

## Hemispheric Specialization During Episodic Memory Encoding in the Human Hippocampus and MTL

Daniel J. Casasanto† ([dcasasan@mail.med.upenn.edu](mailto:dcasasan@mail.med.upenn.edu))

William D. S. Killgore† ([killgore@mclean.harvard.edu](mailto:killgore@mclean.harvard.edu))

Guila Glosser† ([glosser@mail.med.upenn.edu](mailto:glosser@mail.med.upenn.edu))

Joseph A. Maldjian‡ ([maldjian@oasis.rad.upenn.edu](mailto:maldjian@oasis.rad.upenn.edu))

John A. Detre†‡ ([detre@mail.med.upenn.edu](mailto:detre@mail.med.upenn.edu))

Departments of Neurology and Radiology, University of Pennsylvania Medical Center  
3400 Spruce Street, Philadelphia, PA 19104 USA

### Abstract

Hemispheric specialization during episodic memory encoding was examined using three functional magnetic resonance imaging (fMRI) tasks. Stimuli for the three tasks differed in the degree to which they elicited subjects' use of verbal and image-based encoding strategies. Intentional encoding of visually presented scenes, sentences, and faces was associated with neural activity in the hippocampus and surrounding mesial Temporal Lobe (mTL) structures. Across tasks, material-specific lateralization of neural activity was observed in the posterior mTL. In contrast, hippocampal activation did not lateralize according to material type for two of the three tasks. These results suggest a functional dissociation between the hippocampus and other mTL subcomponents, and indicate that material-specificity may not fully explain hemispheric specialization in the mTL memory system.

### Introduction

The human hippocampus and adjacent mesial temporal lobe (mTL) structures are believed to subservise encoding of new information into episodic memory: the form of long-term memory that supports conscious recollection of ongoing experiences (Squire and Zola-Morgan, 1991; Tulving, 1998). The role of the mTL in long-term memory processing has been investigated extensively ever since Scoville and Milner (1957) reported profound global anterograde amnesia in patient HM following bilateral resection of the hippocampus, uncus, and amygdala. Numerous studies of unilateral mTL resection have documented that in left-language dominant patients, resection of the left anterior temporal lobe consistently produces verbal memory impairment, and although the findings are less robust, that resection of the right, non-language-dominant anterior temporal lobe produces visuospatial memory impairment (Milner, 1958; Blakemore and Falconer, 1967; Milner, 1968; Jones-Gotman, 1986). Such findings gave rise to the ipsilateral deficit model, or *material-specific model*, which asserts that memory function lateralizes with cerebral function: in left-language dominant individuals, the left hemisphere mediates verbal memory, and the right hemisphere visuospatial memory (Saykin, et al., 1992).

Neuroimaging results have not been entirely consistent with lesion data regarding material-specificity during memory processing. Although several studies have demonstrated material-specific laterality in the frontal lobes (Wagner, et al., 1998; McDermott, et al., 1999) and in the mTL (Grady, et al., 1995; Stern, et al., 1996; Nyberg, et al., 1996a; Kelly, et al., 1998; Detre, et al., 1998), numerous studies suggest that hemispheric effects depend upon the memory process being instantiated (encoding vs. retrieval), rather than the type of stimulus material (Tulving, et al., 1994; Schacter, et al., 1995; Nyberg, et al., 1996b). Other studies suggest that the right and left medial temporal regions respond differentially to novel and familiar stimuli (Tulving, et al., 1996; Fujii, et al., 1997), or that laterality of activation varies with depth of encoding (Nyberg, et al., 1996a; Martin, et al., 1997), success of encoding (Casasanto, et al., 2000), or with task parameters such as the stimulus presentation rate (Kelly, et al., 1998).

The present study examined fMRI activation during intentional encoding of unfamiliar faces, complex visual scenes, and four-word declarative sentences. The goal of the study was to determine whether activation in the mTL lateralizes according to the type of stimulus material presented. Other variables that may affect hemispheric laterality, such as stimulus novelty, task instructions, and stimulus presentation parameters, were held constant across the three tasks. It was hypothesized that encoding of unfamiliar faces would be associated with preferential activation of right-hemisphere mTL structures, encoding of sentences with preferential activation of left-hemisphere mTL structures, and encoding of complex visual scenes, which are amenable to both verbal and visuospatial encoding, would be associated with symmetrical bilateral mTL activation.

### Materials and Methods

#### Subjects

Healthy, normal volunteers between the ages of 18 and 30 were consecutively recruited from the University of Pennsylvania community, and paid \$20 for their

participation (Scenes task: N=19, 6 male; Sentence Task: N=15, 6 male; Face task: N=11, 5 male). All subjects were right-handed by self-report, and all of the sentence task participants were native speakers of English.

### **Cognitive Task Design**

For each encoding task, subjects viewed a total of 60 stimuli, presented over six 40-second blocks (10 stimuli per block, 3500 ms presentation, 500 ms ISI) while lying supine in the bore of the MRI scanner. Stimulus blocks alternated with blocks of control images, matched with target stimuli for size, color, luminosity, and presentation rate. Scene stimuli were obtained from a commercial library of digitized images (PhotoDisc, Inc., 1995, Seattle, WA). (See figure 1a.) Face stimuli were constructed from University of Pennsylvania ID card photographs. Consent for use of the photographs was solicited via an e-mail advertisement to approximately 3000 members of the University community, and only photographs from those providing consent were used. The face photographs were equated for size and image quality, and were cropped so as to include the brow, eyes, nose, and mouth, but exclude ears, hair, and any extraneous objects such as eyeglasses or jewelry. (See figure 1b.) Sentence stimuli were four-word, active, declarative sentences culled from children's books estimated to be at the fifth-grade reading level, and presented in Chicago 24-point font. Simple sentences were chosen so that this task could be administered to neurologically impaired patients with cognitive deficits, although all data reported presently pertain to healthy subjects. (See figure 1c.) For the faces and scenes tasks, the control images were visual noise patterns, created by transforming a stimulus image with a random retiling algorithm iterated 10,000 times. For the sentence task, the control image was a set of four strings, composed of asterisks, of the same mean length as the stimulus words. Stimulus presentation routines were developed on a Macintosh Powerbook (Apple Computer, Cupertino, CA), using Psycscope software (Cohen, et al., 1993). Stimuli were back-projected using an Epson LCD projector (model ELP-5000) onto a viewing screen positioned approximately 7 feet from the subject's eyes, which was easily visible via a mirror mounted in the scanner head coil. Subjects were instructed to remember the stimuli for a recognition test immediately following each encoding task, and to attend to the control images, but not to memorize them. The sequence of cognitive tasks was pseudorandomly varied across subjects.

For each recognition test, subjects viewed all sixty of the stimuli presented during the preceding encoding task, randomly intermixed with an equal number of novel distractors. While still lying in the scanner bore, subjects were required to distinguish studied stimuli from unstudied distractors, and to respond using a two-button box interfaced with the Macintosh computer via fiber-optic cable. The forced-choice recognition test was self-paced, and subjects were informed that both the speed and accuracy of their responses was of interest. Functional

imaging data were collected during encoding, but not during recognition testing.

### **Image Acquisition**

Imaging data were collected on a 1.5 Tesla GE Signa MRI scanner equipped with a fast gradient system for echo-planar imaging, using a standard quadrature radiofrequency (RF) whole-head coil. Foam padding was used to comfortably restrict head motion. Sagittal and axial T1-weighted structural images were obtained for each subject. Prior to functional activation, data were acquired for correction of image distortion due to static susceptibility effects (Alsop, 1995). T2\*-sensitive, gradient echo, echoplanar functional images were then obtained with BOLD contrast (TR = 2000 ms, TE<sub>eff</sub> = 50 ms) in 18 to 20 contiguous 5-mm-thick axial slices, in a 24-cm field of view with a 64x64 acquisition matrix, resulting in a nominal pixel resolution of 3.75 x 3.75 x 5 mm. For each encoding task, functional activation was measured over a single 240-scan run consisting of six 80-second task/control cycles. Raw imaging data were extracted onto digital audiotape (DAT) for subsequent analysis.

### **Image Processing and Data Analysis**

Imaging data were reconstructed offline on SUN UltraSparc workstations, (SUN Microsystems, Mountain View, CA) using software developed in Interactive Data Language (Research Systems, Boulder, CO). Raw data were corrected for static susceptibility-induced distortions, and a motion-compensation algorithm targeting translational artifacts occurring along three orthogonal vectors was applied to each data set. Data were convolved in space using a three-dimensional nonisotropic gaussian kernel (full width half-maximum [FWHM] = 8 X 8 X 10 mm). Using SPM97 software (Wellcome Laboratories, London, UK), a linear model for temporally autocorrelated observations was applied voxelwise to each data set. FMRI signal at each voxel was correlated to a reference function obtained by convolving the square wave describing the task/control alternation with an estimate of the subject's hemodynamic response function (Friston, et al., 1994). Statistical parametric maps (SPMs) were generated for each subject's encoding runs. Multisubject SPMs were then constructed for each task using the random effects model, with SPMt maps as input. Normalized group maps were viewed in Talairach atlas space, with across-subject averaged functional images superimposed on a standard pseudosubject structural image. Cognitive subtraction (task condition – control condition) produced a difference image showing activation associated stimulus encoding for each task.

Anatomical regions were defined using the SPL anatomy browser (Kikinis, et al., 1996), interfaced with IDL and SPM98 software. Based on these anatomical regions, an mTL region of interest (ROI) was defined comprising the hippocampus, parahippocampus, and

fusiform gyrus. Although whole-brain data were collected, secondary analysis was restricted to this a-priori defined region of interest. Only activation exceeding a mapwise statistical threshold ( $\alpha = .05$ ) was considered. Suprathreshold activation was quantified for each lateralized anatomical structure within the mTL ROI, by counting the number of active suprathreshold voxels. The hemispheric asymmetry of activation correlating with each cognitive task was determined by calculating an asymmetry ratio for each search region ( $AR = \text{Voxels}_R - \text{Voxels}_L / \text{Voxels}_R + \text{Voxels}_L$ ). The significance of activation asymmetry was assessed by comparing the proportion of active suprathreshold voxels in each lateralized search region, using a standard test for the independence of two proportions (Hinkle, et al., 1988).

Recognition test performance was assessed by computing a discriminability index for each subject (Discriminability = (% hits) – (% false positives)).

## Results

### Behavioral Results

Performance on the post-scan recognition tests confirmed that subjects were able to encode target stimuli satisfactorily. Results show that all subjects performed significantly above chance on all tasks. Subjects' mean discriminability score for the face task was 0.46 (SD +/- .18,  $t = 8.25$ ,  $p = .0001$ ), for the scene task 0.80 (SD +/- .17,  $t = 19.18$ ,  $p = .0001$ ), and for the sentence task 0.70 (SD +/- .17,  $t = 13.97$ ,  $p = .0001$ ).

### Imaging Results

Suprathreshold activation associated with encoding was found in the mTL region of interest across all three tasks. Table 1 presents the Talairach locations of peak activation during encoding for each anatomical structure within the ROI. Figure 2 presents selected slices of the multisubject functional activation maps for each encoding task. It was observed, for the face and scene tasks, that active suprathreshold voxels in the parahippocampus were contiguous with those in the fusiform gyrus, constituting a "cluster" of active voxels. Hippocampal activations formed separate clusters. Therefore, for analysis of hemispheric effects, the region of interest was divided into two subregions: a hippocampal ROI comprising the hippocampus proper (horn of Ammon, subiculum, and dentate gyrus), and a posterior mTL ROI comprising the parahippocampus (perirhinal and entorhinal cortices) and the fusiform gyrus. Figure 3 shows the hemispheric asymmetry of activation across tasks, as indicated by the asymmetry ratio computed for each search region. For the face task, bilateral activation was found in the hippocampus, nonsignificantly greater left than right ( $AR = -0.20$ ,  $ns$ ), and in the posterior mTL, significantly greater right than left ( $AR = 0.46$ ,  $p < .0004$ ). For the scene task, bilateral activation was found in the hippocampus, significantly greater right than left ( $AR = 0.33$ ,  $p < 0.02$ ), and bilateral activation was found in the posterior mTL ( $AR = -0.07$ ,  $ns$ ). For the sentence task,

unilateral left hemisphere activation was found both in the hippocampus ( $AR = -1.0$ ,  $p < .04$ ) and in the posterior mTL ( $AR = -1.0$ ,  $p < .002$ ).

## Discussion

Across encoding tasks, the pattern of activation in the posterior mTL is consistent with the material-specific hypothesis. Greater right than left hemisphere activation was found during face encoding, nearly symmetrical bilateral activation during scene encoding, and exclusively left-sided activation during sentence encoding. The hemispheric laterality of activation can be interpreted as "code-specific" (McDermott, et al., 1999): that is, varying with the extent to which the stimuli can be processed using verbal and nonverbal *representational codes* (Paivio, 1991), the neural substrates of which have been shown to be differentially lateralized (Kounios and Holcomb, 1994; Kelly, et al., 1998).

Surprisingly, we observed that within task, the laterality of activation in the posterior mTL was not always consistent with the laterality of activation in the hippocampus. Hippocampal activation was bilateral during face encoding, preferentially right-sided during scene encoding, and exclusively left-sided during sentence encoding. In contrast to the material-specific activation observed in the posterior mTL, activation in the hippocampus during face and scene encoding did not lateralize according to the material-specific hypothesis. Previous studies have reported activation of left mTL structures during intentional encoding across all material types (Martin, 1997; Kelly, et al., 1998). However, the dissociation we observe between the laterality of activation in the hippocampus and posterior mTL structures during face and scene encoding has not been reported previously. It may be possible to account for our findings in terms of the neural connectivity of the mTL and surrounding structures. Hemispheric specialization for verbal and nonverbal materials has been well established in the neocortex. Because the parahippocampus receives direct input from the cortical sensory association areas, whereas the hippocampus receives the majority of its cortical input indirectly, via the parahippocampus (Eichenbaum and Bunsey, 1995), material-specific hemispheric effects may be observed more readily in parahippocampus than in the hippocampus. Furthermore, hemispheric specialization in the hippocampus may be masked due to integration of the right and left hippocampi, which are reciprocally connected via the hippocampal commissure.

Our findings are compatible with the two-component model of mTL memory processing developed by Eichenbaum and colleagues (1994), which suggests a functional dissociation between the hippocampus and posterior mTL structures. Specifically, the model implicates the parahippocampal region in the intermediate-term storage and maintenance of *individual mental representations*, and the hippocampus in the formation of *relations among mental representations*.

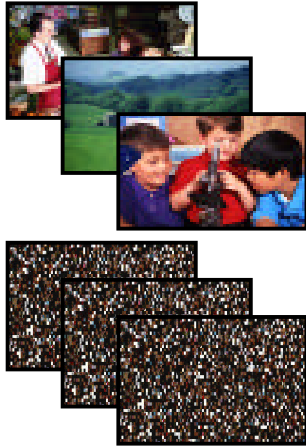


Figure 1a:  
SceneTask and Control Stimuli.



Figure 1b:  
Face Task and Control Stimuli.

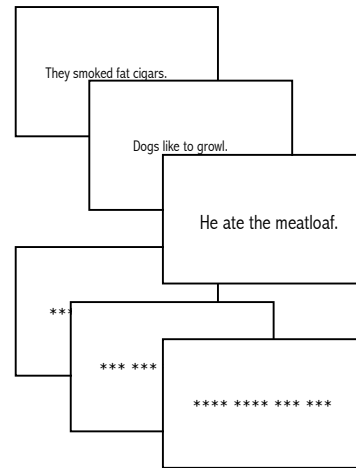


Figure 1c:  
Sentence Task and Control Stimuli.

Table 1: Talairach coordinates and Z-scores of the local maxima within ROI.

Region	x	y	z	Total Volume	Active Volume	Mean Z	Maximum Z
<b>Faces</b>							
Left Hippocampus	-20	-12	-10	71	6	1.91	2.33
Left Parahippocampus	-16	-8	-25	78	3	2.03	2.19
Left Fusiform Gyrus	-48	-52	-20	148	8	2.18	3.31
Right Hippocampus	24	-20	-15	75	4	1.81	1.91
Right Parahippocampus	24	-12	-35	81	3	1.96	2.18
Right Fusiform Gyrus	36	-52	-25	133	27	2.30	4.24
<b>Scenes</b>							
Left Hippocampus	-28	-36	-10	71	8	2.59	3.09
Left Parahippocampus	-32	-44	-15	78	21	2.68	3.37
Left Fusiform Gyrus	-48	-56	-20	148	48	3.17	4.47
Right Hippocampus	12	-40	-10	75	16	2.07	3.18
Right Parahippocampus	24	-44	-20	81	27	2.90	3.77
Right Fusiform Gyrus	20	-48	-15	133	33	2.88	4.24
<b>Sentences</b>							
Left Hippocampus	-32	-20	-10	71	3	1.87	2.11
Left Parahippocampus	-20	-40	-5	78	1	1.76	1.76
Left Fusiform Gyrus	-52	-56	-20	148	10	2.11	2.59
Right Hippocampus	--	--	--	75	0	--	--
Right Parahippocampus	--	--	--	81	0	--	--
Right Fusiform Gyrus	--	--	--	133	0	--	--

Note. Mean Z score indicates the average of all suprathreshold voxels within the ROI. Active volume represents the number of voxels within the ROI exceeding the significance threshold ( $\alpha = .05$ ).

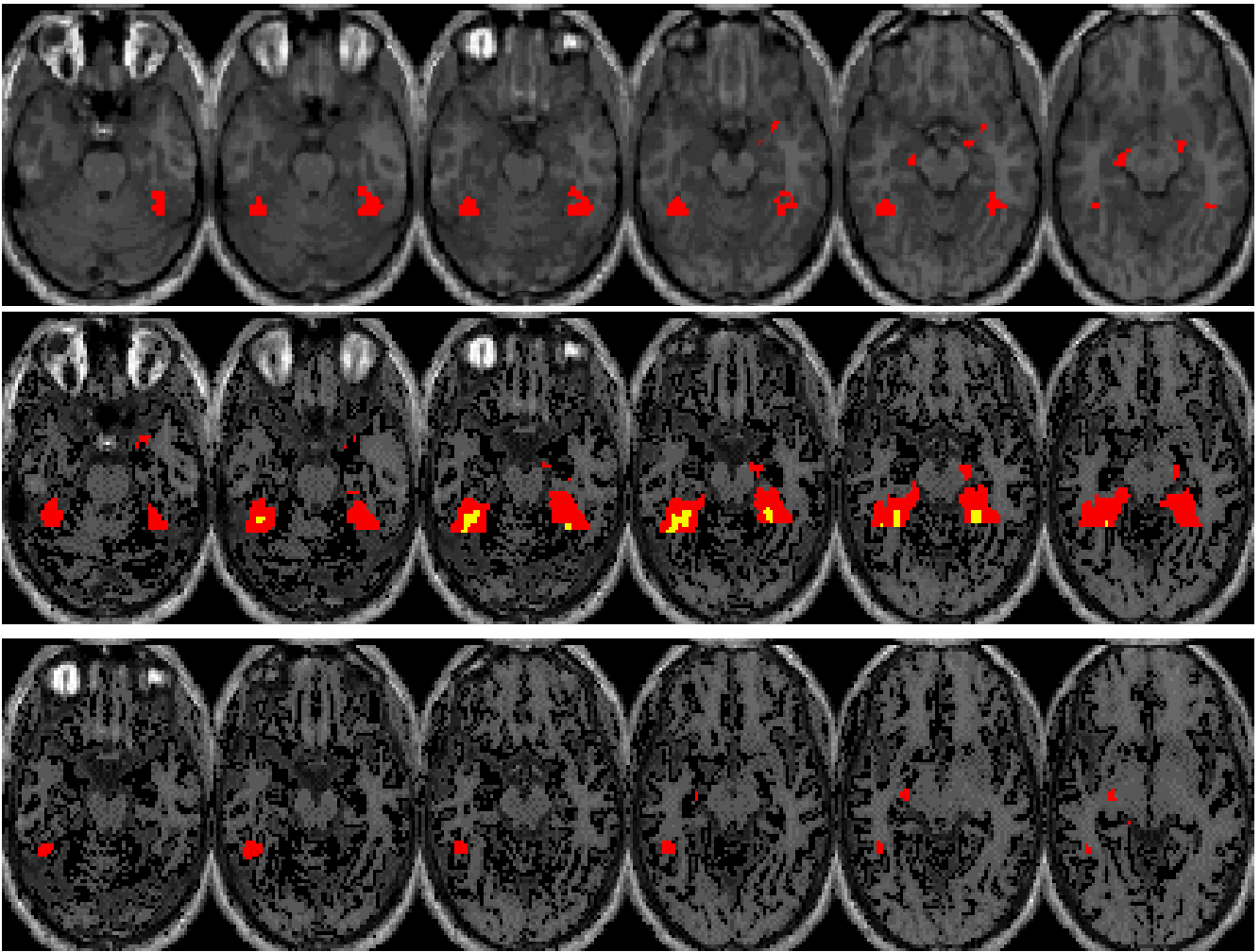


Figure 2: Multisubject statistical parametric maps (SPMs) of functional activation within the mTL region of interest correlating with each encoding task (top row: face encoding; middle row: scene encoding; bottom row: sentence encoding). The left side of each image corresponds to the left side of the brain. Regions demonstrating suprathreshold activation ( $\alpha = .05$ ) during the task - control conditions are displayed in the red-to-yellow color scale.

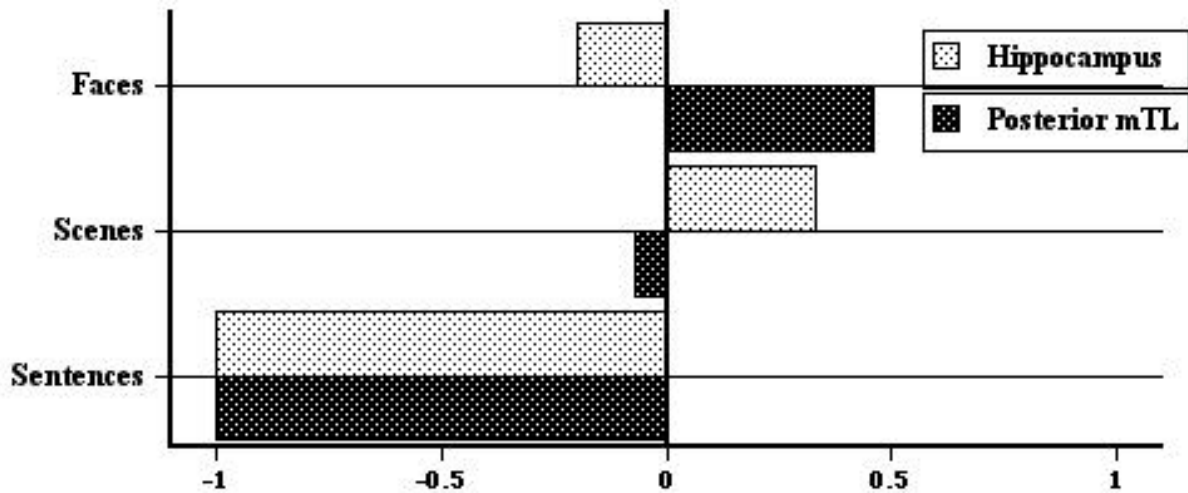


Figure 3: Hemispheric asymmetry of activation across encoding tasks in the hippocampus and posterior mTL. The horizontal axis indicates the Asymmetry Ratio (AR) calculated to show the hemispheric distribution of active suprathreshold voxels ( $\alpha = .05$ ) within each search region ( $AR = \text{Voxels}_R - \text{Voxels}_L / \text{Voxels}_R + \text{Voxels}_L$ ).

This model, based primarily on lesion studies in humans and animals, is supported by recent human electrophysiological data that show a temporal dissociation between parahippocampal and hippocampal activation during encoding (Fernandez, et al., 1999), and by PET data that show increased hippocampal activation during relational vs. non-relational memory processing (Henke, et al., 1999). *Individual* mental representations may be either verbal or nonverbal, whereas *relational* representations may combine verbal and nonverbal codes. Although the Eichenbaum model makes no explicit predictions regarding material-specificity, it provides a theoretical framework in which to consider our finding that the posterior mTL shows greater sensitivity to material type than the hippocampus.

### Conclusions

Whereas hemispheric laterality during memory encoding in the posterior mTL appears to be strongly code-dependent, laterality in the hippocampus may depend upon other variables, as well. Within the frontal lobes, hemispheric effects have been shown to depend upon material type for certain anatomical structures, and upon cognitive set (encoding vs. retrieval) for other nearby structures (McDermott, et al., 1999). This pattern may be extensible to the mesial temporal lobes. Future studies may identify variables affecting the laterality of activation in specific mTL subcomponents, and may help to reconcile neuropsychological findings that suggest material-specific hippocampal involvement in memory processing with conflicting neuroimaging results.

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