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Memory and the medial temporal lobe: Hemispheric specialization reconsidered

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The role of the medial temporal lobe in learning and memory has been well established in research on humans and other animals. In humans, clinical and neuroimaging studies typically suggest material-specific lateralization in which the left and right temporal lobes are associated with verbal and nonverbal memory, respectively. It is often assumed that the temporal lobes are functionally alike, differing only in terms of the content to be learned. Here we present data that challenge this notion, showing that the type of material used during a memory task can influence fMRI activation patterns beyond the expected left-verbal/right-nonverbal dichotomy. Our results also suggest some degree of functional asymmetry in the medial temporal lobe that is independent of material type, pointing to underlying processing differences between the left and right temporal lobes.

Introduction

The importance of the medial temporal lobe (MTL), and particularly the hippocampus, in memory formation and retention has long been recognized (Eichenbaum, 2000; Squire, 1992). Since Scoville and Milner first reported that bilateral removal or damage to the MTL can result in profound and long standing anterograde amnesia (Scoville and Milner, 1957), there have been many behavioral, clinical, and neuroimaging studies attempting to clarify the specific contribution of MTL structures to memory processing.

One of the most prevalent findings has related to material-specific lateralization, in which the left MTL has typically been associated with verbal memory and the right MTL with nonverbal memory, assuming left cerebral language dominance. It has been suggested that memory processing is dependent on perceptual analysis of neighboring cortical areas that preferentially treat linguistic or visuospatial information in the left or right hemisphere, respectively (Glosser et al., 1995). This pattern has been found in clinical studies of patients with unilateral temporal lobe dysfunction, who show specific memory deficits for verbal or nonverbal material consistent with the side of damage (Blakemore and Falconer, 1967; Glosser et al., 1998; Jones-Gotman, 1986; Kimura, 1963; Milner, 1968). More recently, there have been converging findings from neuroimaging studies demonstrating that encoding for verbal or nonverbal information can preferentially activate the left or right MTL (Branco et al., 2006; Golby et al., 2001; Kelley et al., 1998; Powell et al., 2005).

Although the left-verbal/right-nonverbal dichotomy has become almost a basic rule in cognitive neuroscience, some clinical studies have suggested that this distinction may not be so clear-cut. Whereas impairments in verbal memory have been consistently associated with dysfunction of the left MTL, some authors have argued that it is more difficult to demonstrate a reliable relationship between nonverbal memory deficits and damage to the right MTL (Ivnik et al., 1987; Pigott and Milner, 1993). Even with verbal memory, some research has shown that clear right MTL dysfunction can result in significant recall deficits for linguistic material [for example, see Dobbins et al. (1998)]. Such conflicting findings have led to debates regarding the selection of neuropsychological measures used to assess material-specific deficits. In particular, there is controversy regarding the degree to which various measures of nonverbal memory are truly nonverbal (Lee et al., 2002). Furthermore, there have been suggestions in the clinical literature that part of the reason why some authors have not observed material-specific lateralization effects in clinical studies has been their use of single-trial memory tasks as opposed to tasks emphasizing learning over trials (Jones-Gotman et al., 1997).

Based on studies of patients with temporal lobe epilepsy, Jones-Gotman and colleagues proposed a slightly different relationship between lateralization and material type (Jones-Gotman et al., 1997; Majdan et al., 1996). They found that patients with a left MTL seizure focus had minimal trouble with initial learning for words but demonstrated significant impairment on recall following a delay. Patients with a right MTL focus demonstrated impaired

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learning of abstract designs compared with the control and left MTL groups, but remembered what they did learn. Thus it seemed that left temporal lobe dysfunction had the greatest effect on retention or retrieval, whereas the effect of right temporal lobe dysfunction was greater on the acquisition of new learning. This constituted a functional difference between the two temporal lobes that had not been noted previously. However, the authors pointed out that the materials (words and designs) differed not only in the degree to which they might be verbalized but also in terms of their novelty. The words were high-frequency common nouns, whereas the designs were completely novel drawings that had never been seen before—thus the degree of novelty of the stimuli might have been responsible for the observed differential patterns of impairment. Specifically, the authors suggested that familiar words may be preferentially processed in pre-existing semantic memory networks in the left hemisphere, leading to rapid learning, but that such items would also be subject to rapid forgetting because of susceptibility to interference. In contrast, they suggested that representation of novel items may be distributed widely because there are fewer pre-existing networks to draw upon, and such representations must therefore be mostly made *de novo*. This could make learning progress more slowly, but as there is less likelihood of interference those items would be more resistant to forgetting.

This notion of novelty should not be confused with the concept of "novelty detection" referred to in more recent neuroimaging studies examining the influence of stimulus recency in the MTL. Several studies have shown significant decreases in MTL activation with repeated presentations of a given item. Although often observed in the left anterior hippocampus (Badgaiyan, 2006; Dolan and Fletcher, 1997; Saykin et al., 1999; Strange et al., 1999, 2005), similar recency effects have been found in other areas of MTL, including the perirhinal cortex, parahippocampal cortex, right anterior hippocampus, and bilateral MTL (Fahy et al., 1993; Kohler et al., 2005; Meltzer and Constable, 2005; Menon et al., 2000; Sperling et al., 2001; Tulving et al., 1996). In those reports, the term "novelty" is used to refer to the adaptation of MTL regions to repeated presentation of a particular item in the context of a given experiment. In this paper, we make a distinction between "generic" novelty, that is, items that are entirely new and would not have been encountered before, and "situational" novelty or the relative recency of presentation of a specific item (Tulving et al., 1996). Furthermore, although we use a verbal vs. nonverbal dichotomy, we recognize that these are relative rather than absolute distinctions. People do attempt to use naming to aid memory even for nonverbal material, and in our experiment the drawings of familiar objects, which we classed as "nonverbal" stimuli, have names, although we have designed recognition foils such that those names should not facilitate eventual memory performance.

In light of some of the unresolved issues concerning lateralization of different memory functions in the MTL, the goal of the current study was to assess hemispheric differences in functional activity among subregions in the MTL during memory encoding and retrieval. During retrieval, we were interested in activation associated with the general process of deciding whether a stimulus had been presented before (retrieval *attempt*), and in activation occurring when the target items shown during encoding are presented again during the recognition phase (*target-specific* retrieval). Finally, we wanted to determine how material type (verbal vs. nonverbal; familiar vs. novel) might shape these various encoding and retrieval processes. We used four types of stimuli: abstract designs, drawings of objects, abstract words, and pseudowords. The abstract words were originally selected from a list of 925 nouns published by Paivio et al. (1968); those chosen were rated lowest in image-provoking properties (thus most "purely" verbal), and rated highest for frequency of use (thus most common). They and the abstract designs are stimuli that we have used successfully in studies with patients, and we chose them for the present experiment because they had already been shown to be sensitive to unilateral MTL dysfunction (Jones-Gotman et al., 1997).

Traditional verbal and nonverbal memory tests often differ not only in terms of the material used but also in their task demands. In order to diminish such task-related differences, the same memory protocol was used throughout, differing only in the type of material to be remembered.

Methods

Subjects

Sixteen native English speakers (8 women; mean age±s.d.= 24.4±4.9) participated in the study. All were right-handed, with normal or corrected vision, and did not report any past or present neurological or psychiatric condition. This study was performed in accordance with the Declaration of Helsinki and approved by the Montreal Neurological Institute's Research Ethics Board.

Stimulus materials

Stimuli were presented visually using NBS Presentation software (http://www.neurobs.com) and back-projected onto a screen using an LCD projector. There were four types of target stimuli: 20 abstract designs (nonverbal, novel), 20 drawings of common objects (nonverbal, familiar), 20 pronounceable pseudowords (verbal, novel), and 20 abstract real words (verbal, familiar). Three foils were devised for each stimulus (total number of foils per stimulus type=60). All foils were highly similar to their respective targets; for the "nonverbal" stimuli the foils differed from targets in terms of subtle visual details to emphasize the nonverbal aspects of those items and to make verbal strategies ineffective during recognition testing. Baseline stimuli used during encoding were one of two strings of letters (verbal) or one of two abstract designs (nonverbal) that recurred in random order throughout the encoding scans and were easily differentiated from the targets and foils (Fig. 1). Different baseline stimuli were used during the recognition trials to avoid any potential retrieval effects associated with using the encoding baseline items. During a training session, subjects were shown all baseline stimuli used in both the encoding and recognition blocks. This was done to ensure that subjects would know the baseline stimuli well and treat them differently from targets and foils.

Task procedure

Prior to scanning, subjects underwent a 10 min training session in the scanner to familiarize them with the procedure, the apparatus, and the baseline stimuli. During encoding, targets were presented in four 5-item blocks interspersed with 5-item blocks of baseline stimuli (Encoding 1). To ensure attention during encoding, subjects were asked to decide whether each stimulus (target or baseline) was primarily "curvy" or "straight." For verbal stimuli, this judgment was based on the first letter of each letter string.

For recognition trials, three block types were presented in a pseudorandom fashion (i.e., multi-factorial "castle" design): (1)

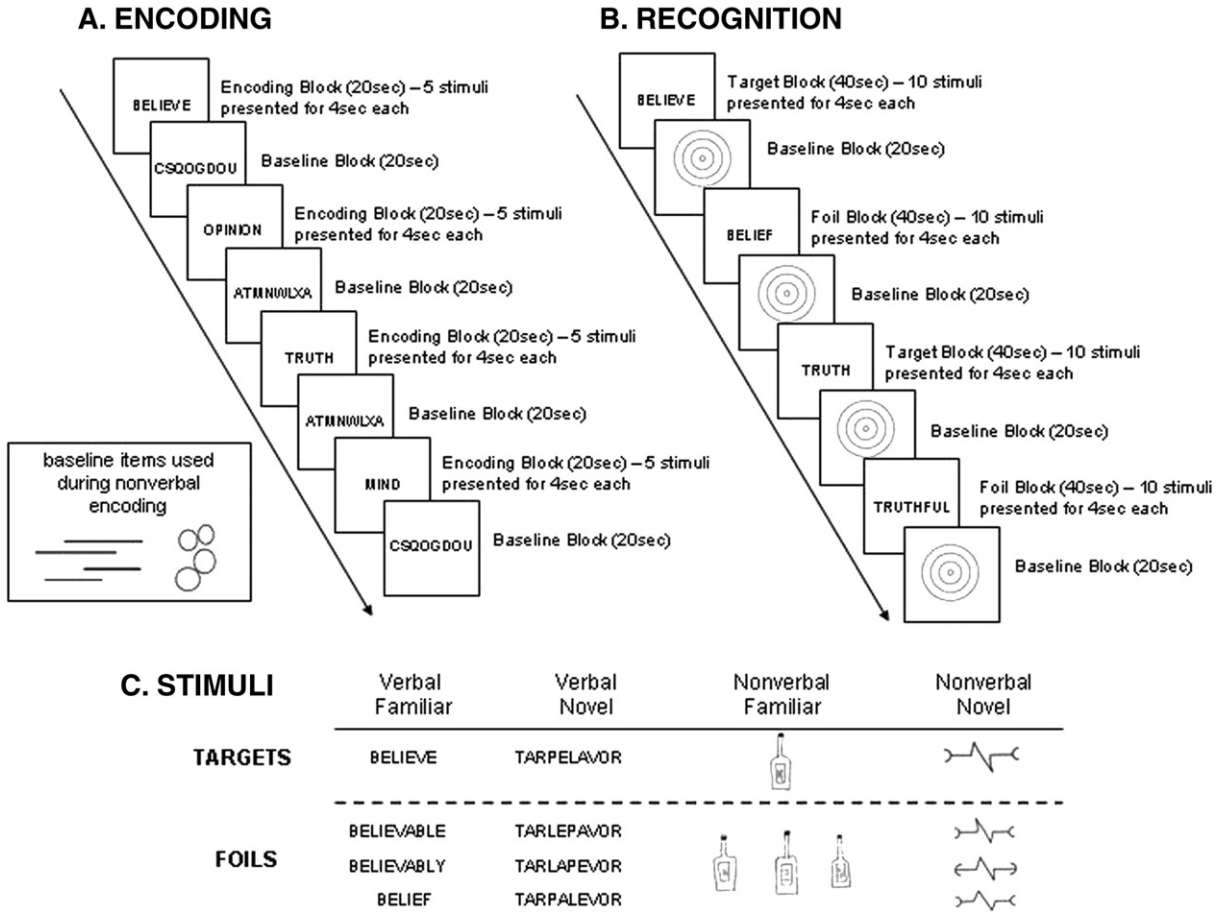

Fig. 1. Experimental paradigm. (A) Encoding paradigm — blocks of targets alternated with blocks of baseline stimuli; (B) recognition paradigm — probabilistic blocks of targets and foils alternated with blocks of baseline stimuli; (C) examples of targets and related foils.

target blocks consisting of 9 targets and 1 foil, (2) foil blocks consisting of 9 foils and 1 target, and (3) baseline blocks consisting of concentric circles. These "probabilistic" blocks were used to decrease the possibility that subjects would be able to guess the nature of the blocks and strategically alter their responses, while achieving a higher signal-to-noise ratio and requiring less scanning time than an event-related design; this method has been used successfully in similar fMRI studies (e.g., Stark and Squire, 2000). "Yes" or "no" responses were recorded during recognition trials, and subjects pushed either button at random during the baseline condition. Pilot studies with this protocol ($n=41$) confirmed that subjects were not able to guess the nature of the blocks. Average memory performance ranged from 72% correct on Recognition Trial 1 to 81% correct on the final Recognition Trial. If subjects had realized that stimuli were being presented in blocks and had used that information to guide their responses, the expected level of accuracy should have been 90% correct, as 9 out of 10 items in each block were of the same type (targets in target blocks, foils in foil blocks).

After the first recognition test, the same targets were presented again for a second encoding trial (Encoding Trial 2). This was followed by a second recognition test (Recognition Test 2) using a different set of foils. The overall learning procedure (i.e., Encoding 1 → Recognition 1 → Encoding 2 → Recognition 2) was carried out in the same way for the next stimulus type until all four types had been presented. Order of presentation according to stimulus type was randomized across subjects. Upon completion of encoding and recognition trials for the final stimulus type, structural scans were conducted for 20 min during which a film was shown to prevent rehearsal. Finally, delayed recognition for all four stimulus types was obtained using a third set of foils.

This protocol allowed for two types of contrast during the recognition phase. Retrieval *attempt* refers to the process of retrieving items from memory without respect to accuracy, and was derived by contrasting blocks in which the individual engaged in active retrieval with a passive baseline task — i.e., pressing a button when presented with concentric circles ([Targets + Foils] minus Recognition Baseline). Target-related activation was defined as the differential activation in regions of the MTL that were sensitive to the presentation of target blocks as opposed to similar foil blocks during recognition (Targets minus Foils).

Imaging procedure

Images were acquired using a 1.5 T Siemens Vision MRI scanner. Behavioral responses were collected using a 4-button fiber optic pad. Functional images were acquired using a T2*-weighted gradient echo, echo-planar sequence (EPI) sensitive to BOLD contrast (TR: 4000 ms, TE: 50 ms, FA: 90 deg). For each image, 27 contiguous 5 mm slices were acquired, perpendicularly aligned

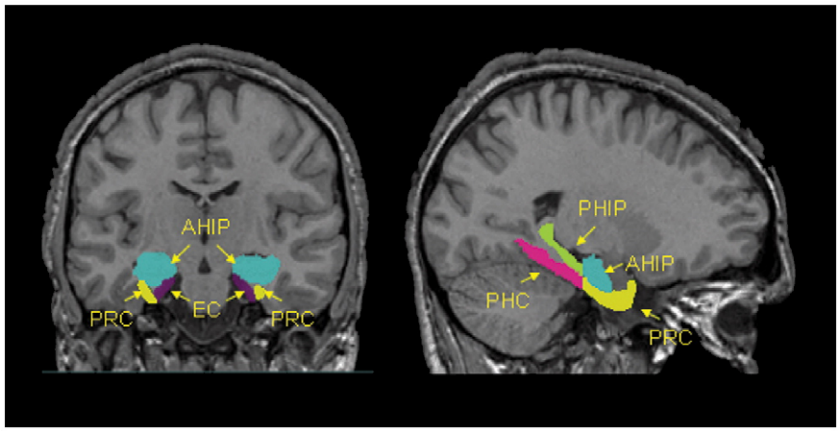

Fig. 2. Example of anatomical ROIs for an individual subject. AHIP = anterior hippocampus; PHIP = posterior hippocampus; PRC = perirhinal cortex; EC = entorhinal cortex; PHC = parahippocampal cortex.

with the hippocampus. High-resolution structural images were acquired using a T1-weighted sequence (slice thickness: 1 mm^3). There were a total of eight functional scans: four runs of 208 volumes (one for each stimulus type), followed by a structural scan, then four runs of 128 volumes (delayed recognition for each stimulus type).

Analyses of behavioral data

Recognition memory performance was calculated as the total number of correct responses (hits + correct rejections). In cases where data were missing (less than 1.5% of all possible responses), scores were adjusted to reflect the proportion of correct responses (out of a possible of 40). A repeated-measures ANOVA was conducted using Trial (Recognition 1 vs. Recognition 2 vs. Delayed Recognition), Material Type (Verbal vs. Nonverbal), and Stimulus Novelty (Novel vs. Familiar) as within-subjects variables. Follow-up analyses were conducted when significant main effects or interactions were obtained in the original repeated-measures ANOVA.

Imaging analyses

All fMRI data were motion corrected, smoothed (8 mm), and transformed into standard space based on the ICBM 152 brain template (MNI) using in-house software (available at: http://packages.mni.mcgill.ca). Statistical analysis of functional images was conducted using fmristat (Worsley et al., 2002). For each subject, a GLM with correlated errors was used to construct *t*-statistic, effect, and standard deviation maps for each contrast. Group activation maps were computed using a random effects model. The significance threshold was calculated using the minimum of a Bonferroni correction or random field theory to correct for multiple comparisons (Worsley et al., 1996).

Regions of interest (ROIs) within the MTL were identified using custom software (fMRIstat — display). Masks were defined bilaterally for anterior and posterior hippocampus (including CA fields, dentate gyrus, and subiculum), and for entorhinal, perirhinal, and parahippocampal cortex (see Fig. 2). Anatomical boundaries for the hippocampus were created using previously established landmarks (Pruessner et al., 2000). The boundary between anterior and posterior regions of the hippocampus was set as the coronal plane through the posterior edge of the interpeduncular cistern (Binder et al., 2005).

Mean percent signal change scores (sum of % signal change across all voxels/number of voxels) were calculated for each ROI during encoding and retrieval for all conditions. For encoding trials, repeated-measures ANOVAs were conducted for each ROI with mean % signal Δ as the dependent variable, using Hemisphere (left vs. right), Trial (1 vs. 2), Material Type (verbal vs. nonverbal), and Novelty (novel vs. familiar) as within-subject independent variables. Similar analyses were conducted for recognition trials, using Hemisphere (left vs. right), Trial (1, 2 and Delayed), Material Type (verbal vs. nonverbal), and Novelty (novel vs. familiar) as the within-subject variables. For recognition, separate analyses were conducted for target-specific activation (Target minus Foil) and retrieval attempt ([Target + Foil] minus Baseline). Post-hoc analyses were conducted when significant main effects or interactions were obtained in the original ANOVAs.

Results

Behavioral results: recognition memory

Repeated-measures ANOVA revealed better memory performance for nonverbal material (abstract designs and drawings of objects) compared to verbal material (pseudowords and abstract real words) across all recognition trials ($F_{1,15}=22.99$, $p<0.001$) (Table 1). As well, familiar items were recognized better then novel ones ($F_{1,15}=21.36$, $p<0.001$). There was a significant main effect

Table 1
Behavioral performance

Recognition trial	Nonverbal material		Verbal material	
	Novel	Familiar	Novel	Familiar
	Abstract designs	Object drawings	Pseudowords	Abstract words
1	28.1 (5.7)	30.6 (4.4)	25.1 (4.2)	26.7 (4.7)
2	32.3 (4.9)	35.2 (2.6)	29.5 (2.9)	31.2 (4.4)
Delayed	32.6 (3.8)	34.8 (2.6)	28.0 (3.4)	29.4 (4.0)

Hits + Correct Rejections for all stimulus types, Mean (SD); Maximum = 40.

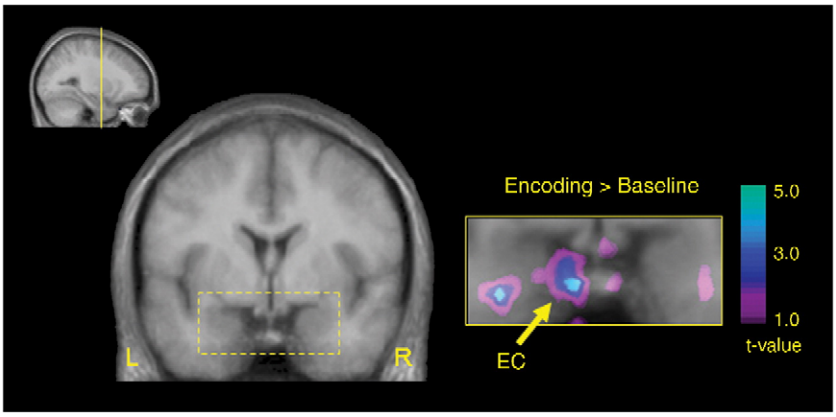

Fig. 3. Entorhinal cortex (EC) activation across both encoding trials for all stimulus types (Encoding – Baseline).

of recognition trial ($F_{2,14}=36.68$, $p<0.00001$); follow-up analyses confirmed an improvement in performance from Trial 1 to Trial 2 ($F_{1,15}=75.34$, $p<0.000001$) and a decrease from Trial 2 to delayed recognition ($F_{1,15}=9.46$, $p<0.01$). There was also a significant interaction between Recognition Trial and Material Type ($F_{2,14}=6.35$, $p<0.025$); post-hoc analyses showed that this was largely due to forgetting of verbal material following the delay ($F_{1,15}=24.98$, $p<0.001$), which was not observed for nonverbal material ($F_{1,15}=0.089$; $p=0.77$).

Imaging results: material-specific lateralization

During encoding trials, we observed material-specific lateralization in the posterior hippocampal region, manifested by a significant Hemisphere × Material Type interaction ($F_{1,15}=6.29$, $p<0.05$). In follow-up analyses, this was shown to be due to increased relative activation in the right posterior hippocampus during encoding for nonverbal material ($F_{1,15}=8.97$, $p<0.01$). There were no lateralization findings during encoding for verbal material ($F_{1,15}=0.048$, $p=0.83$).

We also found material-specific lateralization in various MTL regions during retrieval attempt, as shown by significant Hemisphere × Material Type interactions in the anterior hippocampal region ($F_{1,15}=10.15$, $p<0.01$), posterior hippocampus ($F_{1,15}=8.40$, $p<0.05$), entorhinal cortex ($F_{1,15}=11.97$, $p<0.01$), and perirhinal cortex ($F_{1,15}=10.08$, $p<0.01$). Subsequent analyses revealed that for nonverbal material, retrieval attempt was associated with significantly greater activation in the right than the left anterior hippocampus ($F_{1,15}=9.57$, $p<0.01$) and posterior hippocampus ($F_{1,15}=9.10$, $p<0.01$). Conversely, retrieval attempt for verbal material was associated with relatively greater activation in the left perirhinal cortex ($F_{1,15}=9.22$, $p<0.01$).

Lateralization independent of material type

During encoding, we found a significant main effect of Hemisphere ($F_{1,15}=7.54$, $p<0.05$), showing relatively greater BOLD activation in the left than the right entorhinal cortex (Fig. 3). There was no Hemisphere × Material Type interaction in this region ($F_{1,15}=0.24$, $p=0.64$), indicating that this asymmetry was independent of the verbal/nonverbal nature of the stimulus.

Material specificity independent of lateralization

We noted significantly greater activation in the parahippocampal cortex during encoding of nonverbal than verbal material (main effect of Material Type — $F_{1,15}=7.35$, $p<0.05$). There was no Hemisphere × Material Type interaction ($F_{1,15}=0.82$, $p=0.38$); thus, this activation was essentially bilateral.

Similar material-specific effects were also present during retrieval attempt for nonverbal material, shown by significantly increased activation in posterior regions of the MTL, namely the posterior hippocampus ($F_{1,15}=12.47$, $p<0.01$) and parahippocampal cortex (main effect of Stimulus Type — $F_{1,15}=24.51$, $p<0.001$). In the case of the parahippocampal cortex, there was no Hemisphere × Material Type interaction ($F_{1,15}=3.30$, $p=0.09$).

Table 2a
Summary of significant results during encoding, retrieval attempt, and target-specific retrieval

	Encoding		Retrieval		
			Retrieval attempt		Target retrieval
	Nonverbal	Verbal	Nonverbal	Verbal	
Anterior hippocampus	ns	ns	R>L	ns	ns
Posterior hippocampus	R>L	ns	R>L	ns	ns
Entorhinal cortex	L>R	L>R	ns	ns	ns
Perirhinal cortex	ns	ns	ns	L>R	ns
Parahippocampal cortex	Nonverbal>Verbal		Nonverbal>Verbal		ns

Lateralization and material specificity contrasts.

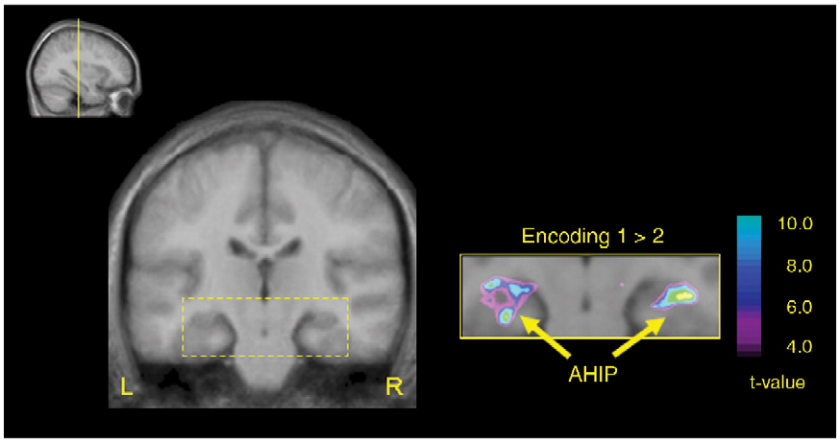

Fig. 4. Bilateral (left > right) anterior hippocampus (AHIP) activation in response to repeated presentation during encoding across all stimulus types ([Encoding Trial – Baseline 1] – [Encoding Trial 2 – Baseline 2]).

See Table 2a for a summary of more general lateralization and material-specific effects.

Decreased activation associated with repeated presentation during encoding

We found a significant decrease in mean percent signal change when comparing Encoding Trial 1 to Encoding Trial 2 in several regions of MTL, including the anterior hippocampus ($F_{1,15}=47.58$, $p<0.001$), posterior hippocampus ($F_{1,15}=72.13$, $p<0.001$), and parahippocampal cortex ($F_{1,15}=63.11$, $p<0.001$). In the anterior hippocampus, this decrease in activation from Encoding Trial 1 to Trial 2 — reflecting an effect of repeated presentation — was asymmetric (Hemisphere × Trial interaction, $F_{1,15}=7.83$, $p<0.025$). Subsequent analyses indicated that it was much greater in the left ($F_{1,15}=41.23$, $p<0.0001$), though still present in the right anterior hippocampus ($F_{1,15}=16.77$, $p<0.001$) (Fig. 4).

A different pattern was found in posterior regions of MTL, where the decrease in BOLD activation across encoding trials was dependent on whether the material was verbal or nonverbal; this was observed in the posterior hippocampus (Encoding Trial × Material Type interaction, $F_{1,15}=46.41$, $p<0.001$) and parahippocampal cortex ($F_{1,15}=8.44$, $p<0.05$). Follow-up analyses indicated that situational novelty effects were particularly prominent for verbal material, both in the posterior hippocampus ($F_{1,15}=115.23$, $p<0.0000001$) and parahippocampal cortex ($F_{1,15}=37.30$, $p<0.0001$) (Fig. 5a). Similar analyses for nonverbal material showed that this effect was not as important in the parahippocampal cortex ($F_{1,15}=4.70$, $p<0.05$), and was non-significant in the posterior hippocampus ($F_{1,15}=1.34$, $p=0.26$) (Fig. 5b). There were no significant three-way interactions with the side of activation (Hemisphere × Trial × Material Type), either in the posterior hippocampus ($F_{1,15}=0.082$, $p=0.778$) or parahippocampal cortex ($F_{1,15}=2.36$, $p=0.145$), suggesting that these effects were essentially bilateral.

Target-specific activation with repeated presentation during recognition trials

We found a significant effect in the anterior hippocampal region across all three recognition trials when comparing target vs. foil blocks (main effect of Recognition Trial — $F_{1,15}=5.24$, $p<0.05$).

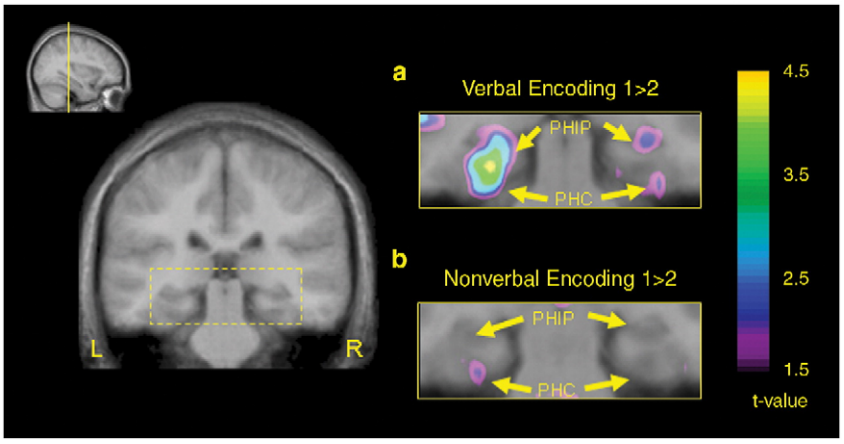

Fig. 5. Decreased activation in posterior MTL associated with repeated presentation ([Encoding 1 – Baseline 1] minus [Encoding 2 – Baseline 2]) during encoding for verbal (a) and nonverbal (b) material. Significant effects were found in the posterior hippocampus (PHIP) and parahippocampal cortex (PHC) for verbal material, and in the PHC for nonverbal material.

Table 2b

	Encoding		Retrieval			
	Trial 1>Trial 2		Retrieval attempt		Target retrieval	
	Nonverbal	Verbal	Trial 2>Trial 1	Delayed Trial>Trial 2	Trial 2>Trial 1	Delayed Trial>Trial 2
Anterior hippocampus	Bilateral; L>R	Bilateral; L>R	ns	ns	Bilateral	Bilateral
Posterior hippocampus	ns	Bilateral	ns	ns	ns	ns
Entorhinal cortex	ns	ns	ns	ns	ns	ns
Perirhinal cortex	ns	ns	ns	ns	ns	ns
Parahippocampal cortex	Bilateral; Nonverbal>Verbal		ns	ns	ns	ns

Repeated presentation. L=left; R=right; ns=non-significant; hemispheric effects are relative; 'Bilateral' indicates significant activation in both hemispheres.

Follow-up analyses showed a steady increase in anterior hippocampal activation from Recognition Trial 1 to Trial 2 ($F_{1,15}$=4.67, p<0.05) and from Recognition Trial 2 to Delayed Recognition ($F_{1,15}$=6.06, p<0.05) (Fig. 6). There were no interactions with Hemisphere during any of the above analyses (p>0.1), suggesting that these effects were largely bilateral. Table 2b provides a summary of trial-related effects of lateralization and material specificity.

Effect of generic novelty on BOLD activation

There were no significant effects of generic novelty, either as a main effect or as an interaction, in any of the analyses. However, one might expect to observe an effect in the first encoding trial, when all stimuli of this experiment were seen for the first time and the difference between the novel and familiar stimuli should be greatest. Therefore, to determine whether there was an effect of generic novelty on the first presentation of the stimuli, we performed a repeated-measures ANOVA comparing Novel vs. Familiar for the first encoding trial (Encoding 1) only. The overall pattern of results mirrored that found when analyzing both encoding trials together and, importantly, there was still no effect of generic novelty on BOLD activation (p>0.1 in all ROIs).

Discussion

The objective of this fMRI study was to assess potential differences in left vs. right MTL function during memory encoding and retrieval, and to investigate how the type of information to be learned might affect these processes. While we did find some asymmetries in various subregions of the MTL related to the verbal/nonverbal nature of the information, our findings clearly support the view that material specificity and hemispheric specialization are not equivalent concepts. This is not the first challenge to the strict notion of material-specific lateralization in the MTL (see for example Lee et al., 2002); however, to our knowledge, ours is the first study to address this issue directly using neuroimaging.

We did observe some instances of material-specific hemispheric specialization in the MTL in keeping with the traditional left-verbal/right-nonverbal model. During encoding, the right posterior hippocampus was more active than the left when the subjects were learning nonverbal material. Unlike previous reports (Branco et al., 2006; Golby et al., 2001; Kelley et al., 1998), we did not find greater left-sided activation during encoding for verbal material. However, this finding is very much in keeping with the encoding pattern previously shown in patients with temporal lobe epilepsy (Jones-Gotman et al., 1997), as dysfunction in the right MTL was specifically associated with impaired learning of nonverbal material; conversely, a left MTL focus was not associated with impaired learning of verbal material.

Most fMRI studies that have found material-specific lateralization have been limited to encoding (Branco et al., 2006; Golby et al., 2001; Powell et al., 2005). Yet we also found a verbal/nonverbal dissociation during retrieval attempt, with increased right, relative to left, MTL activation during the decision process of recognizing nonverbal material and a similar increase in activation in the left, relative to right, MTL while attempting to recognize verbal material. These do not represent parallel processes in the two hemispheres, however, as the regions involved within the left and right MTL differed. Whereas retrieval attempt for nonverbal material was associated with the right anterior and posterior hippocampus, retrieval for verbal material elicited preferential involvement of the left perirhinal cortex.

Hemispheric specialization does not equal material specificity

Two distinct patterns of findings emerged supporting the notion that hemispheric specialization and material specificity are not equivalent concepts. First, we found instances of asymmetry between the left and right MTL that were unrelated to material type. During encoding, the left entorhinal cortex was significantly more active than the right across all stimulus conditions (i.e., for both verbal and nonverbal material). This region did not show a decrease with repeated presentation (situational novelty), suggesting that it is involved specifically in encoding, regardless of material type. A material-independent effect of repeated presentation was seen in a greater relative decrease in activation in the left vs. right anterior hippocampus across all material types. Such a finding is in keeping with several neuroimaging studies associating the left anterior hippocampal region with situational novelty (Badgaiyan, 2006; Dolan and Fletcher, 1997; Saykin et al., 1999; Strange et al., 1999, 2005).

Our observation that encoding is associated with increased left-sided activation in anterior regions of the MTL is interesting given prior models specifically implicating left-sided cerebral regions with memory encoding (Tulving et al., 1994; Habib et al., 2003b). The "hemispheric encoding/retrieval asymmetry" (HERA) model argues that there are observable hemispheric differences according to the stage of memory processing — encoding being preferentially associated with left-sided, and more specifically left frontal, involvement, and memory retrieval being related to right-sided (frontal) activation. However, we did not observe preferential

right-sided activation during retrieval (either during retrieval attempt or target-specific retrieval). Although the HERA model was developed to account for material-independent lateralization in the frontal lobes during certain memory tasks, our findings might eventually be incorporated into a more comprehensive model that includes the medial temporal lobes.

The second set of findings that supports dissociation between lateralization and material specificity was the observation of bilateral material-specific effects in certain regions of the MTL. There was overall greater activation in both the left and right posterior regions of MTL (posterior hippocampus and parahippocampal cortex) when processing nonverbal information, during encoding and retrieval attempt. Moreover, we found robust situational novelty effects — decreases in activity with additional exposure — in posterior regions of MTL; these effects were observed primarily in response to verbal material.

Generic novelty and the medial temporal lobe

Using the current protocol, generic novelty appeared to have a negative effect on memory performance in that our novel items (abstract designs and pseudowords) were not recognized as well as the familiar items. This result differs from previous findings of greater forgetting for abstract words (familiar) than for abstract designs (novel); however, those results were found when testing memory by free recall (Jones-Gotman et al., 1997; Majdan et al., 1996). Contrary to our expectations based on the performance of patients with temporal lobe lesions, generic novelty did not affect BOLD activation patterns in the MTL, either on its own or as a modulator of hemispheric specialization. In particular, there was no effect of generic novelty during the first encoding trial, when we expected there to be the largest difference between novel and familiar items. One possible explanation for this is that although the greater difficulty inherent in learning novel information may accentuate lateralization differences between clinical groups on memory tasks (Redoblado et al., 2003), this may not significantly impact the strategies or processes underlying learning, at least in a healthy brain. Future fMRI studies with individuals with documented unilateral TL dysfunction may help clarify whether their differential performance on memory tasks related to generic novelty will be associated with underlying patterns of fMRI activation that differ from normal.

Target-specific activation independent of learning

In the anterior hippocampus, we found a significant increase in activation in the presence of targets (as opposed to foils) across all recognition trials. The repeated presentation of targets over trials thus appears to increase their "distinctness" (at least in terms of BOLD activation) when compared to similar foils. Interestingly, this increase in distinctness in the anterior hippocampus does not appear to translate into better recognition performance. Paradoxically, whereas the neuroimaging data show increased differentiation between targets and foils after a delay (see Fig. 6), behaviorally we see a significant degree of forgetting from the second to the delayed recognition trial. The reasons for such a finding remain unclear, as the use of a block design did not allow for a more detailed item-by-item analysis of target-specific activation.

Functional segregation within the medial temporal lobe

In several ways our findings are inconsistent with prior neuroimaging work that attempted to identify clear functional divisions within the MTL during the performance of memory tasks. Although we did not specifically compare encoding vs. retrieval in the present protocol, our findings do not indicate any clear differences within the subregions of the MTL according to stage of processing, as has been reported by other authors (Gabrieli et al., 1997; Lepage et al., 1998; Parsons et al., 2006; Schacter and Wagner, 1999). Rather, our results are more in keeping with the concept of "neural context," the principle by which a brain region may serve different cognitive processes depending on what other regions are co-activated with it (Habib et al., 2003a). For example, we saw three distinct patterns of activation in the anterior hippocampus, depending on the stage of memory processing and the type of material used. First, we observed decreases in activation — reflecting increased sensitivity to situational novelty — in response to repeated presentation of material; this effect was greater on the left side, regardless of stimulus type. Second, we found increased right-sided activation in the anterior hippocampus associated with retrieval attempt for nonverbal information. Finally, both anterior hippocampi were associated with target-specific activation that increased progressively over each of the recognition trials. The coexistence

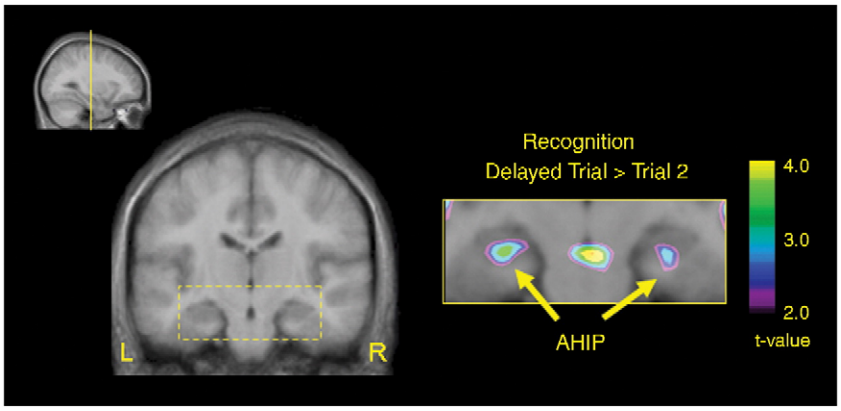

Fig. 6. Bilateral increases in activation in anterior hippocampus during target-specific recognition across all stimulus types. Blocks of target vs. foils are contrasted between the second and the delayed recognition trials ([Target Delayed Trial – Foil Delayed Trial] – [Target Trial 2 – Foil Trial 2]).

of functionally dissimilar roles within the same anatomical region is consistent with findings from a recent study using *in vivo* recordings from microwire electrodes implanted in human epilepsy surgery patients. Rutishauser et al. (2006) reported the anterior hippocampus and amygdala contain two separate classes of neurons that fire selectively to new or old stimuli and are purported to serve as novelty or familiarity detectors, respectively. Given the large voxel size and smoothing protocol used in this study, we cannot make any exact claims about precise functional–anatomical correlations. However, our results demonstrate that some regions are more specialized, while others may be involved in different capacities in all stages of memory processing.

Limitations and future directions

A potential confound in this study is that subjects may have been re-encoding the target material during the recognition blocks, which could have affected the activation patterns that we observed. However, it has been shown that the brain processes the same stimuli differently depending on the task demands (e.g., Zatorre et al., 2000; Djordjevic et al., submitted). Thus, we believe that the explicit instructions to memorize information during the encoding blocks and to retrieve information during the recognition blocks should have ensured that subjects were processing information accordingly throughout the experiment.

As this was a block-design study, we were not able to investigate activation related to correct or incorrect identification of targets, but the design did allow us to examine how the nature of memoranda affects memory processing at different stages. Future studies using an event-related paradigm may succeed in characterizing further the relationship between material type and hemispheric specialization.

Conclusion: Hemispheric specialization reconsidered

Our main objective was to investigate potential processing differences between the left and right medial temporal lobes during learning and retention, and to determine whether such differences might be influenced by subjects' familiarity with the material to be memorized. Although generic novelty did not have a significant impact on the neuroimaging findings, our results clearly support the idea that the left and right temporal lobes do not learn and remember in precisely the same way. Indeed, our findings indicate some processing asymmetries that are independent of material type. We also found clear evidence for material-specific effects that were unrelated to which hemisphere was involved. Finally, even when material-specific lateralization was observed, these processes were not necessarily supported by homologous regions in the two temporal lobes. Results from this investigation suggest that the left and right medial temporal lobes can be dissociated both by the type of material they process most efficiently and by the way in which they process it.

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