\times 4$) and encoding task (semantic or perceptual) on the accuracy of word-stem cued recall with a repeated measures analysis of variance (ANOVA).

**PET Data**

All images were corrected for interscan movement and were transferred into a standard stereotactic space using SPM 99 (Wellcome Department of Cognitive Neurology, London, UK). Images were smoothed with a 2D Gaussian filter of width 15 mm FWHM.

We used SPM99 to perform two types of statistical analyses. First, we used a mixed effects model (conditions as fixed and subjects as random effects) to test for the effects of repetition and encoding task on brain activation during word retrieval. This was achieved by creating contrast images for each subject and pooling them in a one-sample $t$-test. Based on previous studies (Schacter et al., 1996a,b; Heckers et al., 1998), we had strong localizing hypotheses for the hippocampus and bilateral frontal lobes. Therefore, the voxels reported in these regions were significant at $P < 0.001$ uncorrected ($z > 3.09$), whereas all other voxels outside these 

**Results**

**Behavioral Data**

Word repetition during encoding increased subsequent recall accuracy by 73% [main effect of repetition: $F(1,11) = 72.0$, $P < 0.0001$; Fig. 1]. The use of a semantic encoding task resulted in a 25% higher recall accuracy when compared to a perceptual encoding task [main effect of encoding task: $F(1,11) = 15.3$, $P =$

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Table 1

<table>
<thead>
<tr>
<th>Region (Brodmann area)</th>
<th>z-score</th>
<th>Coordinates (MNI)</th>
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<tbody>
<tr>
<td></td>
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<td>$x$</td>
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<tr>
<td><strong>Main effect of repetition</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 × Presentation &gt; 1 × presentation Left hippocampus</td>
<td>3.44</td>
<td>−32</td>
</tr>
<tr>
<td>4 × Presentation &gt; baseline task Left hippocampus</td>
<td>3.11</td>
<td>−32</td>
</tr>
<tr>
<td>1 × Presentation &gt; 4 × presentation Right parahippocampal/lingual</td>
<td>5.07</td>
<td>26</td>
</tr>
<tr>
<td>Left DLPFC (10)</td>
<td>4.02</td>
<td>−40</td>
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<tr>
<td>Right DLPFC (10)</td>
<td>3.44</td>
<td>20</td>
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<tr>
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<td>3.86</td>
<td>20</td>
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<tr>
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<td>16</td>
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<td><strong>Main effect of encoding task</strong></td>
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<tr>
<td>Semantic &gt; perceptual Right hippocampus</td>
<td>3.49</td>
<td>26</td>
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<tr>
<td>Left hippocampus</td>
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<td>−30</td>
</tr>
<tr>
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<tr>
<td>Left hippocampus</td>
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<tr>
<td>Left DLPFC (10)</td>
<td>3.70</td>
<td>−28</td>
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</tbody>
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Figure 1. Behavioral data. Word-stem cued recall accuracy scores (means ± SD) after single ($\times 1$) or repeated ($\times 4$) word encoding using a perceptual or a semantic task.

*a priori* defined region s were significant at $P < 0.0001$ uncorrected ($z > 3.72$). To confirm that the activation associated with the two main effects (i.e. repetition and encoding task) represented increases in rCBF (regional cerebral blood flow) during the condition of interest rather than decreases in the control condition, we tested whether significant differences were also found in a comparison of the condition of interest with the low level baseline task (i.e. lexical retrieval).

Second, we performed a fixed effects analysis of all scans for which we had recall accuracy scores (i.e. four scans per subject: semantic × 1, semantic × 4, perceptual × 1, perceptual × 4). To test the hypothesis that hippocampal blood flow values correlate with recall accuracy scores, we used a threshold of $P < 0.005$ uncorrected ($z = 2.58$) for all voxels in the hippocampus, but the more conservative threshold of $P < 0.0001$ uncorrected ($z = 3.72$) for all voxels outside of the hippocampus.
The increase in recall accuracy due to word repetition was greater when using the semantic task (91%) as compared to the perceptual task (54%; repetition × encoding strategy interaction: \( F(1,11) = 19.5, P = 0.001 \)).

**PET Data**

*Retrieval after Repeated and Semantic Encoding*

Word repetition during encoding resulted in greater rCBF during subsequent recall in only one brain region, the left hippocampus (Table 1, Fig. 2). The same pattern of hippocampal activation was also seen when recall after repeated word presentation was compared to the baseline lexical retrieval task (Table 1). On the other hand, brain activation during word retrieval after single compared with repeated word presentation during encoding resulted in greater regional cerebral blood flow in the right parahippocampal/lingual gyrus and in bilateral DLPFC (BA 10; Table 1).

The use of a semantic encoding task resulted in greater rCBF during subsequent recall in the right hippocampus (Table 1, Fig. 3). A less significant rCBF increase was also found in the left hippocampus (Table 1). The same pattern of hippocampal activation was seen when recall after semantic encoding was compared to the baseline lexical retrieval task (Table 1). On the other hand, the use of a perceptual encoding task resulted in greater regional cerebral blood flow in a left hemisphere network that included the orbitofrontal cortex and DLPFC (BA 47 and 10; Table 1).

*Figure 2.* Increased left hippocampal blood flow during recall after repeated compared to single word encoding. Areas of significant activity (\( P < 0.001 \), uncorrected) are mapped onto a template structural MRI scan of a single subject, transformed into a standard stereotactic space.
Repetition × Semantic Encoding Interaction
The analysis of the recall accuracy scores revealed that subjects received greater benefit from word repetition when performing a semantic encoding task compared to a perceptual encoding task. To reveal the neural basis for this behavioral effect, we compared the rCBF increase during word retrieval due to word repetition following either semantic or perceptual encoding. We found that the significantly greater benefit of repetition during semantic encoding was associated with blood flow increases in only two brain regions: (i) the right mesencephalon, which mapped onto the ventral tegmentum \((z = 4.12, \text{coordinates } 8, -24, -10; \text{Fig. 4})\) and (ii) the left inferior parietal cortex (BA 40; \(z = 3.84, \text{coordinates } -44, -30, 36\)). Two further analyses provided additional evidence for the right mesencephalon activation attributable to word repetition during semantic encoding. First, contrasting the two semantic memory retrieval conditions (i.e. semantic × 4 – semantic × 1) revealed greater activation attributable to word repetition \((z = 3.29, \text{coordinates } 2, -26, -12)\). Second, because the main effect of semantic encoding and the repetition × semantic encoding interaction were orthogonal contrasts, we performed a conjunction analysis to reveal common patterns of brain activation. We found conjunctions in three brain regions: the right mesencephalon \((z = 4.08, \text{coordinates } 8, -24, -10)\), left parietal cortex \((z = 4.17, \text{coordinates } -44, -28, 38)\) and right hippocampus \((z = 4.00, \text{coordinates } 26, -16, -6)\). These analyses provide evidence for a

Figure 3. Increased right hippocampal blood flow during recall after semantic compared to perceptual encoding. Areas of significant activity \((P < 0.001, \text{uncorrected})\) are mapped onto a template structural MRI scan of a single subject. The activation in the midbrain is not above the a priori defined threshold of \(P < 0.0001\) for regions outside of the regions of interest.
role of the right mesencephalon during word retrieval following semantic encoding.

Hippocampal Blood Flow Increase Predicts Recall Accuracy
Word repetition and semantic encoding were associated with changes in mean hippocampal blood flow values averaged across the 12 subjects. We tested the hypothesis that hippocampal blood flow during the four recall conditions predicts the recall accuracy scores in each of the twelve subjects. We found that left ($z = 2.84$, coordinates $-30, -8, -14$) and right ($z = 2.74$, coordinates $18, -28, -4$) hippocampal blood flow in the four recall conditions was positively correlated with the four recall accuracy scores in each subject (Fig. 5). No other brain regions showed a similar relationship between rCBF and recall success.

On the other hand, a strong inverse correlation between recall accuracy scores and rCBF was found in the anterior cingulate cortex (BA 24; $z = 4.09$, coordinates $2, -2, 34$).

Discussion
This PET study complements previous investigations of MTL and prefrontal cortex function during memory retrieval (Schacter and Wagner, 1999; Cabeza and Nyberg, 2000; Buckner and Wheeler, 2001). Our data also support the hypothesis that, within individual subjects, hippocampal blood flow during retrieval predicts recall accuracy. This result extends the previous finding that hit rate and hippocampal rCBF are correlated across subjects (Nyberg et al., 1996). In addition, we provide two novel findings. First, we show that word repetition and
encoding task modulate subsequent word-stem cued recall via distinct hippocampal mechanisms. Second, we provide evidence that the greater benefit of stimulus repetition during semantic (as compared to perceptual) encoding on subsequent cued recall is associated with activation of the right mesencephalon.

Word Retrieval after Repeated Encoding Activates the Left Anterior Hippocampus
Repeated word presentation during learning is a well-known method for increasing the accuracy of subsequent retrieval. We found the activity of only one brain region, the left anterior hippocampus, to differ between retrieval following repeated compared to single word presentation. This finding indicates that, at the time of retrieval, the left anterior hippocampus mediates the beneficial effect of word repetition during learning on recall accuracy.

A number of recent neuroimaging experiments have demonstrated a rise in MTL activity during the recovery of stored information (Schacter and Wagner, 1999; Cabeza and Nyberg, 2000; Buckner and Wheeler, 2001). This pattern has been interpreted as recovery of stored memory traces (Nyberg et al., 1996), as an index of successful, conscious recollection (Schacter et al., 1996a; Eldridge et al., 2000), or as recovery of semantic information (Cabeza et al., 2001). Our finding supports the notion that left hippocampal activation is related to retrieval success after repeated word presentation during learning.

Completing the stem of words seen only once during learning resulted in greater activity in the posterior temporal lobe. This finding is consistent with the notion that poorly encoded, visually presented words lead to posterior MTL activation but do not reach the anterior MTL, since the memory trace is weak (Ungerleider, 1995; Cabeza et al., 2001).

The importance of left MTL activity in memory function is not specific to memory retrieval. Previous studies have also demonstrated that left MTL activation during word encoding can predict the accuracy of the simple recognition (Wagner et al., 1998) or free recall of words (Alkire et al., 1998). Studies of memory encoding and retrieval have now provided evidence that the left MTL is involved in the encoding and remembering of words and that both components of memory function depend on the integrity of the hippocampus (Eichenbaum, 2000).

Hippocampal Recruitment during Word Retrieval after Semantic Encoding
Semantic encoding has long been known to confer a benefit during subsequent retrieval (Craik and Tulving, 1975). The neural basis for this benefit is now becoming clear, as it appears that semantic and perceptual tasks are associated with distinct patterns of brain activation during encoding (Grady et al., 1998). Some authors have also found increased activity in the prefrontal cortex and the hippocampus during the recognition of deeply encoded words compared to shallowly encoded words (Nyberg et al., 1996; Rugg et al., 1997, 1998; Buckner et al., 1998), but others have not (Grady et al., 2001).

We found right (and, less significantly, left) hippocampal activation during word retrieval following semantic, compared to perceptual, encoding. Whereas the focus of the right-sided activation was in the posterior hippocampus, the left hippocampal focus was in the region of the uncus, the same hippocampal region where we also found a main effect of repetition. This pattern seems to indicate that the left anterior hippocampus is associated with increased recall accuracy due to both repetition and semantic encoding effects, whereas the right posterior hippocampus is linked only to the effect of semantic encoding. The location of the right hippocampal activation is almost identical to our three previous studies (Schacter et al., 1996a,b; Heckers et al., 1998), in which the effects of repetition and semantic encoding were confounded. It is likely that our previous finding of greater right than left hippocampal activation during word retrieval was attributable to the right hippocampal mechanism underlying retrieval after semantic encoding.

We found bilateral hippocampal activation during word-stem cued recall whereas others (Rugg et al., 1998) found purely left hippocampal activation during simple recognition of deeply encoded words. It appears that word-stem cued recall involves a right hippocampal mechanism, in addition to the one in the left, which is present during both simple recognition and cued recall.

A Role for the Mesencephalon in Retrieval after Semantic Encoding
Repetition during encoding resulted in greater recall accuracy when subjects performed a semantic (as compared to a perceptual) encoding task. Here we report that this behavioral effect is mediated via neural activity in the mesencephalon. We
are aware of the limited spatial resolution of PET, as were previous authors who have linked midbrain/brainstem activation to discrete neuronal populations (Weiller et al., 1995; Damasio et al., 2000). However, the activation as revealed by the statistical parametric map coincides with the human ventral tegmental area (VTA), which extends ~6 mm rostrocaudally medial and dorsal of the substantia nigra (Lewis and Sesack, 1997). The location is relevant for two reasons. First, it is contralateral to the left hippocampus, associated with retrieval after repeated encoding, and ipsilateral to the right hippocampus, associated with the effect of retrieval after semantic encoding. Increased blood flow, as seen in our 15O PET study, most likely reflects synaptic activity (Jueptner and Weiller, 1995). Hippocampal and cortical projections terminate on ipsi- and contralateral neurons of the VTA (Amaral and Cowan, 1980) and the pattern of activation is therefore compatible with a modulation of VTA neurons by cortical and/or hippocampal projections. Second, the location is medial to the substantia nigra, which coincides with the location of the dopaminergic cell group A10, projecting to the medial temporal lobe and prefrontal cortex. We therefore interpret the activation seen in our PET experiment as evidence for an involvement of the dopaminergic neurons of the A10 group.

Dopaminergic neurons of the VTA projecting to the prefrontal cortex are known to modulate working memory (Goldman-Rakic, 1998). The dopaminergic projections to the MTL play a role in the encoding and retrieval of sensory information (Izquierdo and Medina, 1997; Podgornaya et al., 1997; Lisman and Otmakhova, 2001). In non-human primates, electrophysiological recording of midbrain dopamine neurons shows them to be particularly responsive to salient stimuli. Furthermore, the mesolimbic dopamine pathway is implicated in the learning and retrieval of associations (Nader and LeDoux, 1999). A recent microdialysis study in humans established that dopamine is released into the amygdala upon starting a cognitive task and that this release is related to learning performance (Jueptner and Weiller, 1995). Hippocampal and cortical projections terminate on ipsi- and contralateral neurons of the VTA (Amaral and Cowan, 1980) and the pattern of activation is therefore compatible with a modulation of VTA neurons by cortical and/or hippocampal projections. Second, the location is medial to the substantia nigra, which coincides with the location of the dopaminergic cell group A10, projecting to the medial temporal lobe and prefrontal cortex. We therefore interpret the activation seen in our PET experiment as evidence for an involvement of the dopaminergic neurons of the A10 group.

**Memory Retrieval and Prefrontal Cortex Activation**

Most neuroimaging studies of memory retrieval have reported activation in distinct modules of the frontal lobe (Cabeza and Nyberg, 2000; Buckner and Wheeler, 2001). In line with these previous studies, we found activation in three prefrontal regions: BA 10, BA 47 and the orbitofrontal cortex. We found DLPFC (BA 10) to be more active during retrieval after single, compared to repeated, word encoding. Ventrolateral prefrontal cortex (BA 47) and orbitofrontal cortex were more active during retrieval after perceptual, compared to semantic, encoding. This pattern could be interpreted as increased frontal lobe activation during less successful and possibly more demanding retrieval, since lack of repetition and perceptual encoding resulted in lower recall accuracy scores. On the other hand, greater activation in the DLPFC (BA 10) during retrieval of words learned once could indicate greater demands on monitoring the result of the retrieval process, since a strong memory trace was absent.

**Hippocampal and Anterior Cingulate Activation Predict Recall Accuracy**

We found a direct correlation between hippocampal activation and recall accuracy. This observation confirms and extends the finding of a direct linear relationship between recall accuracy scores and rCBF in the MTL across subjects (Nyberg et al., 1996). Our finding that left anterior and right posterior hippocampal blood flow predict recall accuracy scores is not surprising, considering that we found hippocampal mechanisms for the two behavioral effects that determine recall accuracy, i.e. repetition and encoding strategy. However, these effects are based on comparisons of mean rCBF values, derived from all 12 subjects. The direct correlation of rCBF in the four retrieval conditions and their respective recall accuracy scores is influenced by additional factors, such as the range of the behavioral scores and the hippocampal rCBF values. Of note, we did not find a correlation between recall accuracy scores and frontal lobe rCBF values, suggesting that retrieval success is more closely linked to modulation of MTL rather than frontal lobe activity.

Activity in the anterior cingulate cortex was inversely correlated with recall accuracy. Recent functional neuroimaging studies substantiate previous evidence from behavioral and electrophysiological studies and implicate the anterior cingulate cortex in complex attentional processes (Bush et al., 2000). It appears that anterior cingulate cortex activation indicates the detection of conflict or error during the processing of information, resulting in the allocation of additional attentional resources (Miller and Cohen, 2001). The inverse correlation of recall accuracy scores and anterior cingulate cortex activation could indicate such a conflict (completion of a three-letter cue with an incongruent word while searching for the target word), resulting in the greater allocation of resources compared to correct word stem completion. Consistent with this idea, a recent study (Maril et al., 2001) reported anterior cingulate activation during tip-of-the-tongue retrieval blocks, when subjects cannot retrieve a word but nonetheless feel that it is on the verge of recovery. They related the anterior cingulate activation to the monitoring of conflict and error during the tip-of-tongue state, when subjects often generate incorrect responses that conflict with the blocked target word.

In conclusion, this experiment links word retrieval after repeated and semantic encoding of words to distinct hippocampal mechanisms. It also provides the novel finding that activation of the right mesencephalon during retrieval confers the greater benefit of word repetition during semantic compared with perceptual encoding.

**Notes**

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**References**


