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Memory Lateralization in Medial Temporal Lobe Epilepsy Assessed by Functional MRI

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Summary: *Purpose:* To determine the utility of functional magnetic resonance imaging (fMRI) in preoperative lateralization of memory function in patients with medial temporal lobe epilepsy (MTLE).

Methods: Nine patients with MTLE underwent standard preoperative assessment including video-EEG and intracarotid amytal testing (IAT). fMRI was performed while subjects encoded four types of stimuli (patterns, faces, scenes, and words). Activation maps were created for each subject representing areas more active for novel than for repeated stimuli. Regions of interest were drawn around the MTL in individual subjects, suprathreshold voxels were counted, and an asymmetry index was calculated.

Results: In eight of nine subjects, lateralization of memory encoding by fMRI was concordant with that obtained from the IAT. Group-level analysis demonstrated greater activation in the MTL contralateral to the seizure focus such that in the left MTLE group, verbal encoding engaged the right MTL, whereas in the right MTLE group, nonverbal encoding engaged the left MTL.

Conclusions: fMRI is a valid tool for assessing of memory lateralization in patients with MTLE and may therefore allow noninvasive preoperative evaluation of memory lateralization. FMRI revealed that memory encoding may be reorganized to the contralateral MTL in patients with MTLE. **Key Words:** Epilepsy—Medial temporal lobe—fMRI—Memory.

Epilepsy surgery is an important tool for the treatment of patients with medically refractory seizures and is particularly effective in patients with medial temporal lobe epilepsy (MTLE). These patients have frequent complex partial seizures originating from a sclerosed hippocampus. In well-selected patients, temporal lobectomy with resection of the mesial structures can significantly reduce or eliminate seizures in up to 90% of patients (1–3). The challenge in epilepsy surgery is to remove the seizure focus completely without causing significant postoperative neurologic deficits; this requires an understanding of the underlying functional anatomy. Patients with longstanding epilepsy may have variable anatomic localization of neurologic functions, such as memory, because of cerebral reorganization induced by the disease process. Understanding this functional anatomy is vital when planning surgical resections and relies on complex preoperative evaluations.

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MEMORY IN MEDIAL TEMPORAL LOBE EPILEPSY

Patients with MTLE may have memory deficits related to dysfunction of the involved MTL. The MTL memory system is essential to declarative memory processes underlying memory for new events and facts (4). This system consists of the hippocampal region (subiculum, CA fields, and dentate gyrus) and the parahippocampal region (parahippocampal and perirhinal cortices), which provides the major inputs to the hippocampal region (5). Lesion studies indicate that left and right temporomesial structures are essential for verbal and visuospatial memory, respectively (6,7). Concordantly, patients with dominant medial temporal sclerosis (MTS) have abnormalities of verbal memory (7–10), whereas those with nondominant foci may have deficits of visuospatial memory (11), although this is less well established (12). These material-specific memory deficits may be more reliable indicators of the laterality of the seizure focus than are differences between performance and verbal IQ (13).

Despite careful preoperative evaluation, preexisting memory deficits may worsen, or new deficits may appear

after surgical resection. Patients with the least hippocampal damage ipsilateral to the seizure focus [by pathologic or magnetic resonance imaging (MRI) volume criteria] have the least memory impairment preoperatively, but have the greatest decrement in postoperative memory function (14,15). Conversely, those with the worst MTS are more impaired at baseline, but have little worsening of memory after surgery, and in some cases may even improve (15). The first finding suggests that if hippocampal damage is limited (in the anterior/posterior extent), other ipsilateral MTL areas may be able to compensate. The latter finding implies that the contralateral MTL or other regions are able to assume memory functions normally performed by the diseased MTL in cases in which the damage is sufficiently extensive and prolonged.

Currently, localization of memory and language functions in epilepsy patients involves invasive procedures: the intracarotid amytal (IAT or Wada) test and intracranial monitoring with implanted electrodes. The IAT was originally developed as a test of language dominance, but is commonly used to assess memory function as well. This test is limited in its ability to distinguish material-specific (i.e., verbal or visuospatial) memory deficits, and its use is restricted to trying to predict and avoid global amnesia in patients who cannot support memory with the contralateral MTL because of unsuspected damage (16). The reliability of the IAT in predicting postoperative memory deficits has been questioned both on anatomic grounds (in most people, the MTL is perfused by the posterior cerebral artery and not by the internal carotid artery) and on clinical outcomes (17,18). Other limitations of the IAT include insufficient time for detailed testing and poor spatial resolution, as the entire hemisphere is anesthetized during the test. At most, laterality of general language and memory functions can be determined.

FUNCTIONAL IMAGING STUDIES

Functional MRI (fMRI) localizes neural activity by measuring its correlate, regional cerebral blood oxygenation. When brain regions are activated, vasodilatation of capillaries and venules occurs. This results in a relative increase in the ratio of oxygenated to deoxygenated hemoglobin due to blood flow oversupply relative to increased neuronal utilization of oxygen (19). Because of the different magnetic properties of deoxyhemoglobin (paramagnetic) and oxyhemoglobin (diamagnetic), it is possible to measure these changes as alterations in blood oxygen level–dependent (BOLD) signal intensity on T_{2*}-weighted images (20,21). Voxels whose signal intensity varies with the timing of stimulus presentation (with appropriate hemodynamic delay) represent activation by the task (22,23). This information may then be overlaid on anatomic images to form functional maps. fMRI has spatial and temporal resolution far in excess of Wada or positron emission tomography (PET), particularly with high field strengths (24). Moreover, fMRI is noninvasive and readily repeatable, in contrast to cortical stimulation testing. Patients can be studied sequentially, allowing the impact of surgery or other intervention to be assessed. There is already some evidence that fMRI provides valid lateralization for language dominance in patients with epilepsy (25,26). Equally valuable would be the use of fMRI to determine memory dominance and lateralization of verbal and nonverbal memory processes.

A major difference between fMRI studies and the IAT and cortical electrode testing is that fMRI, like PET, is a test of activation during certain tasks, whereas the latter are based on performance failure during brain inactivation. Inactivation tests are the standard method for presurgical planning, as they are thought to mimic the effects of surgical resection. Therefore fMRI must be validated against the gold standard of the IAT and invasive cortical mapping. Advantages of fMRI include the ability to study patients repeatedly as necessary to determine hippocampal competency adequately. In addition, unlike the IAT, there are no strict time limitations, allowing detailed testing of specific components of memory such as task specificity.

We previously studied the lateralization of memory-encoding processes in healthy patients with fMRI (27). Brain regions were identified as being involved in encoding experiences into long-term memory if they were more active for novel stimuli than for repeated, highly familiar stimuli. Presumably, greater encoding is required for learning novel information than for re-encoding of known information. Such novelty encoding paradigms have revealed MTL and prefrontal activation during encoding (28–31). By using the same paradigm as in the present study, we showed that verbal memory encoding preferentially engages the left MTL, and nonverbal encoding preferentially engages the right MTL. In the present study, we hypothesized that patients with MTLE would have decreased activation within the affected MTL and that fMRI would demonstrate reorganization of memory-associated activation to the contralateral MTL. These predictions converge on the possibility of using fMRI as a noninvasive tool in the preoperative assessment of patients with MTLE. In addition, fMRI may allow more accurate prediction of postoperative memory deficits than is presently possible.

PATIENTS AND METHODS

Subjects

Thirteen consecutive patients undergoing preoperative evaluation for MTL resection were invited to participate

in the study. Two subjects declined participation. One subject was dropped from the study because of excessive motion during the scan (>2 mm). A second subject was dropped from the study because of scanner malfunction. Demographic data on the remaining nine subjects are presented in Table 1. Informed consent was obtained from each subject in accordance with guidelines approved by human subject's committee of Stanford University and the Declaration of Helsinki (1991). Determination of the side of the seizure focus was made according to standard protocol on the basis of all available data excluding fMRI (video-EEG, neurologic examination, structural MRI, neuropsychologic testing, IAT) by the members of the Comprehensive Epilepsy Center at Stanford University Medical Center.

Intracarotid amytal testing

IAT was performed in the standard fashion. Sodium amytal (125 mg in 5 ml saline) was injected at ~1 ml/s into the internal carotid artery via a transfemoral approach. The side ipsilateral to the suspected seizure focus was injected first. Hemispheric language dominance was assessed by the presence or absence of paraphasia, speech arrest, and errors in naming, repetition, reading, and comprehension of aural commands. Hemispheric memory dominance was assessed by presenting the patient with nine items (three designs, three nameable objects, and three words). After the neurologic examination and EEG had returned to baseline, a recognition memory test was administered. The nine previously presented items were presented again with 18 foils. A memory score (correct identifications – false alarms/2) was calculated. Maximal score is 3 for each item type. An asymmetry index was calculated (memory score using left hemisphere – using right hemisphere).

Functional MRI

Stimulus presentation and response collection

Stimuli were presented visually using a magnet-compatible back-projector (Resonance Technology, Inc., Van Nuys, CA, U.S.A.). A Macintosh computer with PsyScope (32) software generated visual stimuli and controlled experimental parameters. A custom finger-switch response system was used for acquisition of responses and reaction times.

Task design

Four types of stimuli (patterns, faces, scenes, and words) were presented to each subject in separate scans. Before 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 3,500 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). Orders of stimulus type (pattern/face/scene/word) and novelty (old/new) were counterbalanced across subjects. Each class of stimuli had an associated task, detailed below. Responses were made by button push.

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

Face: Color photographs of male and female faces were presented by using the same stimulus paradigm. Half the subjects were instructed to respond to male faces, and half, to female faces.

TABLE 1. *Subject Demographic Data*

Subject	Age/ gender	Handedness	Age at Sz onset	MRI	ROI volumes		Neuropsych			IAT language lateralization	IAT memory lateralization	fMRI memory lateralization
					L	R	PIQ	TIQ	VIQ			
1	33/F	R	8 mos	LMTL hyperintense	3434	4372	104	94	88	L	R > L	R > L
2	26/F	R	18 mos	LMTL hyperintense	4498	4052	84	76	74	L	R > L	R > L
3	33/F	R	7 mos	LMTL hyperintense	3833	3678	80	78	79	R	R > L	R > L
4	27/F	L	18 mos	LMTL hyperintense	3399	4039	N/A	N/A	N/A	L	R > L	R > L
5	42/M	R	31 yrs	R MTLA, hyperintense	3890	3036	77	73	73	R	L > R	L > R
6	26/M	R	10 mos	L MTLA	3590	3802	85	87	89	L	R > L	R > L
7	28/F	R	9 yrs	L MTLA, hyperintense	2839	3365	84	85	88	L	R > L	R > L
8	54/F	R	3.5 yrs	RMTA, diffuse atrophy	2599	1858	78	93	107	R	L > R	L > R
9	43/F	R	39 yrs	RMTA	3873	3254	125	118	111	L	L > R	R > L

Note. Sz = seizure, PIQ = performance IQ, TIQ = total IQ, VIQ = verbal IQ, IAT = intracarotid amytal test, fMRI = functional MRI, MTL = medial temporal lobe, MTLA = medial temporal lobe atrophy.

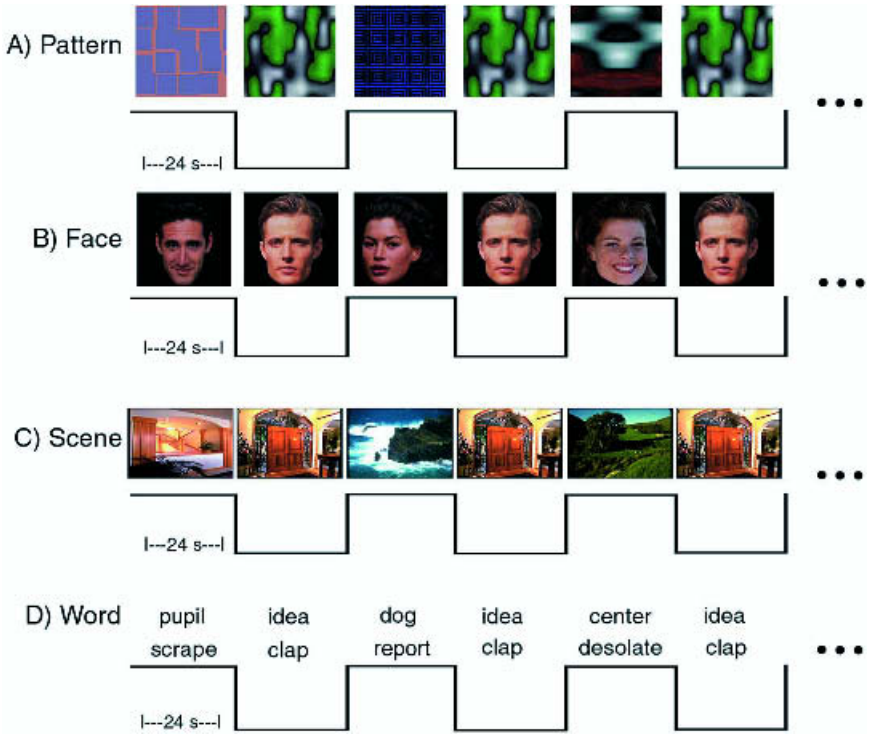

FIG. 1. Experimental design and examples of stimuli: **(A)** patterns, **(B)** faces, **(C)** scenes, and **(D)** words. Each encoding run contrasted blocks of novel and familiar stimuli from one stimulus class.

Scene: Color photographs of indoor and outdoor scenes were presented. Half the subjects were asked to respond to indoor scenes, and half, to outdoor scenes.

Pattern: Color images of abstract patterns were presented. Half the subjects were asked to respond to regular, internally repeating patterns, and half, to irregular, nonrepeating patterns.

After the scanning session, a recognition test was administered. For each type of stimulus, subjects viewed 12 previously presented items and 12 foils. Responses ("new," "old") were collected by button push. The memory tests were administered in the same order as the encoding tasks for each individual subject, and order was thus counterbalanced across subjects.

Data acquisition

The first five participants were scanned with a 1.5-T Signa MRI system, and the last four subjects by using a 3-T Signa LX Horizon Echospeed MRI system when it became available (both General Electric, Milwaukee, WI, U.S.A.). A prototype birdcage head coil was used, and foam padding around the head was used to minimize movement.

Functional scans

1.5 T: Whole-brain functional imaging was performed using a single-interleave gradient-echo spiral pulse sequence (33), imaging 29 contiguous coronal slices perpendicular to the anterior commissure–posterior commissure line (6 mm thickness) at 3 s per image volume. In-plane spatial resolution was 3.75 mm; TR = 3,000 ms; TE = 40 ms; 89° flip angle; 24-cm field of view; 64 × 64 matrix acquisition.

3.0 T: Acquisition was as described, except that images were acquired at 2 s per image volume with a flip angle of 68°.

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 before functional imaging and to correlate functional activation with anatomic structures. A three-dimensional spoiled gradient recalled (SPGR) volumetric scan was acquired for Talairach registration and reslicing along different planes.

Data analysis

After image reconstruction, motion correction in three dimensions and spatial smoothing with an 8-mm gaussian kernel were performed by using SPM99 (Wellcome Department of Cognitive Neurology, London, U.K.).

Statistical analysis was performed with SPM99. Analysis was first performed individually for each subject. Differences between stimulus conditions were examined by using the general linear model, modeling stimulus-related activation as a delayed boxcar function and treating low-frequency signal components as nuisance covariates. Differences in global signal intensity were corrected by using proportional scaling to a common mean. This analysis identified for each subject those regions that were significantly more active for novel than for repeated stimuli, and these individual statistical maps

were then subjected to region-of-interest (ROI) analyses (outlined later).

Group analysis was performed by first spatially normalizing the contrast images obtained from the individual analysis into a common stereotactic space (34) on the basis of the high-resolution volume images. Normalization allows comparison of common regions across multiple subjects and scanning sessions. The normalized contrast images were then analyzed for each of the two groups of subjects (RMTLE and LMTLE). A mixed-effects general linear model, treating subjects as a random effect and conditions as a fixed effect, allowed population inference. Resulting group images were thresholded at $p < 0.01$.

Medial temporal lobe region of interest

Further analysis of ROIs was performed with custom software in Interactive Data Language (35). The MTL region was identified visually and outlined bilaterally on each subject's coronal slices from the amygdala to the atrium of the ventricles. Hippocampal gyrus, parahippocampal gyrus, entorhinal cortex, and subiculum were included, as described by Amaral and Insausti (36). The proportion of voxels within each region reaching a voxel threshold of $Z = 1.96$ was counted, and an index of asymmetry calculated [(left – right)/(left + right)].

RESULTS

Behavioral data

Accuracy and reaction times (RTs) were not available for one subject because of button-box malfunction. Subjects accurately performed the encoding tasks as demonstrated by average accuracy across tasks of 0.89. Mean RT was analyzed with a 4 (stimulus type) × 2 (novelty) repeated measures analysis of variance (ANOVA; Table 2). Reaction time differed across the different classes of stimuli (significant main effect of stimulus type [$F(3, 15) = 6.1$; $p < 0.025$]. The face-discrimination task was performed faster than the scene task [$T(7) = 3.23$; $p < 0.02$], which in turn was performed faster than the pattern task [$T(8) = 4.79$; $p < 0.005$]. The pattern and word tasks did not differ significantly [$T(6) = 0.39$; $p > 0.05$]. Subjects were faster on repeated presentations of stimuli than on novel presentations [main effect of novelty, $F(1, 5) = 16.3$; $p = 0.01$]. The Item type × Novelty interaction also was significant [$F(3, 15) = 6.2$; $p < 0.01$], reflecting a greater novelty effect for words than for patterns [$T(6) = 2.95$; $p < 0.05$], but patterns, scenes, and faces did not differ reliably in RT differences between novel and repeated items. Recognition memory was analyzed in terms of correct hits (CHs) 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 [$F(3, 18) = 1.97$; $p > 0.05$] or by laterality of seizure focus [$F(1, 6) = 0.12$; $p > 0.05$].

In comparison to the healthy subjects from our previous study (27), the MTLE patients performed the decision tasks more slowly [main effect of group, $F(1, 10) = 25.3$; $p < 0.001$]. The Novelty × Disease state interaction was not significant [$F(1, 10) = 1.2$; $p > 0.05$], indicating that both groups processed the repeated stimuli more quickly than the novel stimuli. Subsequent memory for the stimuli was poorer in the MTLE patients than in the healthy subjects [$F(1, 14) = 18.8$; $p < 0.001$].

IAT results

IAT revealed memory dominance lateralized away from the side of the suspected seizure focus in all subjects (Fig. 2). Subject 4, believed to have left MTLE, became agitated and uncooperative during the right-side injection, precluding memory testing. During the left injection, however, she was able to identify 73% of the items correctly. Therefore a quantitative comparison of left- and right-hemisphere memory function was not possible, but the physicians interpreting her examination thought that memory was most likely supported by the right MTL. This is indicated by a dashed bar on the figure. Subject 5 became unresponsive during both injections of the IAT because of cross filling. He subsequently underwent supraselective Wada testing, injecting the right (side of the suspected seizure focus) posterior cerebral artery. With the left hemisphere, he had a corrected score of 4 of 9 and was therefore thought to support memory adequately with the left MTL.

TABLE 2. *Reaction Times and Recognition Memory for Stimuli*

Task		Stimulus type			
		Face	Scene	Pattern	Word
Reaction Time ± SE (ms)					
	Novel	1057 ± 113	1414 ± 25	1976 ± 132	2364 ± 265
	Repeat	995 ± 118	1294 ± 29	1606 ± 169	1335 ± 185
CH ± SE (%)	LMTLE	0.13 ± 0.06	0.30 ± 0.15	0.25 ± 0.10	0.28 ± 0.09
	RMTLE	0.08 ± 0.09	0.32 ± 0.26	0.36 ± 0.10	0.36 ± 0.06

Note. CH = corrected hits, LMTLE = left medial temporal lobe epilepsy, RMTLE = right medial temporal lobe epilepsy.

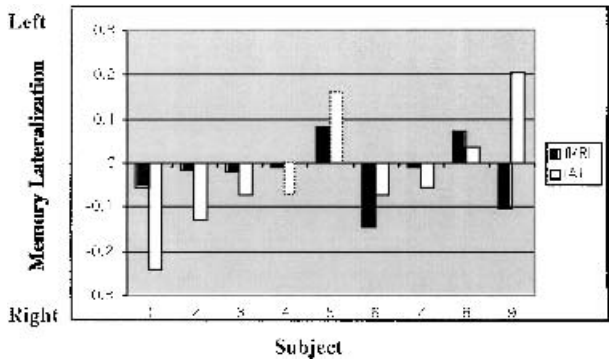

FIG. 2. Relative memory-lateralization indices for intracarotid amytal testing and functional magnetic resonance imaging. Concordant lateralization is seen for eight of nine subjects. An asymmetry index for the intracarotid amytal test (IAT) could not be calculated for subjects 4 and 5 (see text); however, interpretation of the IAT yielded right and left memory dominance, respectively.

Imaging results

Individual analyses

All subjects demonstrated activation in response to the novel versus repeated condition. Activations were seen in the MTL region including hippocampus proper, parahippocampal gyrus, and entorhinal cortex. Additional activations were observed in the prefrontal cortex, primary visual and visual association cortices, fusiform gyrus, and cerebellum. Memory lateralization, as determined by the asymmetry between the proportion of activated voxels on each side, was concordant with the results obtained by IAT in eight of nine subjects (Fig. 2). The patients with LMTLE had relatively greater right-sided novelty-associated MTL activation across tasks, whereas the RMTLE patients had relatively greater left MTL activation. Subject 9 showed discordance between results from the IAT and fMRI. Structural MRI and EEG suggested that the right MTL was sclerotic and the focus of the seizures, but fMRI suggested that the right MTL was more active than the left during memory encoding. However, this patient is unusual in that her onset of seizures was not until age 39 years. In addition, her neuropsychological testing showed superior performance IQ relative to verbal IQ, a result that is not congruent with the other data and complicates the assessment of hemispheric competency.

Figure 3 shows MTL activation from a representative subject with LMTLE, one with RMTLE, and for comparison, two healthy subjects from our previous study. The RMTLE patient (subject 5) demonstrated relatively greater left-sided activation, notably for the pattern task, which is normally the most right lateralized, and for the face task. In this patient who, paradoxically, had language lateralized to the right hemisphere by IAT, word novelty-associated activation was bilateral, greater on the right. The LMTLE patient (subject 2) demonstrated relatively greater right-sided activation within the MTL region. During word novelty, which in healthy subjects is strongly left lateralized, this patient showed bilateral activation.

Group analysis

The random-effects analysis of the data from each group (RMTLE and LMTLE) demonstrated evidence of reorganization of memory function. Figure 4 shows SPM activation maps using a random effects analysis. Areas more active ($p < 0.01$) for novel than for repeated presentations for each of the four stimulus types differed

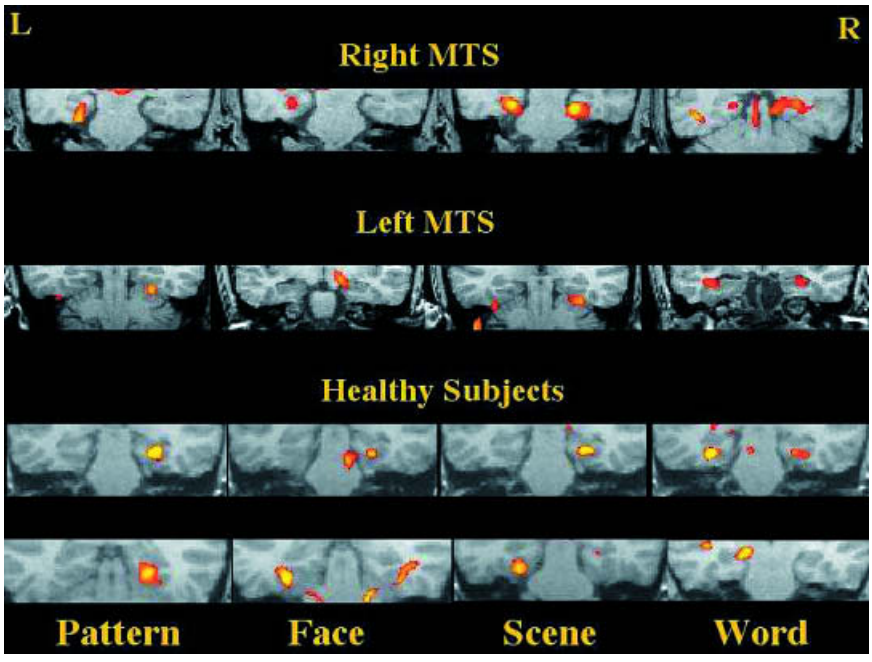

FIG. 3. Statistical activation maps from a patient with right medial temporal lobe epilepsy (MTLE), one with left MTLE, and two healthy subjects demonstrate areas of activation within the medial temporal lobe region of interest (height threshold, $Z = 1.96$; $p < 0.025$; corrected for multiple comparisons at the 0.05 level). The RMTLE patient demonstrates relative leftward displacement of MTL encoding activation for pattern and face encoding and bilateral activation for scene encoding. This patient had paradoxically right-lateralized language by IAT and demonstrated bilateral MTL activation greater on the right. The LMTLE patient has right-sided activation for all nonverbal encoding and bilateral activation during word encoding. Two healthy subjects are shown for comparison, demonstrating the normal lateralization of encoding activations: patterns highly right lateralized, faces and scenes variably lateralized, and words strongly left lateralized.

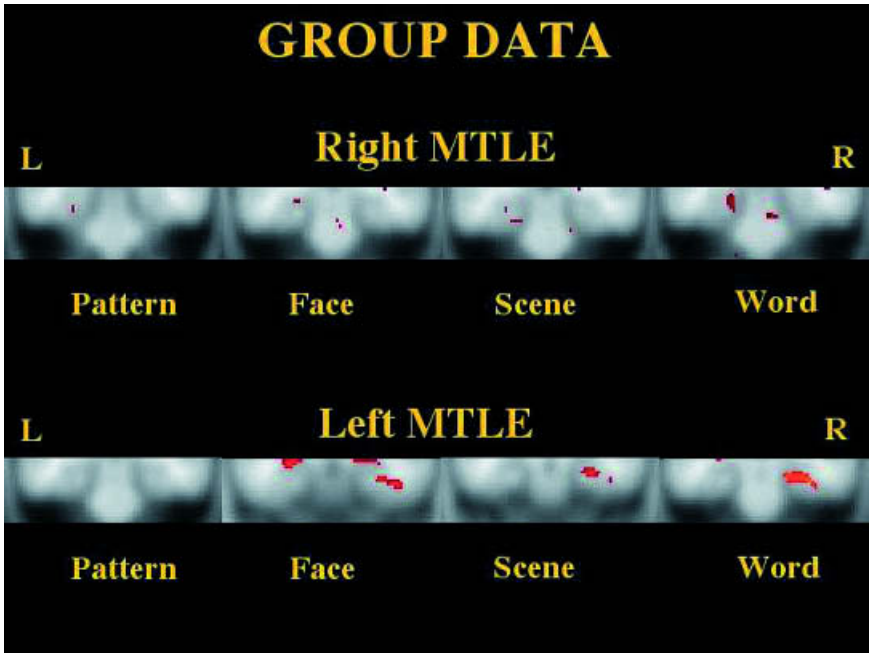

FIG. 4. Random-effects analysis of right medial temporal lobe epilepsy (MTLE) group demonstrates left-side only MTL activation during encoding. Activation associated with pattern encoding, normally the most right-lateralized, demonstrates a small region of left-sided activation within the MTL and no right-sided activation. Left MTLE group demonstrates right-side only activation during encoding. Note that word encoding, normally left lateralized, is associated with right-sided activation in the MTL (threshold $p < 0.01$).

between the two patient groups. For RMTLE patients, pattern novelty elicited a small area of activation within the left MTL but no activation within the right MTL. For LMTLE patients, word novelty produced a large cluster of activation within the right MTL, but no activation within the left MTL. Across all four tasks, the group analysis showed generally right-sided activation for the LMTLE patients and left-sided activation for the RMTLE patients.

Volumetric analysis

The ROI analysis provided an additional measure of structural atrophy, which was used to compute a structural lateralization index in a manner analogous to the fMRI and IAT data. This analysis revealed that in seven of nine subjects, the ipsilateral MTL was relatively smaller; however, in two subjects, this structural measure of disease severity was discordant with both of the functional measures. In the patient with discordant fMRI data, the atrophy score correlated with the IAT result rather than with the fMRI result.

DISCUSSION

In this study we used fMRI to study the lateralization of memory-encoding processes within the MTL in patients with MTLE. The major findings of this study are that the side of the epileptic focus within the MTL influences the lateralization of encoding-associated activations within the MTL, and that this asymmetry is concordant with results from the IAT. Furthermore, our results suggest that there is reorganization of memory encoding to the contralateral MTL region.

This study used a robust behavioral paradigm that we have previously used to examine the lateralization of memory-encoding processes in healthy subjects (27). We examined encoding of four types of stimuli (words, faces, scenes, and patterns) to vary the relative verbal and nonverbal nature of the stimuli. Patients with MTLE encoded these stimuli in a novelty paradigm contrasting blocks of novel stimuli with blocks of repeated stimuli. The hippocampal region has been shown in several functional neuroimaging studies to be activated by novel relative to repeated stimuli (28,30,38,39). Therefore we chose this paradigm as it is relatively straightforward for patients to perform, while providing a high-level baseline that minimizes activations due to perceptual rather than encoding processes. Subjects were able to perform the tasks with good overall accuracy, and their recognition memory after the test was above chance. It is important when studying neurologically impaired subjects that they be able to perform the task adequately, as otherwise, it is not possible to discern whether a lack of activation stems from changes in the neural substrate, or because the subject was simply not performing the task.

With this paradigm, asymmetries of activation in the MTL were demonstrated and were found to agree with memory asymmetries found by IAT. Eight of nine subjects showed greater encoding-associated activation in the MTL on the side that supported memory better during the IAT. However, the ninth subject showed activation that did not agree with the results of the IAT. Therefore there is not complete concordance of results from these two modalities. The IAT remains the gold standard for preoperative memory testing, but there are questions regarding its accuracy in predicting postoperative memory deficits (17,18). A larger study that incor-

porates postoperative neuropsychological outcomes will be necessary to conclude whether fMRI provides equivalent or better prediction of postoperative memory function.

Our data are consistent with the possibility that there is reorganization of memory function to the contralateral MTL. The random-effects analysis, a conservative statistical approach that allows inferences to be made about a population from which the sample is drawn, demonstrated right MTL activation for word encoding by the LMTLE group. The RMTLE group showed left MTL activation for the nonverbal encoding tasks. Neuropsychological studies of patients with MTLE have suggested that there is reorganization of memory function in MTLE. Material-specific memory deficits in patients with MTLE are relatively subtle (40,41), implying that reorganization has allowed other regions to assume some of these functions. Patients with early disease onset and severe MTS have little change in memory function after removal of the epileptogenic MTL (14,15), again suggesting that other regions are subserving these functions. However, it was unknown whether reorganization involved a transference of processing to the contralateral MTL or to ipsilateral neocortical regions. The present study suggests that at least part of the reorganization involves a transference to the contralateral MTL. Another study demonstrated increased left prefrontal activation in patients with LMTLE during episodic memory, suggesting that there also may be intrahemispheric reorganization (42). However, definitive demonstration of reorganization will require longitudinal investigation of changes in functional anatomy associated with longstanding epilepsy.

fMRI is a promising technique for noninvasive investigation of functional anatomy in healthy and clinical populations. Previously fMRI was used in patients with epilepsy to assess language dominance as compared with the Wada test (25,26). Both studies showed that frontal activation during a language task was lateralized to the same side as the IAT language lateralization. Several studies have used fMRI to investigate memory processing in MTLE. Detre et al. (43) compared fMRI with the IAT. By using a scene-encoding task, they found that activation asymmetries in the MTL concurred with the IAT in all cases, including two cases in which memory was paradoxically located ipsilateral to the seizure focus. In another study, Bellgowan et al. (44) reported that MTL activation during a verbal encoding task can differentiate between patients with LMTLE and RMTLE. They found that RMTLE patients had LMTL activation during verbal encoding, but that LMTLE patients did not have LMTL activations. However, these findings were on the group level only and do not allow inferences to be made on an individual-subject basis. Moreover, interpretation of a lack of activation, rather than an altered pattern of activation, can be problematic, as there can be many technical reasons for not finding activations. fMRI also may be useful in predicting postoperative seizure outcome. Killgore et al. (45) found that when combined, fMRI and IAT provided complementary data that resulted in improved prediction of postoperative seizure control compared with either procedure alone. Further studies using this and other paradigms will be necessary to determine whether the functional competency of the MTL can be quantified, and whether this is predictive of postoperative outcome.

fMRI is still principally a research tool and therefore there are not well-established standards regarding its clinical implementation as there are for tests such as the IAT. Differences between centers in scanners and scanning protocols, as well as analysis software and protocols, can all lead to variability in fMRI results. Therefore at this time, it is important that individual centers perform validating trials of the fMRI protocols against the existing gold standard of the IAT.

The decision regarding whether to perform an MTL resection in a given patient with MTLE depends on the preponderance of evidence suggesting the side of seizure onset and the competency of the contralateral side in supporting memory. A risk–benefit analysis examines these data in the context of an individual patient's neurologic and psychosocial function. Given the results of the present study as well as previous reports (43,44) demonstrating the agreement of fMRI assessments of memory dominance with the IAT, it is possible that some patients with good concordance between noninvasive preoperative assessments and fMRI determination of memory dominance may be able to avoid the IAT and its attendant risks and discomfort.

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