Material-specific lateralization in the medial temporal lobe and prefrontal cortex during memory encoding

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Summary

Numerous observations in patients with unilateral lesions of the medial temporal lobe (MTL) and the prefrontal cortex indicate that memory processes are lateralized according to content. Left-sided lesions interfere with verbal memory processes, whereas right-sided lesions interfere with visuospatial (non-verbal) memory processes. However, functional imaging studies have resulted in contradictory data, some studies showing lateralization in the prefrontal cortex determined by stage of processing (encoding versus retrieval) and others suggesting that lateralization is dependent on the type of material. Few studies have examined this issue in the MTL. In order to test the hypothesis that the lateralization of encoding processes in the MTL and frontal regions is dependent on the verbalizability of the material, we performed behavioural and functional imaging studies.

We demonstrated differing verbalizabilities of three classes of non-verbal stimuli (scenes > faces > abstract patterns) using a dual-task verbal interference behavioural paradigm. A functional neuroimaging study of encoding was carried out using these three types of stimuli, plus words. During whole-brain functional MRI at 1.5 T, eight normal right-handed adults were presented with alternating blocks of novel and repeated stimuli under intentional memory encoding conditions. Verbal encoding resulted in left-lateralized activation of the inferior prefrontal cortex and the MTL. Pattern encoding activated the right inferior prefrontal cortex and the right MTL. Scenes and faces resulted in approximately symmetrical activation in both regions. The data indicate that the lateralization of encoding processes is determined by the verbalizability of stimuli.

Keywords: memory; medial temporal lobe; prefrontal cortex; lateralization; encoding

Abbreviations: BA = Brodmann area; fMRI = functional MRI; HERA = hemispheric encoding/retrieval asymmetry; IPC = inferior prefrontal cortex; MTL = medial temporal lobe; ROI = region of interest; RT = reaction time

Introduction

Lesion and functional neuroimaging studies have often provided convergent evidence about the neural substrates of memory processes, such as the importance of medial temporal lobe (MTL) and frontal lobe regions for declarative memory (for review, see Gabrieli, 1998). One apparent divergence, however, has concerned the principles underlying hemispheric asymmetries of declarative memory processes (i.e. processes important for the explicit recall and recognition of events) (Cohen and Squire, 1980; Graf and Schacter, 1985). When asymmetries have been found after unilateral MTL or frontal lobe lesions, they have been for poor memory of verbal material after left hemisphere lesions and of non-verbal material after right hemisphere lesions. Thus, asymmetrical memory deficits arise according to material type and the

processes typically engaged by these materials (Milner, 1972; Milner and Petrides, 1984). Functional imaging studies, in contrast, have often found lateralization to be dependent on the stage of memory processing, encoding producing left-lateralized activations and retrieval producing right-lateralized activations (Tulving *et al.*, 1994; Nyberg *et al.*, 1996*b*). The hemispheric asymmetries in imaging studies have often seemed unaffected by material type. Further examination of results from both lesion and imaging studies, however, reveals that lateralization of declarative memory processes may be dependent on several variables, including material type, stage of processing, meaningfulness and mnemonic strategies.

Several studies have demonstrated that patients with

dominant MTL sclerosis or excision have impairment of verbal memory (Milner, 1972; Delaney *et al.*, 1980; Hermann *et al.*, 1987; Loring, 1997), whereas those with non-dominant foci have deficits of visuospatial memory (Kimura, 1963; Taylor, 1969). The interpretation of such findings can be problematic for at least two reasons. First, these lesions frequently do not respect anatomical boundaries. For example, both pre- and postoperative lesions in patients with mesial temporal lobe epilepsy usually extend beyond the MTL to adjacent structures of the lateral temporal lobe (Ojemann and Dodrill, 1985). Therefore, the material-specificity observed in patients with MTL lesions may partially reflect processes mediated by the lateral temporal cortex. Secondly, patients with epilepsy usually have long-standing brain dysfunction that may result in variable functional reorganization. Patients with more severe hippocampal sclerosis are more impaired pre-operatively in verbal memory (Trenerry, 1996) and naming (Davies *et al.*, 1998), but experience less decline following resection of the diseased hippocampus than those with less severe hippocampal sclerosis. This implies that the disease process has caused the contralateral hemisphere to assume functions normally performed by the ipsilateral temporal lobe. Overall, lesion studies have demonstrated that large unilateral MTL resections result in material-specific deficits in a variety of learning tasks (Petrides and Milner, 1982; Petrides, 1985), although the deficit associated with non-dominant (right-sided) lesions has been more difficult to characterize (Rausch, 1991). These findings have led to the material-specific model, which postulates that memory function lateralizes with cerebral function (Saykin and Robinson, 1992).

Typically, verbal and non-verbal memory processes are assessed with verbal and non-verbal materials, respectively. It is clear, however, that multiple memory processes may be engaged by a single class of materials. One study examined the effect of unilateral MTL lesions on 'remember' (a vivid recollection of the encoded event) and 'know' (a vaguer feeling of familiarity) recognition memory judgements (Blaxton and Theodore, 1997). Healthy subjects could alter their encoding strategies on the basis of experimental constraints to emphasize either distinctiveness (verbal labels) or perceptual features and could thereby alter the proportion of 'remember' and 'know' judgements. In contrast, right-MTL patients consistently made more 'remember' than 'know' judgements and left-MTL patients made more 'know' than 'remember' judgements. This may be consistent with the material specific-model because right-MTL patients have to rely on left-hemisphere verbal (semantic) encoding strategies that are known to increase recollective judgements (Gardiner, 1988). Conversely, left MTL patients have to rely on right-hemisphere perceptual processes that increase familiarity judgements (Rajaram, 1993). This indicates that, whereas healthy subjects may have recourse to multiple encoding strategies subserved by different neural substrates, patients with unilateral MTL damage may be restricted to strategies subserved by the single remaining intact MTL.

In contrast to the effects of lesions of the MTL, the effects of frontal lobe lesions on declarative memory are far less severe and disproportionally affect difficult memory judgements, such as free recall and source, recency or frequency (for review, see Petrides, 1991). This deficit can extend to performance on tests of cued recall and recognition (Wheeler *et al.*, 1995). Left-sided lesions result in more errors when performing these types of verbal memory tasks, whereas right-sided lesions are associated with errors in analogous non-verbal tasks (Glosser *et al.*, 1998). Laterality effects are more difficult to demonstrate after frontal than after MTL lesions, but when found they generally depend on material type (Milner and Petrides, 1984). Differential laterality effects, dependent both on the nature of the stimulus and on the special demands of the task (e.g. recency judgements versus self-ordering), have been observed in patients with unilateral frontal lobe lesions (Milner, 1971; Milner *et al.*, 1985). Patients with left frontal excisions have difficulty in both verbal and non-verbal self-ordering tasks, whereas those with right-sided excisions have impairment only in the non-verbal task (Petrides and Milner, 1982). However, patients with either left or right frontal lesions are severely impaired in both a spatial and non-spatial conditional associative learning task (Petrides, 1985). These results suggest both that there may be process-specific areas within the prefrontal cortex and that some tasks may invoke both verbal and non-verbal strategies. In summary, although unilateral frontal lobe damage has not consistently resulted in asymmetries of memory performance, when observed these have followed the verbal/non-verbal distinction seen after MTL lesions.

Studies of patients with lesions resulting in memory difficulties are limited because a memory deficit cannot be ascribed to the failure of a discrete stage of memory processing, such as encoding, storage or retrieval. Functional imaging with PET or functional MRI (fMRI) has allowed the decomposition of these stages. Rather than finding the expected material-specific lateralization of activation, several functional imaging studies have reported that, irrespective of material, episodic encoding processes are associated with left prefrontal activation and retrieval processes are associated with right prefrontal activation. These observations, encapsulated in the hemispheric encoding/retrieval asymmetry (HERA) model, were originally made with verbal materials (Tulving *et al.*, 1994) and were later extended to non-verbal materials (Nyberg *et al.*, 1996*b*). Studies supporting the HERA hypothesis, however, each investigated a single material type and therefore did not explicitly contrast the effects of stimulus type on activation laterality (Nyberg *et al.*, 1996*a*). It is likely that lateralization within distinct regions of the prefrontal cortex is influenced by both process-specific (encoding/retrieval) and material-specific (verbal/non-verbal) task demands. For instance, the anterior left inferior prefrontal cortex (IPC) [Brodmann area (BA) 45] has been implicated in semantic processing and the posterior left IPC (BA 44) in phonetic processing (Kapur *et al.*, 1996;

Poldrack *et al.*, 1999), whereas more dorsal and anterior areas (BA 9/46) appear to subserve encoding processes in a material-independent manner (Fletcher *et al.*, 1998).

In an effort to reconcile functional imaging and lesion findings, subsequent imaging investigations have specifically contrasted the influence of material type on the lateralization of activation (Kelley *et al.*, 1998; Wagner *et al.*, 1998*a*; McDermott *et al.*, 1999). In the dorsolateral prefrontal cortex, intentional encoding of verbal material (words) has resulted in left-lateralized activation (Kelley *et al.*, 1998; Wagner *et al.*, 1998*a*; McDermott *et al.*, 1999). Right-lateralized activation has been demonstrated during intentional encoding of non-verbal information (faces or textures) (Kelley *et al.*, 1998; Wagner *et al.*, 1998*a*; McDermott *et al.*, 1999). Furthermore, two event-related studies found that left frontal activations predicted subsequent memory for words (Wagner *et al.*, 1998*b*), whereas right frontal activations predicted subsequent memory for complex scenes (Brewer *et al.*, 1998).

Fewer studies have investigated the lateralization of encoding processes in the MTL. Kelley and colleagues found that activation during intentional encoding versus fixation was left-lateralized for word-encoding, bilateral for object-encoding and right-lateralized for face-encoding, although these effects were not apparent during incidental encoding (Kelley *et al.*, 1998). In another study, Martin and colleagues found that the left MTL responded preferentially to meaningful rather than nonsense stimuli and the right MTL responded more strongly to objects than to words (Martin *et al.*, 1997). As in the frontal lobe, activation in the left parahippocampal and fusiform regions predicted how well words were remembered (Wagner *et al.*, 1998*b*), whereas activation in bilateral parahippocampal regions predicted how well scenes were remembered (Brewer *et al.*, 1998).

The goal of the present study was to examine more comprehensively the relationship between the encoding of different types of materials into declarative memory and the asymmetries (or lack of asymmetries) in MTL and dorsolateral prefrontal regions of interest (ROI). The foregoing review has emphasized simple relationships between materials or stages of processing and hemispheric asymmetries, but there is considerable evidence that the relationships are more complex. The lateralization of encoding processes in the MTL, for example, may depend on multiple variables in addition to material type, such as the meaningfulness and novelty of the stimuli (Martin *et al.*, 1997). Furthermore, some kinds of materials may be encoded by both verbal and visuospatial processes (Blaxton and Theodore, 1997). For example, meaningful and easily named line drawings have been reported to result in activation in bilateral prefrontal and MTL regions (Kelley *et al.*, 1998). This symmetrical activation was interpreted as reflecting left-lateralized verbal and right-lateralized visuospatial dual encoding processes that may account for the picture superiority effect (Paivio, 1969). Furthermore, there are dissociable activations for different kinds of visuospatial materials in the posterior cortex (e.g. faces (Kanwisher *et al.*,

1997) and places or scenes (Epstein and Kanwisher, 1998). It is unclear whether such posterior encoding differences will be sustained in prefrontal encoding mechanisms.

For these reasons, we compared activations for the encoding of four kinds of materials—words, faces, scenes and textures. Encoding has been operationalized in multiple ways, including comparison with fixation (Kelley *et al.*, 1998), comparison between materials (Wagner *et al.*, 1998*a*), comparison between levels of processing (Kapur *et al.*, 1995; Vandenberghe *et al.*, 1996), correlations with subsequent memory (Brewer *et al.*, 1998; Wagner *et al.*, 1998*b*) and comparison between novel and familiarized (through repeated exposure) stimuli (Stern *et al.*, 1996; Tulving *et al.*, 1996; Gabrieli *et al.*, 1997). Each of these approaches probably highlights some aspects of multiple encoding processes, including detection, perception, evaluation and categorization. The present study employed a comparison between novel and familiarized materials, a comparison that holds constant both the materials and encoding task within a scan. The hypothesis of this study was that different types of materials would engage memory-encoding regions asymmetrically according to the degree to which the stimuli were verbalizable. We predicted that verbal stimuli would engage left-hemisphere regions preferentially, whereas non-verbal stimuli would engage right-hemisphere regions preferentially. Furthermore, the degree to which non-verbal stimuli are amenable to verbal encoding strategies would influence the amount of left-hemisphere activation.

Four types of material that vary in their verbalizability were studied: patterns, faces, scenes and words. Experiment 1 was a dual interference behavioural study to establish the degree to which the three non-verbal stimuli (patterns, faces and scenes) engage verbal encoding processes. Dual-task interference studies have demonstrated task-specific resources such that verbal tasks cause the most interference when performed with other verbal tasks, while visuospatial tasks cause the most interference when performed concurrently with other visuospatial tasks (Brooks, 1968; Allport *et al.*, 1972). These studies provided the rationale for the present experiment, in which subjects encoded the three types of non-verbal stimuli both with and without verbal interference. Task-specific resources predict that verbal rehearsal will interfere selectively with verbal processing, and therefore least disrupt the most non-verbal task. Experiment 2 was an fMRI study using all four material types to establish the relative contributions of the left and right MTL and frontal regions to the encoding stimuli of varying verbalizability.

In addition to theoretical issues concerning the asymmetry of memory-encoding activations, there is potential clinical relevance for such a study. One practical application of fMRI may be in characterizing the laterality of memory processing in MTL or frontal regions in patients who are candidates for surgical resection. There is already evidence that fMRI provides valid lateralization for language dominance in patients with epilepsy (Desmond *et al.*, 1995; Binder *et al.*, 1996*b*). Even more clinically valuable would be the use of

fMRI to determine laterality for verbal and non-verbal memory processes. For such a purpose, tasks that maximize asymmetries in activation would be most informative about the localization of memory processes.

Experiment 1: dual interference study
Methods
Subjects
Eighteen healthy right-handed native English-speaking volunteers (eight males, 10 females, aged 17–21 years) were enrolled in the study. Informed consent was obtained from each subject in accordance with guidelines approved by Stanford University and the Declaration of Helsinki (1991).

Design
A 2 (interference) ×3 (stimulus type) within-subjects experimental design was employed. Each participant performed six encoding runs: each stimulus type was studied with and without interference. The order of tests was counterbalanced across stimulus type and interference conditions.

Stimuli
Stimuli were presented visually using a Macintosh computer equipped with PsyScope (Carnegie Mellon University, Pittsburgh, Pa., USA) (Macwhinney *et al.*, 1997). Three types of visual stimuli were used: (i) face: colour photographs of male and female faces (Althoff and Cohen, 1999); (ii) scene: colour photographs of indoor and outdoor scenes; and (iii) pattern: colour images of abstract patterns.

Task design
Each run contained 20 trials. All trials started with 500 ms of fixation. Non-interference trials then had a 500 ms pause followed by a 1000 ms presentation of the visual stimuli. Subjects made a two-choice decision for each stimulus: (i) face: male or female; (ii) scene: indoor or outdoor; or (iii) pattern: symmetrical or asymmetrical. A response made by pushing a button triggered the next trial. Interference trials presented a five-consonant letter string for 3000 ms followed by a 500 ms pause. Visual stimuli were presented for 1000 ms as in the non-interference condition. Following the forced-choice response, the word 'RECALL' was presented on the screen, prompting the subject for verbal recall of the consonant string. The examiner recorded the response and triggered the next trial. Recognition memory for the visual stimuli was assessed at the end of the experiment. Subjects viewed 20 previously presented stimuli and 20 foils from each class and made an old/new judgement by pressing one of two keys.

Results
The effect of verbal interference on each of the three tasks was assessed by changes in reaction time (RT) and recognition memory (corrected hits) (Table 1). Paired *t*-tests of RT with and without interference demonstrated significant slowing with interference for the face task [$t(17) = 2.42$, $P < 0.05$] and the scene task [$t(17) = 4.12$, $P < 0.001$], but not for the pattern task [$t(17) = 1.10$, $P > 0.05$]. The effect of interference on recognition memory was assessed by paired *t*-tests of corrected hits with and without interference. As predicted, recognition memory was worse with interference than without interference [faces $t(17) = 3.00$, $P < 0.005$; scenes $t(17) = 4.02$, $P < 0.001$; patterns $t(17) = 3.23$, $P < 0.005$]. In order to compare directly the magnitudes of the interference effects given different overall scores, a ratio of the number of corrected hits with interference to the number of corrected hits without interference was calculated. By this criterion, memory for scenes was more affected by interference than faces [$t(17) = 2.31$, $P < 0.05$] or patterns [$t(17) = 2.80$, $P < 0.01$], but faces and patterns did not differ significantly from one another. When both these measures were used, processing of all three material types worsened with verbal interference. This suggests that verbal processes contribute to the encoding of all three kinds of non-verbal stimuli, at least for the encoding tasks in the present study. Processing of the three different kinds of non-verbal materials, however, appeared to differ in reliance on verbal processes. The encoding of scenes was most affected, patterns were least affected and faces were intermediate.

Experiment 2: fMRI study
Methods
Subjects
Eight healthy volunteers (four male and four female) were enrolled in the study. Informed consent was obtained from each subject in accordance with guidelines approved by the Human Subjects Committee of Stanford University and the Declaration of Helsinki (1991). All subjects were right-handed native English-speakers as confirmed by the Briggs handedness inventory. An additional subject was dropped from the study because of inability to complete the scan.

Stimulus presentation and response collection
Stimuli were presented visually using a magnet-compatible back-projector (Resonance Technology, Van Nuys, Calif., USA). A Macintosh computer with PsyScope (Macwhinney *et al.*, 1997) software generated visual stimuli and controlled the experimental parameters. A custom finger-switch response system was used for the acquisition of responses and RTs.

Task design
Four types of stimuli (words, scenes, faces and patterns) were presented to each subject in separate scans. Prior to
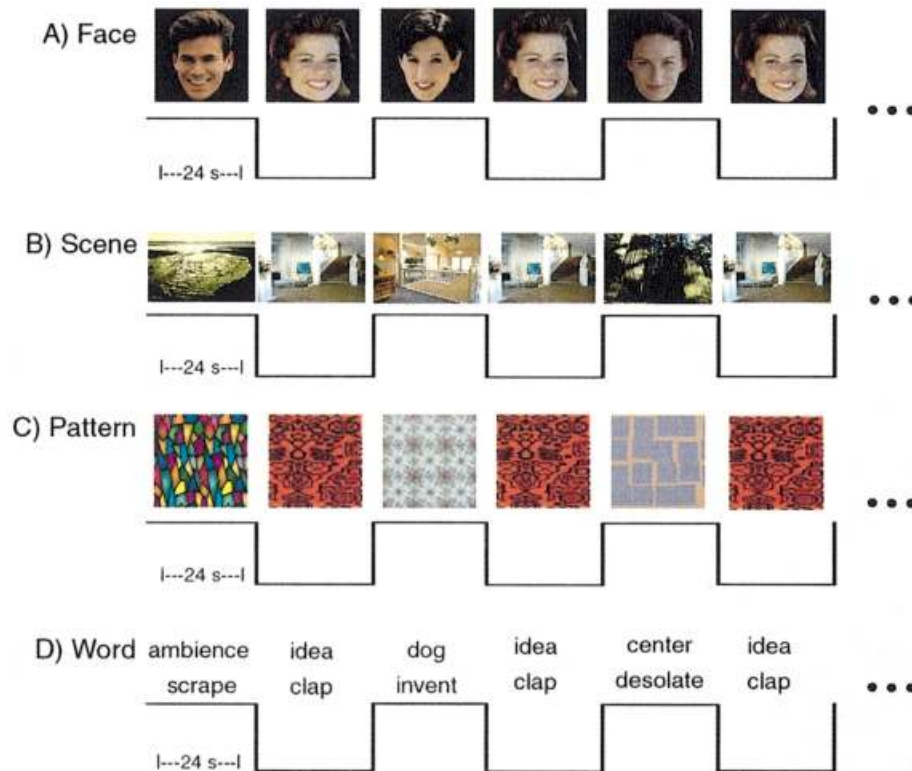
Fig. 1 Experimental design and examples of stimuli. (**A**) Faces. (**B**) Scenes. (**C**) Patterns. (**D**) Words. Each encoding run contrasted blocks of novel and familiar stimuli from one stimulus class.

Table 1 *Reaction times and recognition memory for Experiment 1*

Task	Stimulus type		
	Face	Scene	Pattern
Reaction time ± SE (ms)			
With interference	827 ± 70	1020 ± 81	1247 ± 90
Without interference	652 ± 47	663 ± 42	1081 ± 139
Corrected hits ± SE (%)			
With interference	0.02 ± 0.11	–0.05 ± 0.10	0.30 ± 0.13
Without interference	0.17 ± 0.14	0.23 ± 0.14	0.47 ± 0.14

SE = standard error.

starting each scan, subjects were explicitly instructed to try to remember the stimuli for a later test. In each scan, subjects were presented with 96 stimuli in 16 blocks of six stimuli per block. Stimuli were visible for 3500 ms with an interstimulus interval of 500 ms. Alternating blocks contained either all new stimuli or the same two stimuli repeated throughout the study (Fig. 1). Order of stimulus type (face/scene/pattern/word) and novelty (old/new) were counterbalanced across subjects. Each class of stimuli had an associated task, as detailed below. Responses were made by a button push.

Word. Pairs of common words (nouns, verbs and adjectives) were presented visually. Subjects were instructed to try to generate a sentence silently using both words. For repeated words they were told to generate the same sentence each time. Subjects were asked to respond as soon as they completed the task.

Face, scene and pattern. The same stimuli and tasks were used as described in Experiment 1.

Following the scanning session, a recognition test was administered. For each type of stimuli, subjects viewed 12

previously presented items and 12 foils. Responses ('new', 'old') were made by a button push. The memory tests were administered in the same order as the encoding tasks for each individual subject, and the order was thus counterbalanced across subjects.

Data acquisition

Participants were scanned using a 1.5 T Signa MRI system (General Electric, Milwaukee, Wis., USA) with a prototype birdcage headcoil. A bite-bar, formed with the subject's dental impression, was used to minimize head movement.

Functional scans. Whole-brain functional imaging was performed using a single-interleave gradient echo spiral pulse sequence (Glover and Lai, 1998), imaging 29 contiguous coronal slices perpendicular to the anterior commissure–posterior commissure line (6 mm thickness) at 3 s per image volume with an in-plane spatial resolution of 3.44 mm. TR (repetition time) was 3000 ms, TE (echo time) 40 ms, flip angle 89°, field of view 22 cm and matrix acquisition 64 × 64.

Structural scans. T_1-weighted spin echo images were acquired for all slices that received functional scans. These were used to verify proper slice selection prior to functional imaging and to correlate functional activation with anatomical structures. A 3D SPGR (spoiled gradient recalled) volumetric scan was acquired for Talairach registration and reslicing along different planes.

Data analysis

Following image reconstruction, motion correction in three dimensions was performed offline by automated image registration (Woods *et al.*, 1998). Images were spatially normalized using SPM96 (Wellcome Department of Cognitive Neurology, London, UK) into a common stereotactic space (Talairach and Tournoux, 1988) on the basis of the high-resolution volume images; this allowed comparison of common regions across multiple subjects and scanning sessions.

Statistical analysis was performed using SPM96. Analysis was first performed individually for each subject. Differences between stimulus conditions were examined using the general linear model, modelling stimulus-related activation as a delayed boxcar function (taking into account the haemodynamic response lag) and treating low-frequency signal components as nuisance covariates. Differences in global signal intensity were corrected using proportional scaling to a common mean. This analysis identified, for each subject, those regions that were significantly more active for novel than repeated stimuli, and these individual statistical maps were then subjected to ROI analysis (outlined below).

Group analysis was performed by first creating adjusted mean images for each condition for each subject using the SPM96 adjusted mean procedure, modelling stimulus-related

response as a boxcar function (taking into account the haemodynamic response lag) and removing global intensity and low-frequency signal components. Adjusted mean images were then analysed across subjects using a mixed-effects general linear model, treating subjects as a random effect and conditions as a fixed effect and thus allowing population inference. Correction for multiple comparisons was performed according to the theory of Gaussian random fields (Worsley *et al.*, 1992), providing a corrected *P* value ($P < 0.05$) across the entire imaged volume based upon the observed height and spatial extent of each activated cluster. Common activation across item types was examined using conjunction analysis in SPM96 (Price and Friston, 1997).

Medial temporal lobe region of interest. Further analysis of ROIs was performed using custom software in Interactive Data Language (Research Systems, Boulder, Col., USA). The medial temporal lobe region was identified visually and outlined bilaterally on each subject's coronal slices from the amygdala to the atrium of the ventricles. The hippocampal gyrus, parahippocampal gyrus, entorhinal cortex and subiculum were included, as described by Amaral and Insausti (Amaral and Insausti, 1990). Voxels within each region reaching a voxel threshold of $P < 0.001$ were counted and an index of asymmetry was calculated [(right – left)/ (right + left)]. Voxel counts and asymmetry indices within the ROI were analysed by repeated measures ANOVA (analysis of variance) with the Huynh-Feldt correction for non-sphericity. Subsequent analysis was performed with paired *t*-tests. The ROI analysis was repeated at other thresholds (0.05, 0.025 and 0.01) to confirm that the results were not due to a particular cut-off.

Frontal region of interest. Anatomical ROIs corresponding putatively to BA 6, 9, 10, 44 and 45 were derived from the Talairach atlas (Lancaster *et al.*, 1997). Voxels within each region reaching the threshold *P* value were counted. Voxel counts within the ROI were analysed using repeated measures ANOVA with the Huynh–Feldt correction for non-sphericity. *Post hoc* comparisons were made with paired *t*-tests. The ROI analysis was performed at a voxel threshold of $P < 0.001$ and repeated at other thresholds as in the MTL analysis. As in the MTL, an asymmetry index was calculated.

Correlation between frontal and MTL regions. We computed the average within-subject correlation between frontal and MTL asymmetry indices across the four stimulus types. Significance was tested using a random effects procedure based on a multilevel modelling approach (Kenny *et al.*, 1998). We tested whether the mean unstandardized regression coefficient across the eight subjects differed significantly from zero.

Table 2 *Reaction times and recognition memory for Experiment 2*

Task	Stimulus type			
	Face	Scene	Pattern	Word
Reaction time ± SE (ms)				
Novel	822 ± 149	836 ± 122	1103 ± 94	2450 ± 125
Repeat	640 ± 78	653 ± 57	695 ± 43	1088 ± 165
Corrected hits ± SE (%)	0.57 ± 0.06	0.51 ± 0.15	0.65 ± 0.07	0.59 ± 0.07

SE = standard error.

Results

Behavioural data

RTs were not available for two subjects because of button box malfunction. Mean RT was analysed with a 4 (stimulus type) × 2 (novelty) repeated measures ANOVA (Table 2). Reaction time differed across the different classes of stimuli [significant main effect of stimulus type, $F(3,15) = 57.3$, $P = 0.0001$]. The word task was performed significantly more slowly than the pattern task [$t(5) = 7.88$, $P < 0.001$]. The pattern task, in turn, was performed more slowly than the scene [$t(5) = 3.03$, $P < 0.05$] and face [$t(5) = 3.13$, $P < 0.05$] tasks, which did not differ from one another. Subjects were faster on repeated presentations of stimuli than on novel presentations [main effect of novelty, $F(1,5) = 40.28$, $P = 0.001$]. The item type × novelty interaction was also significant [$F(3,15) = 18.13$, $P = 0.006$]. There were greater differences in RT between the novel and repeat conditions for the word task than for the pattern task [$t(5) = 3.58$, $P = 0.02$] and for the pattern task compared with both the face task [$t(5) = 4.92$, $P < 0.005$] and the scene task [$t(5) = 4.21$, $P < 0.01$]. Recognition memory was analysed in terms of corrected hits for each stimulus class. Recognition memory for the presented stimuli revealed similar levels of memory for the four types of stimuli (Table 2) that did not differ reliably by item type [$F(3,21) = 0.43$, $P > 0.05$].

Imaging results

Group analyses of novel versus repeated conditions for all tasks demonstrated activations within the MTL and frontal lobes. A conjunction analysis over all four encoding tasks revealed bilateral prefrontal activation in the inferior and middle frontal gyri as well as cingulate activation (Fig. 2B). Word novelty produced the greatest left lateralization, pattern novelty produced the greatest right lateralization, and the face and scene tasks were intermediate. Contrasting word novelty and pattern novelty highlights the asymmetry of activation. Within the prefrontal cortex, areas more active for word-encoding (novel–repeat) than for pattern-encoding were exclusively left-sided (Fig. 2A), whereas areas more active for pattern-encoding than for word-encoding were exclusively right-sided (Fig. 2C). In order to test the hypothesis that the verbalizability of the content to be encoded affected the lateralization of brain activity in the MTL and frontal lobes, quantitative analyses were performed for these two regions.

Medial temporal lobe activation. Medial temporal activation was demonstrated in the novel versus repeat comparison for all four stimuli types (Fig. 3). In each case there were asymmetries in the activation, as measured by the number of suprathreshold voxels, between the left and right MTL (Fig. 4A). An item type (face, scene, pattern word) × hemisphere (left, right) repeated measures ANOVA was performed on the voxel counts obtained from the MTL analysis. A significant main effect was seen for item type [$F(3,21) = 7.6$, $P < 0.01$]. Scenes and patterns, which did not differ significantly from one another, resulted in significantly greater activation than faces [$t(5) = 3.65$, $P < 0.01$] and words [$t(5) = 3.22$, $P < 0.02$], which also did not differ significantly. As predicted by the hypothesis of the study, the item type × hemisphere interaction was significant [$F(3,21) = 4.4$, $P < 0.05$]. This reflects asymmetries in the MTL activations that differed across material types. However, the asymmetries in activation were not absolute: all tasks resulted in suprathreshold voxels bilaterally but the relative ratios differed according to item type.

Pattern encoding. Analysis of the data from the pattern scan revealed bilateral novelty-associated MTL activation, which was greater on the right than on the left. Seven of eight subjects had more suprathreshold voxels on the right compared with the left. There was significant right-sided asymmetry over the group [$t(7) = 2.24$, $P < 0.05$].

Face encoding. All subjects had bilateral MTL activation in response to face novelty. In six of eight subjects there were more suprathreshold voxels within the right MTL compared with the left. The laterality effect, however, was not statistically significant ($P > 0.05$).

Scene encoding. Scene novelty yielded voxel counts that were greater on the right than the left for five subjects. Over
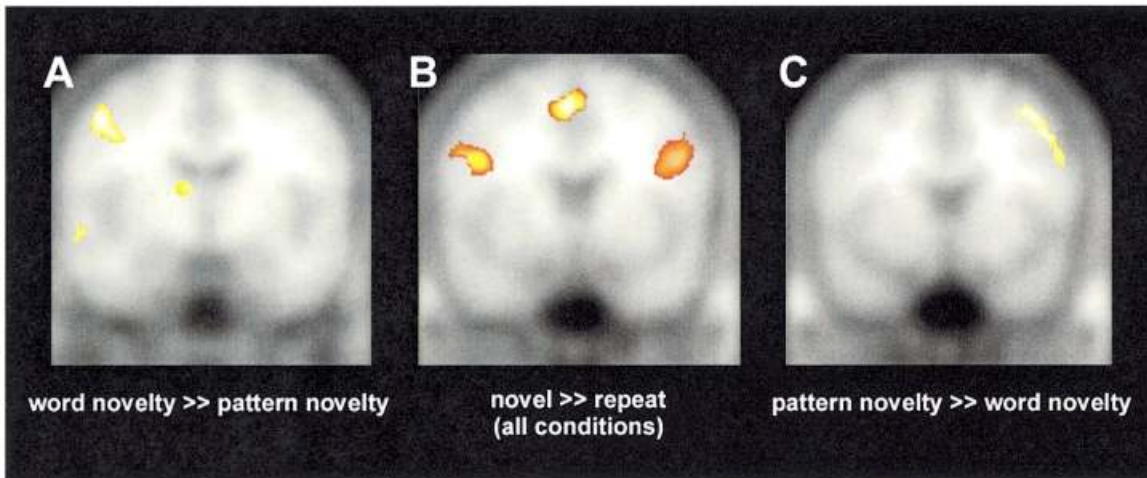
Fig. 2 Coronal section through the frontal cortex demonstrating suprathreshold voxels ($Z = 2.33$, $P < 0.01$) for the random effects analysis. (**A**) Areas more active for word novelty than for pattern novelty showing left prefrontal activation ($x = -50$, $y = 12$, $z = 48$). (**B**) Areas activated by the conjunction across all four conditions showing bilateral prefrontal activation ($x = -48$, $y = 0$, $z = 30$ and $x = 50$, $y = 4$, $z = 32$) in response to novelty. (**C**) Areas more active for pattern novelty than for word novelty showing right prefrontal activation ($x = 36$, $y = 16$, $z = 44$).
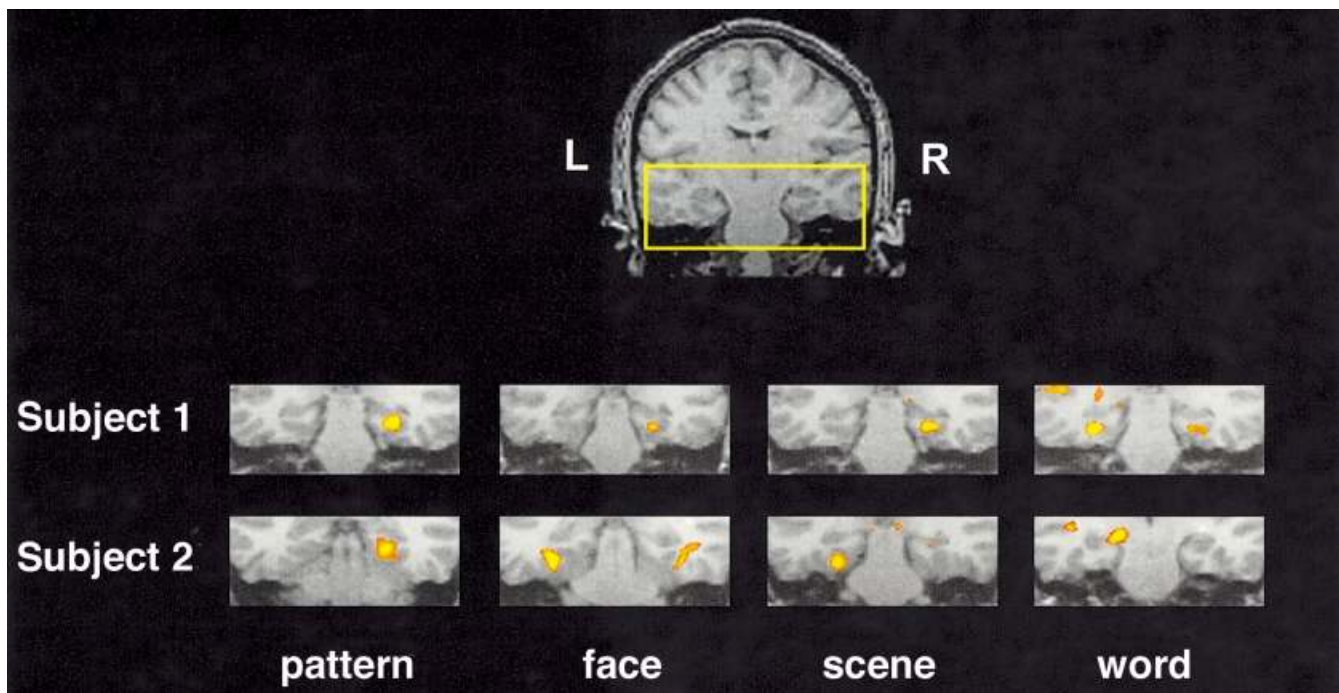

Fig. 3 Statistical activation maps from two representative subjects, demonstrating areas of activation within the medial temporal lobe ROI (height threshold $Z = 1.96$, $P < 0.025$, corrected for multiple comparisons at the 0.05 level). Greater activation is seen on the right for pattern encoding and on the left for word encoding. Face and scene encoding yield bilateral activation, right greater than left. Activations outside the ROI are not shown.

the group there was a trend for a rightward asymmetry [$t(7) = 1.79$, $P = 0.06$].

Word encoding. Analysis of the word task revealed bilateral MTL activations that were larger on the left. Six of eight subjects had a greater number of active voxels on the left than on the right (two had minimal and equal activation

bilaterally). Over the group, the asymmetry of the number of suprathreshold voxels was significant towards the left [$t(7) = 2.35$, $P < 0.05$].

Frontal lobe activation. Inspection of individual statistical maps revealed robust prefrontal activation in response to novel versus repeated stimuli. All tasks resulted
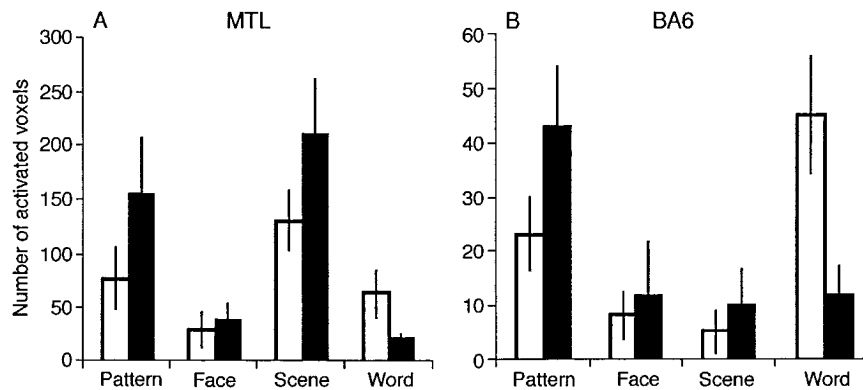
Fig. 4 Graph representing number (± standard error of the mean) of suprathreshold voxels ($P < 0.001$) within the (**A**) MTL and (**B**) BA 6 ROIs. White columns = left; black columns = right.
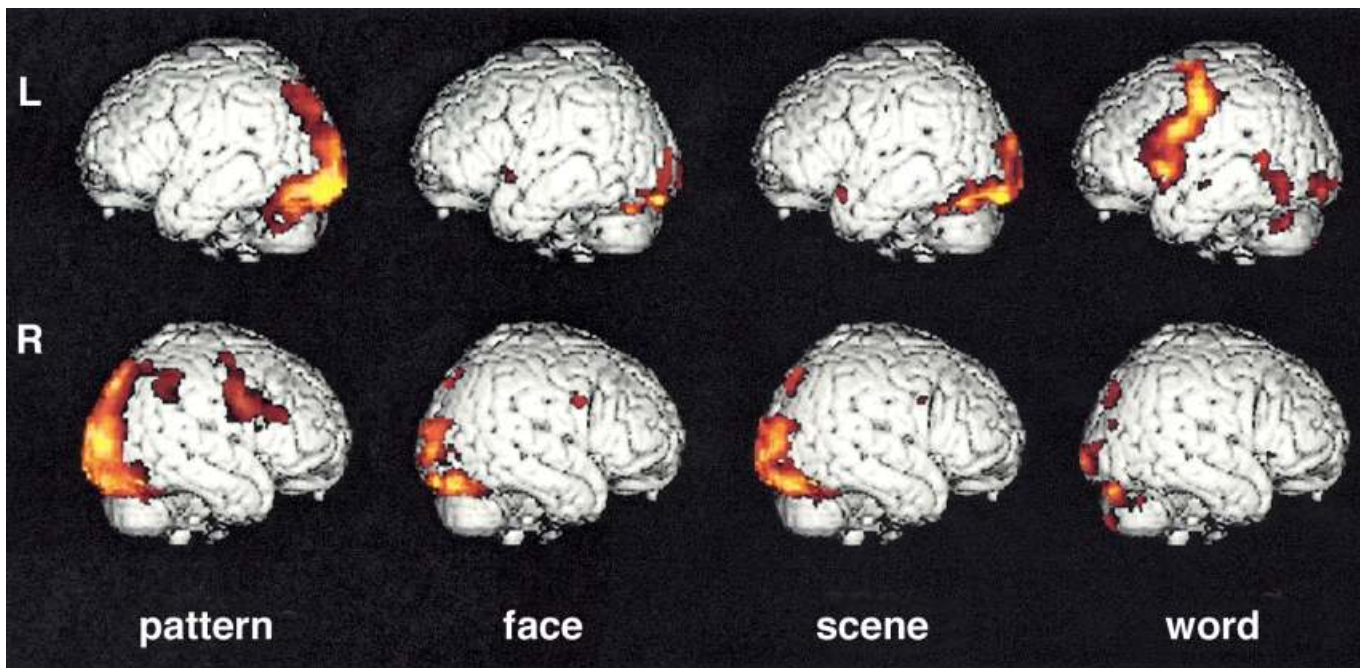

Fig. 5 Brain renderings from the group random effects analysis, demonstrating areas of activation (threshold $Z = 2.33$, $P < 0.01$) associated with the four stimulus classes. The right IPC ($x = 50$, $y = 2$, $z = 30$) is most activated for pattern encoding. Faces and scenes activate a common, smaller area within the same region ($x = 50$, $y = 6$, $z = 34$). Word novelty results in activation of a homologous region on the left ($x = -50$, $y = -12$, $z = 42$).

in bilateral prefrontal activation, but the degree of asymmetry varied with the task. Random effects analysis of the novel versus repeat condition was performed to detect consistent areas of activation across the group and the inference for healthy populations (Fig. 5). Pattern encoding elicited a very large area of activation over the right frontal region, with smaller areas of activation in the cingulum bilaterally and in the right parietal, left parietal and left frontal lobes. Faces and scenes produced a common area of activation within the right inferior frontal gyrus—a subset of the right frontal activation seen for pattern encoding. There were also smaller activations in the anterior cingulate bilaterally and over the

left sylvian fissure. By contrast, the word task produced a large left frontal activation extending over the inferior frontal gyrus and the middle frontal gyrus. There were smaller clusters of activation in the cingulum bilaterally (left greater than right) and in the right prefrontal cortex.

Frontal ROI. Of the BA areas investigated (BA 6, 9, 10, 44 and 45), BA 6 had suprathreshold voxels in all subjects across all materials for the novel minus repeat condition, whereas the other BA regions had suprathreshold voxels in only scattered measurements. Further analysis was therefore confined to BA 6 (Fig. 4B). Repeated measures ANOVA of
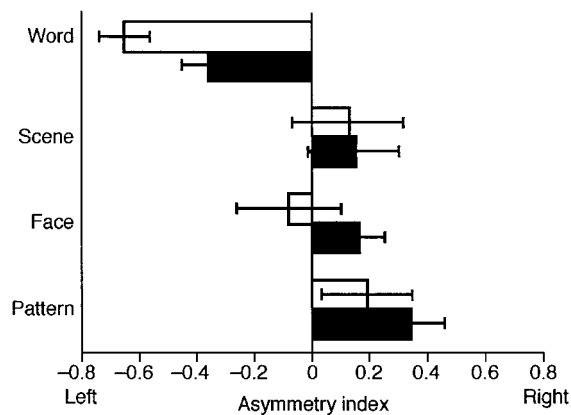
Fig. 6 Graph of asymmetry scores [(right − left)/(right + left) (±standard error of the mean)] for the MTL and BA 6, demonstrating left-sided asymmetry for word-encoding, symmetrical activation for face and scene encoding and right-sided asymmetry for pattern encoding. White = BA 6; black = MTL.

the voxel counts from the BA 6 ROI demonstrated a significant effect of item type [$F(3,21) = 4.67, P < 0.02$] as well as for item type × hemisphere [$F(3,21) = 8.38, P < 0.005$]. Within BA 6, the word task resulted in significantly greater activation in the left hemisphere compared with the right [$t(7) = 4.25, P < 0.001$]. The pattern task resulted in greater right-sided activation compared with the left [$t(7) = 1.86, P = 0.05$]. There was no significant hemispheric difference for face or scene novelty.

Correlation between frontal and MTL regions. Asymmetry indices for each task in both the MTL and BA 6 confirmed the laterality effects discussed above (Fig. 6). The median within-subject correlation of frontal and MTL asymmetry indices across the four tasks was 0.68 [$t(7) = 3.87, P < 0.01$].

Discussion
In the present study, material type influenced the lateralization of memory-encoding processes in the frontal and MTL regions. We examined the encoding of four types of stimuli (words, faces, scenes and patterns) in order to vary the relative verbal and non-verbal nature of the stimuli. A dual interference behavioural study allowed us to rank the relative verbalizabilities of the non-verbal stimuli (scenes > faces > patterns). During encoding, operationalized as the reduction in activation for repeated processing of stimuli, lateralization varied as a consequence of material. Recognition memory for all four stimulus types was approximately equivalent. Encoding verbal materials (words) resulted in predominantly left-lateralized activation in both frontal and MTL regions. Encoding stimuli (faces and scenes) that were intermediate in verbalizability resulted in approximately symmetrical activation. Encoding the least verbalizable stimuli (patterns)

resulted in the most right-lateralized activation. These material-dependent asymmetries were seen in virtually all subjects as well as across the group. The encoding activations are better characterized as asymmetrical rather than unilateral, because even the most lateralized activation for words and patterns included activation in the contralateral hemisphere.

We also found a correlation between the frontal and MTL asymmetry indices in individual subjects. Thus, the degree to which a subject had lateralized activation for a task in one region predicted the degree to which that subject had lateralized activation in the other region. This suggests that the material specificity of each MTL derives from ipsilateral neocortical projections from that hemisphere. Support for this hypothesis comes from neuroanatomical studies in humans and animals which have demonstrated reciprocal connections between the structures of the MTL and ipsilateral cortical regions including the prefrontal cortex (for review, see Thierry *et al.*, 2000).

This study differs from others (except Kirchhoff *et al.*, 2000) that have investigated the effect of material on the lateralization of encoding by using a novelty paradigm. We contrasted novel with repeated blocks of the same type of stimuli rather than comparison with a low-level baseline (Martin *et al.*, 1997; Kelley *et al.*, 1998) or direct comparison between material types (Wagner *et al.*, 1998*a*). The use of a novelty paradigm in this study allowed us to hold material type and task constant across each scan. That material-dependent asymmetries are present in this type of comparison indicates that the lateralization is not due to low-level responses to the stimuli. Evidence that activity seen in novelty-encoding paradigms is related to the creation of a memory trace comes from event-related fMRI studies in which the magnitude of activation in the parahippocampal region and lateralized frontal regions predicted how well words (Wagner *et al.*, 1998*b*) and pictures (Brewer *et al.*, 1998) would subsequently be remembered. Kirchhoff and colleagues found that, in the same prefrontal and temporal regions modulated by novelty, the magnitude of encoding activation also predicted subsequent memory (Kirchhoff *et al.*, 2000). Thus, at least four different strategies for measuring encoding activation (low-level baseline, comparison between materials, novelty and subsequent memory) converge on the conclusion that encoding activations are lateralized according to material.

In the present study, participants performed a different, specific task for each stimulus type. Tasks were chosen to be particularly relevant to each type of stimulus (e.g. gender judgements for faces). This approach had the advantage of controlling the strategies that participants used during encoding. It also means, however, that both materials and tasks differed across scans. One consequence of this was that task difficulty and the magnitude of the repetition effect varied across materials. Differences in the RTs indicate that the sentence generation task used for the words and the symmetry judgement used for the patterns were more difficult than the gender discrimination tasks used for the faces and

the indoor/outdoor judgements used for the scenes. This difference in difficulty may explain in part the smaller frontal activations seen for face- and scene-encoding relative to pattern- and word-encoding in the group analysis. However, of the four material types, the scenes yielded the greatest activation within the MTL region. This activation was strongly bilateral, and may have been due to scene-specific activation within the parahippocampal place area (Epstein and Kanwisher, 1998). In the frontal lobe, the greatest asymmetry was seen in the word and pattern novelty, which also had the greatest overall activity. In the MTL region, the greatest asymmetry was still seen in word and pattern novelty, even though these only resulted in mid-level overall activations. Despite the differences in difficulty and in brain activation, the tasks were equally effective in promoting encoding, as demonstrated by the similar subsequent memory for all four material types.

One important concept that emerges from the above is that neither verbalizability nor lateralization is absolute, but rather they exist on a continuum. As demonstrated by the results from the dual interference study, non-verbal stimuli may vary in the extent to which they are amenable to verbal encoding processes. The lateralization of memory-encoding processes has been studied previously using non-verbal stimuli, such as faces and scenes, which may evoke verbal descriptions. Individual subjects may be using different strategies when encoding these intermediately verbalizable stimuli. In support of this view, whereas individual subjects had varied lateralization for the face and scene tasks, the random effects analysis yielded only a small common area of activation within the right IPC. Activations which emerge in a random effects analysis probably reflect common processing strategies across subjects. The same analysis yielded highly lateralized activations in response to words and patterns, indicating that these stimuli are closer to the ends of the verbalizability spectrum. Altogether, these results suggest that the degree of flexibility or variation in the way in which lateralized processes are used in encoding is greater for scenes or faces than for words or patterns.

Our results add to the neuropsychological, lesion and functional imaging data that imply specialization of the dominant and non-dominant MTL structures for verbal and non-verbal encoding processes, respectively. Using a variety of encoding paradigms, fMRI and PET studies have shown left-sided activation during word encoding (Binder *et al.*, 1996*a*; Kirchhoff *et al.*, 2000), bilateral activation during scene-encoding (Gabrieli *et al.*, 1997; Kirchhoff *et al.*, 2000), and varied lateralization of activity during face-encoding (Grady *et al.*, 1995; Kapur *et al.*, 1995; Haxby *et al.*, 1996). Pattern-encoding activation in the MTL has not been studied previously. Two studies have investigated systematically the material-specificity of the MTL. Martin and colleagues found that the left MTL responded more strongly to meaningful than to nonsense stimuli, but responded equally to words and objects (Martin *et al.*, 1997). In contrast, the right MTL responded more strongly to objects than to words, but did

not vary in response to word meaningfulness. These results can be viewed as compatible with material-specific lateralization in the MTL. Meaningful stimuli have semantic content and therefore lend themselves readily to verbal encoding strategies compared with nonsense stimuli. Kelley and colleagues used three types of stimuli (words, nameable objects and faces) to investigate specifically the lateralization of memory processing in relation to stimulus type (Kelley *et al.*, 1998). During intentional (but not incidental) encoding, words activated the left MTL, objects activated the MTL bilaterally and symmetrically, and faces preferentially activated the right MTL. The left MTL was engaged by all three materials, suggesting that verbal encoding strategies are being used with all these stimuli.

Neuropsychological studies in patients with unilateral frontal lesions suggest that the frontal lobe plays multiple supporting roles in the establishment of a complete memory trace and that there is at least one functional division into verbal and non-verbal hemispheres (Milner, 1982). However, a large body of imaging studies suggests that hemispheric lateralization depends not on the content of the material but on whether encoding or retrieval is being performed. The HERA framework postulates that the left prefrontal cortex is involved in encoding, whereas the right prefrontal cortex is involved in memory retrieval (Tulving *et al.*, 1994). These results appear to be at odds with observations from lesion studies and with the present study. However, when comparing encoding directly with retrieval using the same class of stimuli, it is possible that the laterality effect due to stimulus type may not be apparent because it is present in both conditions (for examples of stimulus comparisons, see review by Nyberg *et al.*, 1996*a*).

Several studies have addressed the question of material-specificity in the frontal cortex by comparing encoding activations across various stimuli. Kelly and colleagues directly compared encoding of different types of stimuli (words, nameable objects and faces) and found a laterality effect of content in the IPC (Kelley *et al.*, 1998). However, faces produced strongly right-lateralized prefrontal activity in Kelley's study, but only weakly lateralized activity in the present study. Other studies have reported both right and left (Haxby *et al.*, 1996) activity during face-encoding. Encoding strategies for faces may depend on the exposure to the stimulus; shorter times may encourage non-verbal representations while longer exposures may allow verbal representations. In a study of working memory for faces, Haxby and colleagues demonstrated a shift in frontal activation from right to left as the delay between study and test was increased (Haxby *et al.*, 1995). The present study used a relatively long stimulus presentation time that may have allowed some verbal encoding. The variable lateralization found during face encoding and the bilateral activation associated with scene-encoding emphasizes that these stimuli are not strictly non-verbal, but may be amenable to verbal codes. Although it is difficult to control strategies employed by subjects when encoding into memory, the

patterns used in our study are less vulnerable to verbal interference, suggesting that subjects may be less likely to use verbal strategies to encode them. Wagner and colleagues found asymmetrical activation in the IPC when directly comparing words and patterns during both encoding and retrieval (Wagner *et al.*, 1998*a*). McDermott and colleagues found that words produced predominantly left-sided activation and faces produced predominantly right-sided activation during both encoding and retrieval (McDermott *et al.*, 1999). Thus, material-dependent prefrontal asymmetries have been found in a comparison with a low-level baseline, direct comparison between material types and, in the present study, in response to novelty within material types.

Functional MRI has the potential to offer more precise localization of cognitive processes than lesion studies or PET and may, thereby, allow the integration of data that support material-specificity of the prefrontal cortex with the HERA hypothesis. Our results add to the impression from other functional imaging studies that specific regions within the prefrontal cortex are material-invariant while others appear to be material-sensitive (for review, see Wagner, 1999). The present study found material-specific activations within the posterior IPC (BA 44/6), an area which appears to support working memory access, maintenance and evaluation in a material-specific fashion. The posterior left IPC is preferentially engaged by verbal materials, whereas the posterior right IPC is preferentially engaged by visuospatial materials (Wagner *et al.*, 1998*a*). The more anterior left IPC (BA 45/47), which was activated during encoding studies that supported the HERA hypothesis (Tulving *et al.*, 1994; Kapur *et al.*, 1996; Nyberg *et al.*, 1996*b*), was not activated in the present study. It is hypothesized that this region is activated by tasks that require controlled semantic processing, thereby providing semantic assistance to encoding processes (including the encoding of many non-verbal stimuli that are amenable to verbal encoding strategies) (Poldrack *et al.*, 1999). Within a given material type in the present study, similar reliance on phonological and semantic resources was probably required during novel and repeated presentations, resulting in any activations in this area being subtracted out during the novelty comparison. Nevertheless, differential activation was seen in more posterior areas during the novelty comparison. Overall, our results indicate that some regions within the frontal lobe participate in encoding processes with material-specific lateralization.

Many brain structures and psychological processes are involved during memory encoding. fMRI is a promising technique for the non-invasive investigation of functional anatomy in healthy and clinical populations. Already, there is evidence that fMRI can be used to determine language lateralization and that results are consistent with those obtained with the Wada test (Desmond *et al.*, 1995; Binder *et al.*, 1996*b*). Better understanding of the determinants of hemispheric lateralization of memory processes in healthy subjects is an important step in understanding how these structures subserve memory functions. Paradigms similar to that used in the present study may allow preoperative assessment of the competence of each MTL in supporting material-specific memory processes. Specifically, the present study suggests that the encoding of patterns, relative to faces or scenes, may offer a more selective method for identifying neural systems mediating non-verbal memory. Such knowledge could aid in localizing eloquent brain areas, predicting the laterality of seizure focus and preventing postoperative deficits.

Acknowledgements

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