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Functional MRI predicts post-surgical memory following temporal lobectomy

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Summary

Temporal lobectomy is an effective therapy for medically refractory temporal lobe epilepsy (TLE), but may be complicated by amnestic syndromes. Therefore, pre-surgical evaluation to assess the risk/benefit ratio for surgery is required. Intracarotid amobarbital testing (IAT) is currently the most widely used method for assessing pre-surgical memory lateralization, but is relatively invasive. Over the past decade functional MRI (fMRI) has been shown to correlate with IAT for language lateralization, and also for memory lateralization in a small number of patients. This study was carried out to compare fMRI during memory encoding with IAT testing for memory lateralization, and to assess the predictive value of fMRI during memory encoding for post-surgical memory outcome. Thirty-five patients with refractory TLE undergoing pre-surgical evaluation for temporal lobectomy and 30 normal subjects performed a complex visual scene-encoding task during fMRI scanning at 1.5 T using a 10-min protocol. Encoding performance was evaluated with subsequent recognition testing. Twenty-three patients also completed the same task again outside the scanner, an average of 6.9 months following surgery. A region of interest (ROI) analysis was used to quantify activation within hippocampal and a larger mesial temporal lobe ROI consisting of hippocampus, parahippocampus and fusiform gyrus (HPF) as defined by a published template. Normal subjects showed almost symmetrical activation within these ROI. TLE patients showed greater asymmetry. Asymmetry ratios (ARs) from the HPF ROI correlated significantly with memory lateralization by intracarotid amobarbital testing. HPF ARs also correlated significantly with memory outcome, as determined by a change in scene recognition between pre-surgical and post-surgical trials. When absolute activation within the HPF ROI was considered, a significant inverse correlation between activation ipsilateral to temporal lobectomy and memory outcome was observed, with no significant correlation in the contralateral HPF ROI. Although further technical improvements and prospective clinical validation are required, these results suggest that mesial temporal memory activation detected by fMRI during complex visual scene encoding correlates with post-surgical memory outcome and supports the notion that this approach will ultimately contribute to patient management.

Keywords: functional MRI; episodic memory; temporal lobe epilepsy; temporal lobectomy

Abbreviations: AR = asymmetry ratio; fMRI = functional MRI; H = hippocampus; HPF ROI = hippocampal–parahippocampal–fusiform ROI; H ROI = hippocampal ROI; IAT = intracarotid amobarbital test; mTL = mesial temporal lobe; ROI = region of interest; SPM = statistical parametric map; TL = temporal lobectomy; TLE = temporal lobe epilepsy; TR = repetition time; WMS-III = Wechsler Memory Scale III

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Introduction

Anterior temporal lobectomy (TL) eliminates seizures or improves seizure control in 80–90% of patients (Engel *et al*., 1993), and has been prospectively validated as an effective therapy for medically refractory temporal lobe epilepsy (TLE) (Wiebe *et al*., 2001). However, the hippocampus (H) and adjacent anatomically related mesial

temporal lobe (mTL) structures play a critical role in episodic memory function, defined as the acquisition, temporary storage and retrieval of explicit facts and events (Squire and Zola-Morgan, 1991), and memory deficits have been a major complication of this surgery (Pilcher *et al*., 1993). Assessment of the risk–benefit ratio of TL requires pre-surgical identification of patients who are at greatest risk for post-operative amnesia.

The intracarotid amobarbital test (IAT) is currently the most common method used to assess language and memory lateralization (Milner *et al*., 1962). This technique requires that each hemisphere be individually anaesthetized so that the other hemisphere can be isolated and tested for verbal and visual encoding efficiency. Loring and colleagues found that hemispheric asymmetry scores, defined as the difference in recognition scores after ipsilateral injection versus contralateral injection, were associated with verbal memory decline after left TL (Loring *et al*., 1995). The stronger the encoding performance of the hemisphere ipsilateral to the seizure focus relative to the contralateral hemisphere, the greater the tendency for verbal memory loss after surgery. Similarly, Kneebone and colleagues found that a 'passing' score on the IAT of left TL patients when using the ipsilateral hemisphere for encoding was associated with greater verbal memory decline following surgery compared with a 'failing' score (Kneebone *et al*., 1995). No such correlation was observed for right TL patients regarding visual memory. More recently, Chiaravalloti and Glosser (2001) studied memory outcomes of 70 patients with refractory TLE (right TLE = 42; left TLE = 28) who underwent TL. They found that the IAT memory asymmetry score and verbal memory asymmetry score significantly predicted verbal memory change following surgery. Larger asymmetry scores were associated with smaller declines in memory performance following TL. Furthermore, they found that memory performance using the contralateral, non-epileptic hemisphere was also related to change in post-operative memory performance, while there was no relationship between the memory score when relying primarily on the epileptic hemisphere and post-operative memory performance. No correlations were found between IAT asymmetry scores or asymmetry score for visual–spatial memory and visual–spatial memory score change following surgery.

These data suggest that IAT can predict change in verbal memory following TL. A similar predictive value for visual–spatial memory has been more difficult to demonstrate. Further, mesial temporal structures subserving episodic memory are primarily supplied by the posterior circulation, and are not directly anaesthetized following intracarotid amobarbital administration. Thus, memory performance during IAT may reflect deafferentation of perceptual systems feeding into the mTL rather than effects on mTL structures themselves. Finally, the IAT is an invasive procedure that is difficult to repeat and associated with rare but significant complications. Other techniques that could complement IAT for predicting post-surgical memory function, or even lower the number of patients that need to undergo this invasive procedure, would be desirable.

Over the past decade, functional MRI (fMRI) has been shown to effectively lateralize language function in pre-surgical assessment, providing results comparable to IAT (Binder *et al*., 1996; Gao *et al*., 2001; Rutten *et al*., 2002; Adcock *et al*., 2003; Sabbah *et al*., 2003; Woermann *et al*., 2003). Sabsevitz and colleagues also demonstrated recently that fMRI and IAT had comparable predictive values for post-surgical language function (Sabsevitz *et al*., 2003). A few groups have also begun to assess the utility of fMRI for lateralizing memory function in pre-surgical testing of refractory TL patients using episodic memory encoding paradigm with complex visual scenes (Stern *et al*., 1996) or multimodal stimuli (Golby *et al*., 2001). We and others found that pre-surgical activation asymmetry ratio (AR) from mesial temporal regions corresponded with hemispheric memory dominance found with IAT (Detre *et al*., 1998; Golby *et al*., 2002). A complementary role for fMRI and IAT in predicting a seizure-free outcome from TL has also been suggested (Killgore *et al*., 1999). Thus far no study has assessed the value of fMRI memory activation in predicting post-surgical memory performance in TL patients.

The purpose of the present study was to evaluate the utility of fMRI to predict post-surgical memory outcome following TL. We hypothesized that, as with the IAT, a greater asymmetry in activity between the epileptic and non-epileptic mTL would be associated with lower decline in memory performance post-TL. Furthermore, we examined fMRI data in light of two non-mutually exclusive mechanisms underlying the relationships between pre-surgical mTL function and post-surgical memory performance (Chelune, 1995). The functional reserve model posits that it is the ability of the contralateral side to support memory that determines post-surgical memory outcome. Greater function in the mTL contralateral to the seizure focus would be expected to be associated with less memory disruption post-operatively. The functional adequacy model states that memory deficits following surgery are dependent on how well the ipsilateral mTL, which is to be resected, supports memory. Poorer pre-surgical function in the epileptic mTL should result in less memory disruption post-operatively. Lesion studies using hippocampal cell density results and pre-surgical structural MRI volumetric data have supported the functional adequacy model (Hermann *et al*., 1993; Trenerry *et al*., 1993; Chelune, 1995; Baxendale *et al*., 1998). Such methods, however, cannot adequately test the functional reserve model, as they cannot quantify function within the contralateral temporal lobe. A second purpose of this study, therefore, was to reexamine predictions of the hippocampal adequacy and hippocampal reserve models using functional neuroimaging data, which can provide independent measures of functional capacity during memory encoding in the mTL ipsilateral and contralateral to the seizure focus.

Material and methods

Subjects

Thirty-five consecutively recruited patients with medically refractory TLE undergoing pre-surgical evaluation for TL were recruited. All subjects gave informed written consent prior to their participation in the study, which was approved by the internal review board of the University of Pennsylvania. Using extracranial and intracranial EEG, structural MRI and/or PET, 20 patients were classified as having a right mTL seizure focus and 15 as having a left seizure focus. Patient demographics and neurological and neuropsychological test results are detailed in Table 1. All right-sided TLE patients were self-reported right-handed. Seven left-sided TLE patients were right-handed and eight were left-handed. All patients who underwent the IAT were determined to be left hemisphere language dominant, except one who was bilaterally dominant. Left TLE patients and right-sided TLE patients did not differ (*t*-test) in regard to either Full Scale Intelligence Quotient (right mean: 98.7; left mean: 88.7) (Wechsler Memory Scale, 1997) or average age at time of fMRI testing (right mean: 36.6 years; left mean: 37.9 years). Thirty subjects, mostly undergraduate and graduate students (19 women, 11 men; mean age: 24.1 years, SD 3.8; all right handed) were recruited as normals. Normal subjects had no history of psychiatric or neurological illness.

Intracarotid amobarbital testing

Language and memory functions were evaluated in TLE patients using a standard IAT protocol that was performed as part of their

Table 1 *Patient demographics, clinical variables, and IAT results*

Patient no.	Age/(years) gender	Handedness	Pre-surgical FIQ	Seizure type	Seizure laterality	Hippocampal sclerosis	Seizure-free outcome	IAT language dominance	IAT memory dominance	IAT contra-ipsi
1	49/M	Right	67	CPS, GTC	Left	No	N/A	N/A	N/A	N/A
2	39/M	Left	99	CPS, GTC	Left	Yes	N/A	N/A	N/A	N/A
3	40/F	Right	99	SPS, CPS	Left	No	Yes	LHLD	Right	2
4	34/F	Right	127	SPS, CPS, GTC	Right	No	N/A	LHLD	Left	0
5	44/F	Right	91	SPS, CPS	Left	Yes	N/A	N/A	N/A	N/A
6	58/F	Right	91	CPS, GTC	Right	No	Yes	LHLD	Right	−1.5
7	42/M	Right	123	SPS, CPS, GTC	Right	No	Yes	LHLD	Left	−0.5
8	27/M	Right	123	CPS, GTC	Right	Yes	N/A	N/A	N/A	N/A
9	27/M	Right	100	SPS, CPS, GTC	Right	No	N/A	LHLD	Left	2.5
10	28/F	Right	78	SPS, CPS	Right	No	Yes	LHLD	Left	0.5
11	32/F	Right	95	SPS, CPS, GTC	Left	Yes	No	LHLD	Left	−2.5
12	29/F	Right	73	CPS, GTC	Right	No	Yes	LHLD	Right	−1.5
13	57/F	Right	91	CPS, GTC	Right	No	Auras only	LHLD	Left	0.5
14	22/M	Right	96	CPS, GTC	Right	No	No	LHLD	N/A	N/A
15	35/M	Left	90	CPS	Left	No	Yes	LHLD	Right	6
16	32/M	Left	79	CPS, GTC	Left	No	Yes	Bilateral	Left	−0.5
17	56/F	Right	102	CPS, GTC	Right	No	No	LHLD	Left	4
18	29/M	Left	87	SPS, CPS	Left	No	Yes	LHLD	Right	3
19	30/M	Left	92	CPS	Left	No	Yes	LHLD	Right	4
20	31/M	Left	90	CPS, GTC	Left	No	N/A	LHLD	Right	N/A
21	22/M	Right	109	SPS, CPS, GTC	Right	Yes	N/A	LHLD	Left	4
22	49/F	Right	79	CPS	Right	No	No	LHLD	Left	5
23	54/F	Left	84	CSG, GTC	Left	No	Yes	LHLD	Left	−1.5
24	49/F	Right	61	CPS, GTC	Left	Yes	N/A	N/A	N/A	N/A
25	43/F	Right	107	SPS, CPS	Right	Yes	N/A	LHLD	Left	N/A
26	35/F	Right	94	CPS, GTC	Right	No	Yes	LHLD	Left	3
27	35/M	Left	99	CPS, GTC	Left	Yes	Yes	LHLD	Right	2.5
28	31/F	Right	109	SPS, CPS	Right	No	N/A	LHLD	Left	1
29	32/M	Right	90	CPS, GTC	Left	No	Yes	LHLD	Left	−1.5
30	45/M	Right	103	CPS, GTC	Right	No	No	LHLD	N/A	N/A
31	28/F	Right	104	CPS, GTC	Right	Yes	Yes	LHLD	Left	−0.5
32	37/F	Right	108	CPS, GTC	Left	Yes	Yes	LHLD	N/A	N/A
33	46/F	Right	105	CPS, GTC	Right	No	Yes	LHLD	Left	2.5
34	29/F	Right	84	SPS, CPS, GTC	Right	Yes	No	LHLD	Left	5.5
35	41/F	Right	76	CPS, GTC	Right	Yes	No	LHLD	Left	3

Clinical diagnosis was based on structural MRI, PET and EEG. M = male; F = female; SPS = simple partial seizures; CPS = complex partial seizures; GTC = generalized tonic–clonic seizures; LHLD = left hemisphere language dominance; contra-ipsi = difference in IAT memory score for contralateral hemisphere – ipsilateral hemisphere; N/A = not available.

clinical evaluation (Glosser *et al*., 1995). Soon after an injection of 100–125 ml of sodium amobarbital, nine stimuli were presented for memory encoding. Three common objects that could be encoded using verbal or visual representations were shown for naming. Three low-imagery words were presented for oral reading. Three unfamiliar non-verbalizable abstract line drawings were presented for visual inspection. Yes–no recognition memory was tested following return to baseline as determined by neurological examination ~10 min after injection. The nine target stimuli were presented along with 18 matched distracters (six objects, six words and six designs). A recognition memory score was calculated for each hemisphere and corrected for guessing by subtracting one-half of the number of false positive errors from the total correct detections. Because of the known difference in the recognition memory scores for right and left hemisphere injections, one point was added to the score when using the right hemisphere to adjust for drowsiness and aphasia that commonly occurs after left hemispheric injection (Glosser *et al*., 1999). For comparison with fMRI data, IAT was either dichotomized according to hemispheric dominance for memory, or the difference between ipsilateral and contralateral hemispheres was considered (Loring *et al*., 1995; Chiaravalloti and Glosser, 2001). Usable IAT memory results were available from 27 patients. Of the remaining eight patients, five never had IAT testing and three patients had uninterpretable studies for technical reasons.

Cognitive task design for fMRI

During fMRI scanning, subjects viewed 60 complex visual scenes presented over six 40-s blocks (10 scenes per block). Each scene was displayed for 3.5 s followed by 0.5 s of black, blank screen. Pictures were obtained from a commercial library of digitized images (Photodisc, Seattle, WA, USA). Examples of these images are shown in Fig. 1. Images were chosen in an effort to preclude simple verbal coding strategies. Blocks of complex visual scene encoding were alternated with blocks of repeated presentation of a single control image consisting of one of the scene images degraded using a random-retiling algorithm applied in 10 000 iterations (Fig. 1). Stimuli were presented on a Macintosh Powerbook (Apple Computer, Cupertino, CA, USA) using Psyscope software (Carnegie Mellon University, Pittsburgh, PA, USA). Images were rear-projected by an Epson LCD projector (model EPL-5300, Seiko Epson, Tokyo, Japan) onto a Mylar screen, ~7 feet from the subject's head and easily viewed by the subject via a mirror permanently attached to the head coil. Before the presentation of stimuli, subjects were specifically instructed to 'look at and pay attention' to the control image, and to 'memorize' the complex visual scenes for a recognition test following the scan.

After encoding during scanning, memory was evaluated with a self-paced yes–no recognition test. The 60 complex visual scenes viewed during the scan were presented again intermixed with 60 new complex visual scenes as foils. Using a two-button box, subjects indicated whether or not they had just seen the photograph during the encoding session. Response data from one patient (no. 11) was lost due to technical factors. After surgery (6.9 ± 7.9 months, range: 1–26 months), the scene memory test was repeated using an identical task. For post-surgical testing, both encoding and recognition testing were conducted outside the scanner using the same paradigm and stimuli. Recognition memory was quantified by a discrimination score, consisting of the proportion of correct responses (hits) divided by the total correct target stimuli minus the proportion of false positive errors divided by the total foil stimuli, as defined by Two-High Threshold Theory (Snodgrass and Corwin, 1988). Pre-surgical discrimination scores were subtracted from post-surgical scores to yield a discrimination score change value.

Imaging techniques

Imaging data were collected on a 1.5 T GE Signa MRI scanner (General Electric, Milwaukee, WI, USA) equipped with a fast gradient system for echo-planar imaging, using a quadrature radiofrequency head coil. Foam padding was used to comfortably restrict head motion. Axial T1-weighted structural images were obtained for each subject. T2*-sensitive, gradient-echo echo-planar functional images with BOLD (blood oxygenation level dependent) contrast

Fig. 1 Examples of stimuli used for the complex visual scene-encoding task (**A**). During the control task (**B**) subjects viewed a single scene image that was degraded using a random-retiling algorithm applied in 10 000 iterations.

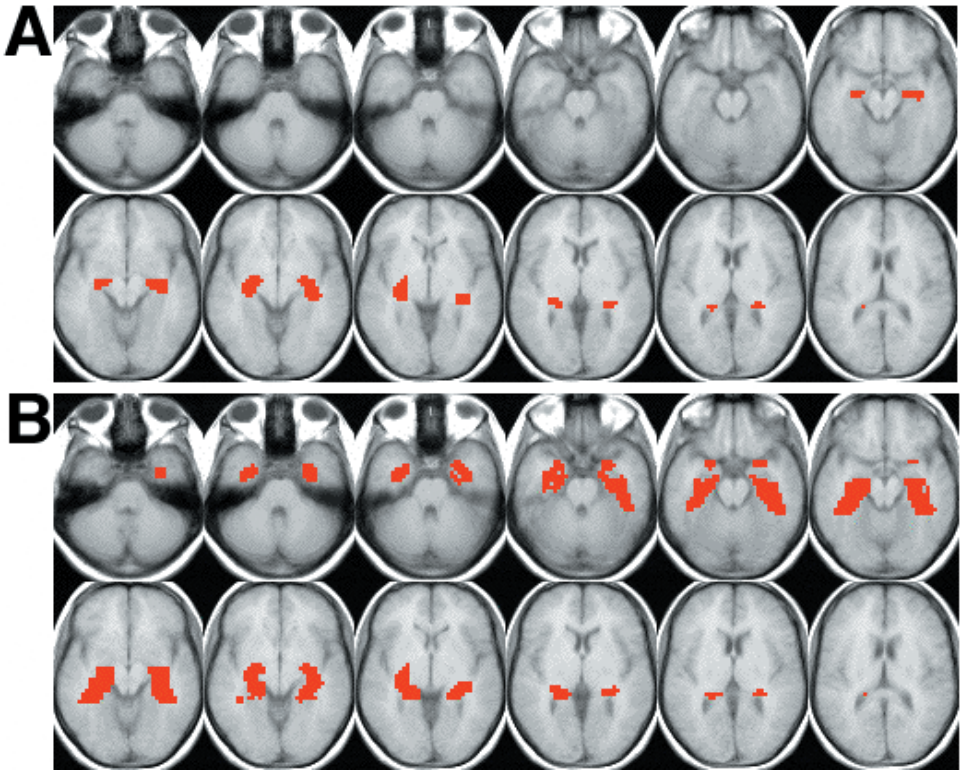

Fig. 2 ROI used for quantification of fMRI results, shown superimposed upon combined normal group anatomical images: (**A**) H ROI; (**B**) larger mTL ROI comprised of hippocampus, parahippocampus and fusiform gyrus (HPF).

(TR = 2 s, TE = 50 ms) were obtained from 20 contiguous 5-mm-thick axial slices in a 24-cm field of view using an acquisition matrix of 64 × 64, resulting in a nominal pixel resolution of 3.75 × 3.75 × 5 mm. Functional activation was measured over a single 240-scan run consisting of six 80-s task/control cycles. Prior to functional activation, chemical shift data were obtained in the same voxels for correction of image distortion due to static susceptibility effects prior to image reconstruction (Alsop, 1995).

Image analysis

fMRI data was analysed using Voxbo software (www.VoxBo.org), which includes motion correction and realignment algorithms derived from statistical parametric mapping (www.fil.ion.ucl.ac.uk/spm/). Raw data were transformed into image time-series using a correction for static susceptibility-induced distortions (Alsop, 1995). Data were then convolved in space with a three-dimensional non-isotropic Gaussian kernel (full-width half-maximum = 4 × 4 × 3 voxels), for isotropic smoothness of 15 × 15 × 15 mm^3, and in time using an empiric estimate of the haemodynamic response function as well as a frequency domain notch filter (Zarahn *et al*., 1997). The choice of a relatively large spatial smoothing kernel was based on a published report (Hopfinger *et al*., 2000) suggesting greater sensitivity for hippocampal activation using a large smoothing kernel and confirmed in our own preliminary analyses. However, to insure that this extent of smoothing did not adversely affect the results, all the primary analyses were subsequently repeated using a more standard smoothing kernel of 2 × 2 × 1.5 voxels for isotropic smoothness of 7.5 × 7.5 × 7.5 mm^3. Use of a more standard smoothing kernel did not alter the interpretation of any of the subsequent correlations, with some showing slightly increased and some showing slightly decreased significance.

A modified general linear model for temporally autocorrelated observations was applied voxel-wise to each data set (Worsley and Friston, 1995). A simple boxcar function was used to perform the cognitive subtraction (task condition – control condition). Statistical parametric maps of activation associated with stimulus encoding were generated for each patient. For normal subjects, a group map was generated using a random effect model comparing mean statistical parametric maps, beta values from individual subjects to zero, with the significance level determined by sign permutation across subjects (Nichols and Holmes, 2002).

Region of interest (ROI) analysis based on a published regional atlas in Talairach space (Kikinis *et al*., 1996) was used to quantify fMRI activation in individual subjects. Two standard ROIs were used, an H ROI and a larger mesial temporal ROI consisting of hippocampus, parahippocampus and fusiform gyrus (HPF). These ROIs are shown in Fig. 2. Data from each ROI was quantified in both right and left hemispheres. To avoid any threshold effects and to allow for hemispheric differences in ROI coverage, the proportion of positive voxels within each ROI, based on beta values, was used as a measure of activation. Within each ROI, absolute ipsilateral and contralateral hemispheric activation was determined along with an AR, determined by subtracting the fractional ROI activation in the hemisphere ipsilateral to seizure focus from that of the hemisphere contralateral to seizure focus, then dividing that value by the sum of both those values [(contralateral – ipsilateral)/(contralateral + ipsilateral)]. The AR can range from + 1 (activation on contralateral

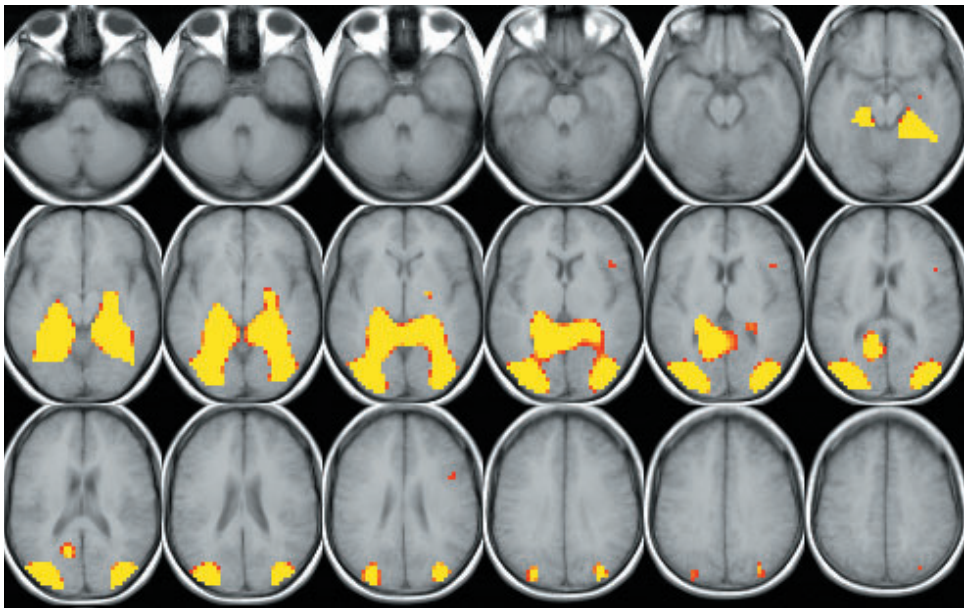

Fig. 3 Group map from normal subjects (n = 30) showing brain regions activated during visual scene encoding as compared with viewing a randomly retiled scene. Activation is shown superimposed upon combined normal group anatomical images and thresholded at $P < 0.05$ (permutation).

side and no activation on ipsilateral side) to −1 (activation on ipsilateral side and no activation on contralateral side). A left–right AR [(left hemisphere – right hemisphere)/(left hemisphere + right hemisphere)] was also calculated for comparison of normal subject data with patient data and for comparison of patient data to IAT data. Statistical analysis comparing ROI data with other indices was carried out in SPSS (SPSS Inc., Chicago, IL, USA).

A *post hoc* assessment of the correlation between presurgical fMRI results and neuropsychological test score changes was carried out in a subset of patients for whom these data were available. To determine if scene memory task activation was differentially related to either verbal or non-verbal memory we examined its association to performance on two material-specific episodic memory tasks. Twenty-two subjects received the Wechsler Memory Scale III (WMS-III) (Wechsler, 1997) both pre- and post-operatively, from which we calculated a non-verbal retention score using the ratio of scores from Visual Reproduction II to Visual Reproduction I. Sixteen subjects received the California Verbal Learning Test (Delis *et al*., 1987) both pre- and post-operatively, from which we calculated a verbal retention score using the ratio of Long Delay score to Trial 5 score.

Results

All subjects tolerated the scanning procedure well. The results of routine motion correction procedures revealed minimal differences in translational or rotational motion between patients and controls. Grand mean translational and rotational motion averaged across repetition times (TRs) in controls was −0.07, 0.13 and −0.07 mm and −0.10, 0.30 and 0.11 degrees for X, Y, Z, yaw, pitch and roll. Grand mean translational and rotational motion in patients was −0.17, 0.08, and −0.08 mm and −0.16, 0.21 and −0.02 degrees for X, Y, Z, yaw, pitch and roll. Roll motion was actually reduced in patients versus controls (P = 0.042, uncorrected for multiple comparisons). Task-correlated motion was most pronounced in Z and pitch, and was present in about 25% of patients and controls. A comparison of the proportion of controls versus patients showing task-correlated motion at P = 0.05 for correlation between the task and the corresponding realignment curve showed no difference except in Y motion where task-correlated movement in controls was greater ($P < 0.05$, chi-square uncorrected for multiple comparisons).

A group map demonstrating task activation in normal subjects during complex visual scene encoding is shown in Fig. 3. Activation appears symmetrical and extends from visual association areas rostrally to bilateral mesial temporal regions. Mean and standard deviation (SD) for the fraction of voxels in the ROI in normals with beta values numerically above zero was 0.76 ± 0.25 and 0.74 ± 0.13 for H and HPF regions, respectively. The calculated ARs for the normal group extracted using the H and HPF regions indicated almost symmetrical activation, with mean AR values of 0.02 ± 0.16 (mean ± SD) and 0.007 ± 0.13 for H and HPF regions, respectively. Patient left–right AR values are summarized in Table 2. Mean values for left- and right-lateralized patients differed, with left-sided patients showing mean negative AR and right-sided patients showing mean positive AR for H and HPF regions. The ‘gold-standard’ for lateralization of seizure foci is seizure-free outcome following surgery. However, differences in left–right AR in right- and left-sided epilepsy patients were not increased in a subgroup of 16 patients with seizure-free outcome at 1 year. An analysis of variance was carried out to compare left–right AR values in normals and TLE patients. This analysis revealed no significant difference in mean AR in normals and the patient group as

Table 2 *Results of fMRI ROI analyses and scene recognition testing*

Patient no.	fMRI AR		fMRI absolute activation				Scene memory discrimination score		
	H	HPF	H right	H left	HPF right	HPF left	Pre-	Post-	Change
1	−0.90	−0.34	0.45	0.02	0.71	0.35	0.17	N/A	N/A
2	0.50	−0.18	0.14	0.44	0.33	0.23	0.03	N/A	N/A
3	0.90	0.50	0.05	0.95	0.31	0.93	0.78	0.43	−0.35
4	0.00	0.00	1.00	1.00	1.00	0.99	0.62	N/A	N/A
5	−1.00	0.25	0.01	0.00	0.06	0.10	0.85	0.92	0.07
6	−0.97	−0.52	0.67	0.01	0.78	0.24	0.83	0.45	−0.38
7	0.27	0.06	0.57	0.99	0.79	0.90	0.9	0.92	0.02
8	0.44	−0.11	0.22	0.58	0.65	0.53	0.92	N/A	N/A
9	0.25	0.25	0.17	0.28	0.37	0.62	0.48	N/A	N/A
10	0.55	0.31	0.26	0.89	0.48	0.92	0.55	0.42	−0.13
11	−0.19	−0.10	0.82	0.55	0.85	0.69	N/A	N/A	N/A
12	0.00	−0.56	0.00	0.00	0.05	0.01	0.48	N/A	N/A
13	0.00	−0.03	1.00	1.00	1.00	0.94	0.87	0.88	0.01
14	−0.30	−0.25	0.75	0.40	0.82	0.49	0.35	N/A	N/A
15	0.03	−0.10	0.80	0.86	0.94	0.76	0.65	0.43	−0.22
16	−0.11	−0.02	0.99	0.79	0.83	0.79	0.28	0.12	−0.16
17	−0.05	−0.07	1.00	0.91	0.91	0.79	0.72	0.38	−0.34
18	0.14	−0.17	0.62	0.82	0.82	0.58	0.85	0.82	−0.13
19	−0.02	−0.01	1.00	0.95	1.00	0.98	−0.63	0.42	−0.21
20	0.08	−0.03	0.57	0.67	0.74	0.70	0.4	N/A	N/A
21	0.00	−0.01	1.00	1.00	1.00	0.98	0.72	0.72	0.00
22	0.91	0.63	0.03	0.55	0.16	0.69	0.12	0.37	0.25
23	−0.34	−0.28	0.82	0.40	0.49	0.28	−0.02	0.2	0.22
24	0.46	0.18	1.00	0.37	0.62	0.89	0.12	N/A	N/A
25	0.13	0.14	0.78	1.00	0.73	0.96	0.38	0.82	0.44
26	−1.00	0.47	0.07	0.00	0.07	0.20	0.5	0.73	0.23
27	0.03	0.02	0.93	1.00	0.94	0.98	0.7	0.62	−0.08
28	0.06	0.04	0.88	1.00	0.88	0.96	0.95	0.78	−0.17
29	0.48	0.11	0.36	1.00	0.73	0.91	0.92	0.9	0.02
30	−1.00	−0.68	0.92	0.00	0.96	0.18	0.68	N/A	N/A
31	0.00	0.01	1.00	1.00	0.98	1.00	0.63	N/A	N/A
32	0.00	−0.13	0.34	0.34	0.50	0.38	0.65	0.87	0.22
33	0.31	0.07	0.47	0.91	0.80	0.93	0.85	0.6	−0.25
34	0.14	0.05	0.71	0.93	0.88	0.96	0.5	0.133	−0.367
35	0.40	0.31	0.39	0.92	0.44	0.84	0.57	0.4	−0.17
Controls (mean ± SD)	0.02 ± 0.16	0.007 ± 0.13	0.75 ± 0.26	0.77 ± 0.24	0.73 ± 0.05	0.76 ± 0.17	0.790 ± 0.165		

N/A = not available. See Material and methods for descriptions of fMRI AR and fMRI absolute activation.

a whole, or when subdivided by clinical seizure laterality. However, a significant difference in AR variability between patients and controls was present in the data ($P < 0.001$ and $P = 0.013$ for H and HPF regions, respectively; Levene statistic). Since normals do not have an affected hemisphere, for the purposes of comparing patient results with the normative range in the analyses below, AR in normals was rounded to 0.0.

fMRI left–right activation asymmetry in H and HPF ROIs was compared with IAT memory dominance. Only HPF AR correlated significantly with IAT laterality ($r = 0.385$, $P = 0.047$, Spearman rank correlation). Mean HPF AR was positive for patients with left-sided memory dominance by IAT and negative for patients with right-sided memory dominance by IAT, but unlike the two prior reports comparing fMRI laterality with IAT laterality (Detre *et al*., 1998; Golby *et al*., 2002) agreement between modalities was not perfect and there was significant overlap between the two groups. There was an almost significant trend between fMRI HPF AR and IAT asymmetry expressed as the difference between contralateral and ipsilateral IAT memory scores ($r = 0.385$, $P = 0.052$, Pearson correlation), which was significant in right-sided TLE patients ($r = 0.601$, $P = 0.014$, Pearson correlation) but not significant in left-sided TLE patients. These findings are illustrated graphically in Fig. 4.

Of the 35 patients who underwent pre-surgical fMRI testing, 13 right and 10 left-sided TLE patients underwent surgery and post-surgical testing on scene memory. Discrimination scores are listed in Table 2. A one-way analysis of variance comparing all three groups together demonstrated a significant effect of group in the pre-surgical discrimination scores ($F(2,50) = 6.618$, $P = 0.003$). Subsequent Newman–Keuls

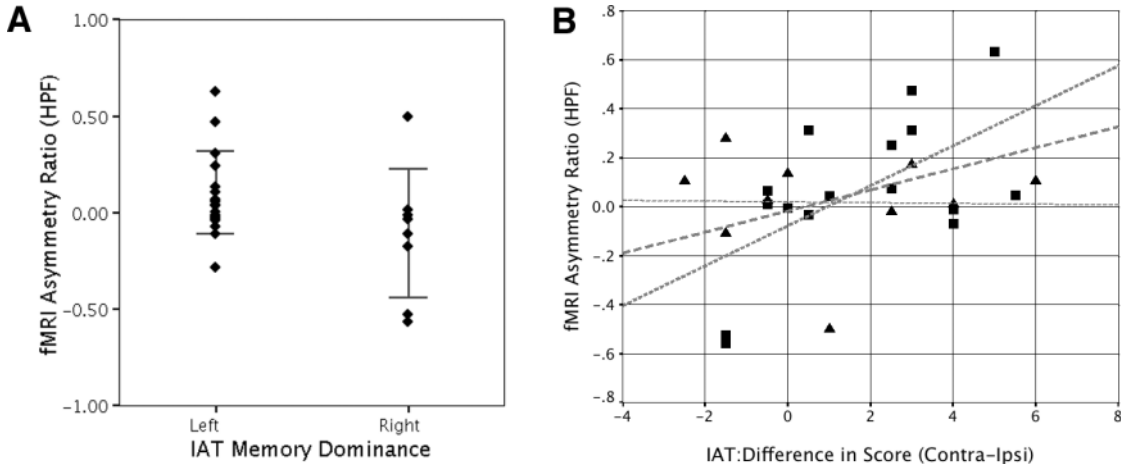

Fig. 4 fMRI AR versus IAT laterality for the HPF ROI. (**A**) Results for dichotomized IAT memory results. Error bars indicate SD from mean AR. (**B**) Results correlating fMRI HPF AR with IAT asymmetry expressed as contralateral – ipsilateral score difference. Plot symbols differentiate left- (triangles) and right-sided (squares) TLE patients. Dashed line shows regression for all patients ($r = 0.378$. $P = 0.063$). Thick dashed line shows regression for right-sided TLE patients ($r = 0.601$, $P = 0.014$) and thin dotted line shows regression for left-sided TLE patients ($r = 0.006$, $P = 0.988$).

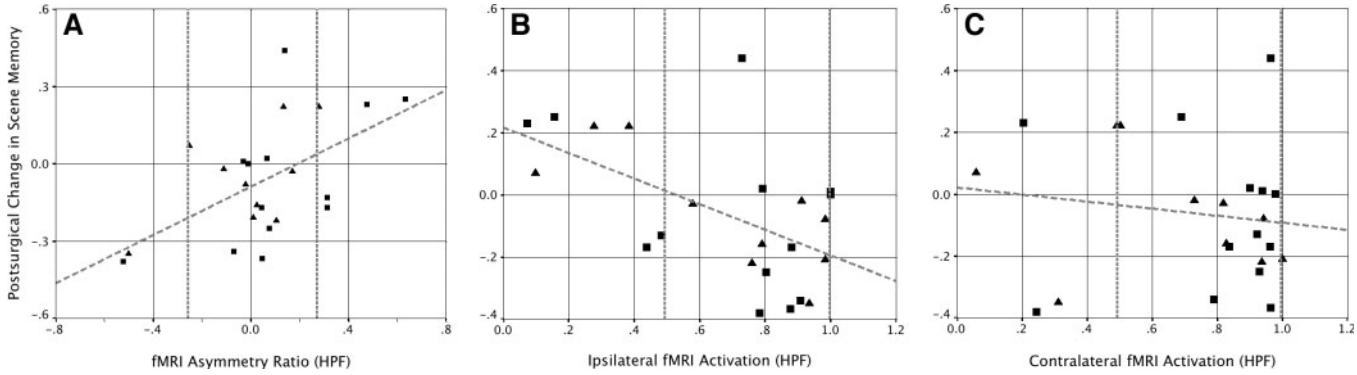

Fig. 5 fMRI results from HPF ROI versus change in discrimination score on scene recognition testing between pre-surgical and post-surgical testing. (**A**) fMRI AR versus discrimination score change. fMRI AR is calculated from fractional positive activation within the ROI using [(contralateral – ipsilateral)/(contralateral + ipsilateral)]. (**B**) Absolute fMRI activation ipsilateral to the clinical seizure focus and resection versus change in discrimination score. (**C**) Absolute fMRI activation contralateral to the clinical seizure focus and resection versus change in discrimination score. Absolute activation is expressed as the fractional positive ROI. Plot symbols differentiate left- (triangles) and the right-sided (squares) TLE patients. Dashed lines show regression results ($r = 0.550$, $P = 0.007$ for HPF AR, $r = -0.560$. $P = 0.005$ for absolute ipsilateral HPF activation, $r = -0.146$, $P = 0.506$ for absolute contralateral HPF activation). Vertical dotted lines indicate 2 SD of normative results.

tests, which compared two groups at a time, showed that the mean pre-surgical discrimination score of right-sided TLE patients was not statistically different from that of left-sided TLE patients (right 0.631 ± 0.219; left 0.501 ± 0.329). Additionally, both groups performed significantly worse on the task than did normal subjects (normal mean: 0.790 ± 0.165; normal versus right: $P = 0.034$; normal versus left: $P = 0.002$).

A significant correlation was observed between pre-surgical fMRI ipsilateral–contralateral AR for the HPF region and post-surgical discrimination score change ($r = 0.55$, $P = 0.007$; Pearson correlation). These results are illustrated in Fig. 5A. The majority of patient AR values remain within 2 SD of the AR mean in normals, though in general these patients with AR scores within 2 SD of normal mean demonstrated the smallest changes in scene memory performance. To determine the relative contributions of affected and unaffected hemispheres to the observed asymmetries, absolute activation in both ipsilateral and contralateral HPF regions was correlated with post-surgical discrimination score change. A highly significant inverse correlation between post-surgical discrimination score change and ipsilateral activation was observed ($r = -0.560$, $P = 0.005$, Fig. 5B), with all but one of the patients with improvements in post-surgical scene memory having ipsilateral activation below 2 SD of the normative range. Of note, left- and right-sided TLE patients are distributed evenly throughout the plotted data, indicating that the observed correlations are not dominated by one or the other seizure

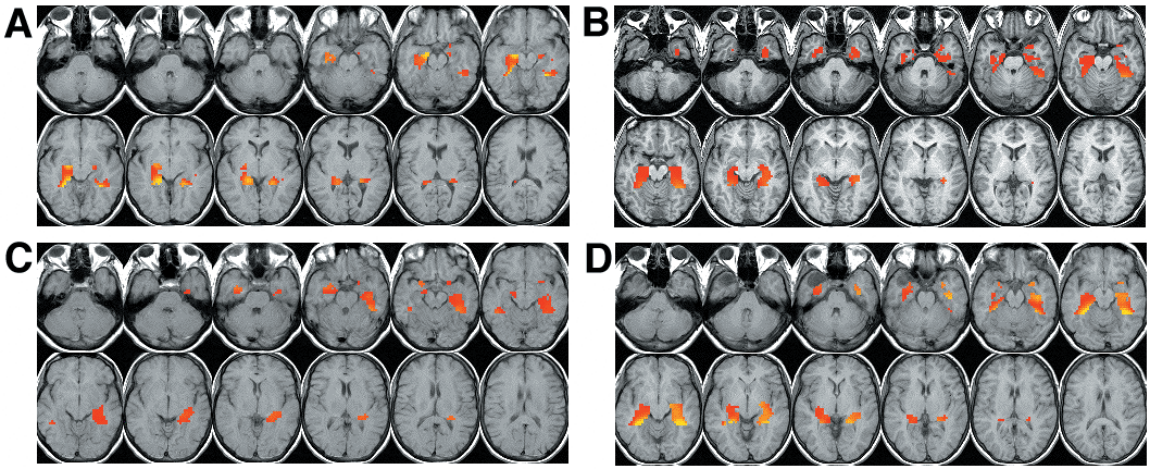

Fig. 6 Positive activation in HPF POI from selected left- and right-sided epilepsy patients with varying post-surgical discrimination score changes showing varying asymmetries in fMRI activation. (**A**) Activation in Patient 32 with left-sided TLE, positive fMRI AR and an improved discrimination score following left TL. (**B**) Activation in Patient 3 with left-sided TLE, a negative AR and a decreased post-surgical memory score following right TL. (**C**) Activation in Patient 22 with right-sided TLE, a positive AR and an improved discrimination score following right TL. (**D**) Activation in Patient 34 with right-sided TLE, a negative AR and a decreased post-surgical memory score following right TL.

laterality. Absolute activation in ipsilateral hippocampal ROI (H ROI) also inversely correlated significantly with the change in scene memory performance ($r = -0.437$, $P = 0.037$, graph not shown). No correlation was found between discrimination score change and absolute contralateral activation for HPF ROI (Fig. 5C) or H ROI (graph not shown). In contrast to fMRI results, IAT laterality did not show any significant correlation with scene memory discrimination score changes.

Figure 6 shows examples of fMRI activation within the HPF ROI in representative left- and right-hemispheric TLE patients with improving or deteriorating post-surgical memory performance. Figure 6A shows reduced left-sided activation in a left-sided TLE patient whose scene memory performance improved following TL, while Fig. 6B shows intact left-sided activation in a left-sided TLE patient in whom memory performance deteriorated. Similarly, Fig. 6C shows reduced right-sided activation in a right-sided TLE patient whose scene memory performance improved following TL, and Fig. 6D shows intact right-sided activation in a right-sided TLE patient in whom memory performance deteriorated.

A non-verbal retention score was calculated using the ratio of scores from Visual Reproduction II to Visual Reproduction I of the WMS-III. Both HPF AR and absolute ipsilateral HPF correlated with change in this nonverbal retention score ($n = 22$; $r = 0.424$, $P = 0.049$ and $r = -0.474$, $P = 0.026$, respectively). In subgroup analysis, this correlation was only significant for right-sided TLE patients. A verbal retention score was calculated using the ratio of Long Delay score to Trial 5 score of the California Verbal Learning Test (CVLT). In right-sided TLE patients, HPF AR correlated significantly with changes in this verbal retention score ($n = 16$; $r = 0.587$, $P = 0.035$). Baseline verbal retention scores (available for 26 subjects) correlated well with baseline scene memory discrimination ($n = 26$; $r = 0.524$, $P = 0.006$), while non-verbal retention scores calculated from WMS-III performance did not. Neither of these two retention scores correlated significantly with changes in scene memory discrimination. IAT laterality correlated just significantly with WMS-III Visual Reproduction changes ($r = -0.538$, $P = 0.047$), but not with California Verbal Learning Test changes.

Discussion

The results of this study suggest that hemispheric asymmetries in mesial temporal memory activation, detected by fMRI during complex visual scene encoding, correlate with post-surgical memory performance. Our data also suggest that the extent of activation within the ipsilateral mTL is predictive of memory outcome. Although numerous challenges remain in the clinical implementation of fMRI memory lateralization, this study generally supports the notion that such data will ultimately contribute to patient management.

The finding of bilateral mTL activation, with complex visual scene encoding, replicates previous reports and supports the notion that complex visual scenes are encoded using both visual–spatial and verbal strategies. The recruitment of both hemispheres is also consistent with deficits in complex visual scene encoding observed following both right and left TL (Zaidel and Rausch, 1981; Pigott and Milner, 1993). We observed some differences between activation in the hippocampus proper (H) versus the mTL ROI comprised of hippocampus, parahippocampus, and fusiform gyrus (HPF). Activation asymmetry in the HPF ROI correlated significantly with memory outcome and IAT laterality, whereas for the H ROI only absolute activation correlated significantly with memory outcome. This difference is at least partially attributable to the smaller size of the H ROI as well as the

reduced sensitivity in this region due to susceptibility effects. However, the involvement of a more posterior mTL region is also consistent with previous fMRI studies in normals, which found activation during memory encoding in caudal aspects of the hippocampus (Stern *et al*., 1996; Fernandez *et al*., 1998), parahippocampal gyrus (Aguirre *et al*., 1996; Stern *et al*., 1996; Gabrieli *et al*., 1997; Brewer *et al*., 1998; Schacter and Wagner, 1999) and the fusiform gyrus (Stern *et al*., 1996; Schacter and Wagner, 1999). The parahippocampus receives convergent input from the various cortical sensory association areas and provides most of cortical input to the hippocampal formation, with which it is reciprocally connected. It is likely that TL disrupts a more distributed mTL memory network that contributes to memory performance, perhaps particularly for visual stimuli entering from posterior visual association areas.

Absolute activation in the mTL ipsilateral to the epileptic focus showed a significant negative correlation with discrimination score change for both H and HPF regions such that lower activation in the epileptic temporal lobe was associated with a smaller decline or improvement in memory performance post-operatively. These findings support the functional adequacy model, which proposes that memory deficits following surgery are dependent on the extent to which the ipsilateral mTL supports memory. These results are in accord with work on IAT by Kneebone and colleagues that indicated the importance of the functional adequacy of the to-be-resected mTL in predicting verbal memory decline following TL (Kneebone *et al*., 1995), though the present results appear to apply equally to right- and left-sided TLE. Our findings are also in accord with a previous fMRI study that demonstrated the value of the ipsilateral but not contralateral hemisphere in classifying side of seizure (Jokeit *et al*., 2001) as well as with a recent small PET study that correlated ipsilateral activity with post-surgical memory change (Henke *et al*., 2003). No support was found for the functional reserve model, which posits that it is the ability of the contralateral side to support memory that determines post-surgical memory outcome. It should be noted that ipsilateral activation and the asymmetry values are highly correlated and provide redundant rather than independent predictive values for memory outcome.

In this study, fMRI activation during complex visual scene encoding was compared with a perceptual control condition consisting of a single repeated scrambled image, the purpose of which was to maintain attention and visual fixation. This contrasts with many studies in which the control task is designed to recruit all but one cognitive process of interest. Other groups have studied memory activation by comparing novel and repeated scenes (Golby *et al*., 2001). As compared with the low-level perceptual control used here, these tasks are more likely to isolate activation due to memory. However, our experience comparing the perceptual control to more active control conditions in normal subjects has indicated more robust mTL activation with the perceptual control. The precise basis for this is uncertain, but it seems plausible that repeated stimuli or scenes requiring a non-memory judgment might still recruit memory systems. Indeed, numerous other studies of episodic memory have relied on covert encoding while making judgments in other cognitive domains. This study was not designed to isolate brain regions involved in episodic memory encoding, but rather to assess memory activation in the mTL, and therefore a perceptual control that would be unlikely to recruit much covert encoding and would maximize mTL was used and then, data analysis was focused on brain regions known to support episodic memory function.

The use of complex visual scene encoding as the sole memory outcome variable certainly limits the scope of the present findings. The test–retest reliability of our brief scene encoding task is unknown, and for this study the assessment of memory outcome using this task may have been complicated by practice and familiarity effects, even though the task was repeated after several months. Further, the pre-surgical task was carried out during fMRI scanning while the post-surgical task was carried out without scanning. Although most epilepsy patients are accustomed to the MRI scanner environment, this pre-surgical environment can certainly affect cognitive performance. In many cases there were also changes in anticonvulsant management between pre-surgical and post-surgical testing that could have affected concentration and consequently memory performance.

A neuropsychological battery was not included in our original study design, and TLE patients in this study were recruited from two separate epilepsy programmes with not entirely consistent approaches to routine neuropsychological testing. However, a *post hoc* assessment of presurgical fMRI results as compared with presurgical to post-surgical changes in non-verbal retention score based on the ratio of scores from Visual Reproduction in the WMS-III and to verbal retention based on the California Verbal Learning Test did show some significant correlations between fMRI results and memory outcomes, at least for right-sided TLE patients. Interestingly, neither of the neuropsychological test scores correlated significantly with changes in scene memory discrimination, suggesting that scene memory is at least partially independent of these more standard memory constructs.

Both right- and left-sided TLE patients were impaired on scene recognition as compared with normal subjects, and the correlations with memory outcome show left- and right-sided TLE patients distributed through the ranges of fMRI activation, though correlation between fMRI and IAT was strongest for right-sided TLE patients. Taken in combination with the correlations with standard neuropsychological testing, these findings suggest that scene encoding does seem to provide a measure of episodic memory ability that taps into both verbal and non-verbal memory systems. Further work will be required to better characterize and interpret scene memory performance and activation in terms of more common neuropsychological measures and patients' real-world experience.

A large body of evidence suggests that there is material specificity in the brain regions subserving memory function, and both neurocognitive and IAT testing typically segregate

performance into visuospatial and verbal domains. Complex visual scene encoding is thought to engage both visuospatial and verbal memory systems, and the resulting activation tends to be bilateral in mTL structures. This is ideal for examining asymmetries in mTL activation between affected and unaffected hemispheres. Our experience in control subjects comparing scene memory encoding with other types of encoding tasks have demonstrated much more robust activation of the mTL with scene memory encoding than with face or sentence encoding. However, for increased specificity and comparison with other modalities it would also be desirable to be able to examine material-specific memory. In the present study, absolute activation within the affected mTL surprisingly provided an even better correlation with encoding performance change than the AR. This finding provides support for the future use of this approach with material-specific memory encoding tasks.

This study was carried out using a single fMRI task comprising of ~8 min of data acquired at 1.5 T, which is less than was used in our previous study (Detre *et al*., 1998) or the study of Golby *et al*. (2002), and was therefore less sensitive than those studies from the standpoint of signal-to-noise. Existing reports suggest substantial variability in activation volume from scan to scan (Machielsen *et al*., 2000), or with thresholding parameters (Machulda *et al*., 2001), though the hemispheric asymmetry of the activation seemed to be relatively preserved in these studies. To avoid introducing a threshold effect for weak fMRI activation, we elected to analyse our data without any threshold, accepting any positive voxel in our quantification. This undoubtedly reduced observed asymmetries, since whatever true asymmetry was present in the data was superimposed upon a baseline of presumably symmetrical noise. However, use of a significance threshold would have eliminated activation from several of our cases.

Some of our results did not conform to expectations based on prior work. For example, we did not observe a statistically significant difference in left–right activation asymmetry between patients with left- and right-sided TLE, as has previously been observed for thresholded fMRI data during implicit memory encoding (Binder *et al*., 2000) or explicit retrieval (Jokeit *et al*., 2001). Despite this, a significant correlation with memory outcome was still observed, suggesting that the observed activation indeed reflected task-specific effects rather than nonspecific differences in mTL activity due to underlying seizure pathology. Our observation that fMRI asymmetry correlated better with IAT laterality than with seizure laterality also supports this notion.

We and others had also previously reported perfect correlations between fMRI and IAT laterality in small cohorts of mostly left-sided TLE cases (Detre *et al*., 1998 Golby *et al*., 2002), whereas in the present study, the best correlation between fMRI and IAT was observed in right-sided TLE patients, and even in that subgroup the correlation was not perfect. It should be noted that fMRI was not actually discordant with seizure or IAT laterality, but rather not significantly correlated. The most optimistic explanation for this would be that the fMRI data were too noisy. There also appear to be hemispheric differences, with right-sided TLE patients showing generally more significant correlations between fMRI results and either IAT laterality or neuropsychological test score changes than left-sided TLE patients. It is conceivable that the scene encoding task is more sensitive for right-sided than left-sided TLE dysfunction, and that this difference is most evident when signal-to-noise is marginal, though the precise basis for the observed hemispheric effects remains uncertain.

A number of recent developments in MRI hardware should greatly increase the sensitivity of fMRI to mTL activation. It has been notoriously difficult to detect hippocampal fMRI activation, in part because it is in a region of comparatively high static susceptibility, resulting in decreased sensitivity for BOLD fMRI. Recent efforts to overcome these obstacles include the use of Z-shimming (Constable *et al*., 2000) or ultra-thin slices (Fransson *et al*., 2001) to minimize susceptibility artefacts, and result in improved visualization of activation in the hippocampal head. Higher field strength magnets and more sensitive RF coils can yield markedly increased BOLD sensitivity from thinner slices with greatly reduced susceptibility artefacts. Similarly, the use of parallel imaging with multicoil arrays also increases signal-to-noise and reduces susceptibility artefact (Griswold *et al*., 1999). Multisubject group maps of our data (e.g. Fig. 2B) also demonstrate robust activation in the hippocampal head, providing further evidence suggesting that detecting this activation is primarily limited by sensitivity. Improvements in data processing may also produce more prognostic results. For example, it is possible that the sensitivity for detecting memory activation in the hippocampal formation could be enhanced by using an event-related design and an analysis strategy that considers only trials that were successfully encoded based on subsequent recognition testing (Wagner *et al*., 1998). This approach might be particularly successful in subjects with poor performance.

The image analysis procedures used in this study included a relatively large smoothing kernel, which had been shown to improve detection of hippocampal activation. Subsequently reanalysis of all our data using a smaller smoothing kernel confirmed that the conclusions of the study were not affected by our choice of this parameter. However, if fMRI of memory is eventually to be used for tailoring mTL resections, more precise localization of activation will be necessary. Hopefully, more robust hippocampal activation obtained through the use of the improved scanning procedures described above will allow data to be analysed reliably using reduced smoothing or even no smoothing at all.

Several applications of fMRI of memory encoding in TLE beyond memory lateralization can be envisioned. Because at least part of the substrate for episodic memory co-localizes with the seizure focus in many TLE patients, it is reasonable to suppose that fMRI results may contribute to the prediction of a seizure-free outcome from TL, as has been demonstrated for IAT (Sperling *et al*., 1994). Very preliminary data from our

laboratory suggest that this may be the case (Killgore *et al*., 1999). If our finding that the extent of ipsilateral mTL activation predicts post-surgical memory deficits is indeed correct, the possibility of using fMRI results to tailor the TL resection could eventually be considered, once fMRI sensitivity evolves to the point where accurate localization of memory activation within the mTL can be obtained reliably. Even without this, post-surgical fMRI of memory encoding might elucidate neuroplastic changes, potentially providing insights into mechanisms of recovery of memory function.

Conclusion

These results provide the first evidence that fMRI during memory encoding can predict post-surgical memory outcome in TLE and support the functional adequacy model of memory function. While these results support the feasibility of using fMRI to predict post-surgical memory outcome, the observed correlations are currently too weak to carry out a meaningful assessment of the sensitivity and specificity of this approach. Future improvements in fMRI acquisition, analysis and task activation protocols and continued prospective assessment will be required for the ultimate clinical validation of this approach.

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