

Imaging memory in temporal lobe epilepsy: predicting the effects of temporal lobe resection

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Functional magnetic resonance imaging can demonstrate the functional anatomy of cognitive processes. In patients with refractory temporal lobe epilepsy, evaluation of preoperative verbal and visual memory function is important as anterior temporal lobe resections may result in material specific memory impairment, typically verbal memory decline following left and visual memory decline after right anterior temporal lobe resection. This study aimed to investigate reorganization of memory functions in temporal lobe epilepsy and to determine whether preoperative memory functional magnetic resonance imaging may predict memory changes following anterior temporal lobe resection. We studied 72 patients with unilateral medial temporal lobe epilepsy (41 left) and 20 healthy controls. A functional magnetic resonance imaging memory encoding paradigm for pictures, words and faces was used testing verbal and visual memory in a single scanning session on a 3T magnetic resonance imaging scanner. Fifty-four patients subsequently underwent left (29) or right (25) anterior temporal lobe resection. Verbal and design learning were assessed before and 4 months after surgery. Event-related functional magnetic resonance imaging analysis revealed that in left temporal lobe epilepsy, greater left hippocampal activation for word encoding correlated with better verbal memory. In right temporal lobe epilepsy, greater right hippocampal activation for face encoding correlated with better visual memory. In left temporal lobe epilepsy, greater left than right anterior hippocampal activation on word encoding correlated with greater verbal memory decline after left anterior temporal lobe resection, while greater left than right posterior hippocampal activation correlated with better postoperative verbal memory outcome. In right temporal lobe epilepsy, greater right than left anterior hippocampal functional magnetic resonance imaging activation on face encoding predicted greater visual memory decline after right anterior temporal lobe resection, while greater right than left posterior hippocampal activation correlated with better visual memory outcome. Stepwise linear regression identified asymmetry of activation for encoding words and faces in the ipsilateral anterior medial temporal lobe as strongest predictors for postoperative verbal and visual memory decline. Activation asymmetry, language lateralization and performance on preoperative neuropsychological tests predicted clinically significant verbal memory decline in all patients who underwent left anterior temporal lobe resection, but were less able to predict visual memory decline after right anterior temporal lobe resection. Preoperative memory functional magnetic resonance imaging was the strongest predictor of verbal and visual memory decline following anterior temporal lobe resection. Preoperatively, verbal and visual memory function utilized the damaged, ipsilateral hippocampus and also the contralateral hippocampus. Memory function in the ipsilateral posterior hippocampus may contribute to better preservation of memory after surgery.

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Abbreviations: ATR = anterior temporal lobe resection; fMRI = functional magnetic resonance imaging

Introduction

Anterior temporal lobe resection (ATLR) leads to seizure freedom from seizure in up to 70% of patients with medically refractory temporal lobe epilepsy (Wiebe *et al.*, 2001); but this may be complicated by memory impairment, typically by verbal memory decline following left ATR (Chelune *et al.*, 1991; Hermann *et al.*, 1995; Loring *et al.*, 1995; Helmstaedter and Elger, 1996; Sabsevitz *et al.*, 2001) and visual memory decline following right ATR (Lee *et al.*, 2002).

One recognized prognostic factor for memory decline after ATR is preoperative performance on neuropsychological tests, with higher preoperative scores indicating a greater risk for postoperative decline (Chelune *et al.*, 1991; Helmstaedter and Elger, 1996; Baxendale *et al.*, 2006; Lineweaver *et al.*, 2006). Language lateralization assessed by the intracarotid amytal test or more recently language functional MRI (fMRI) has been found helpful to predict memory outcome (Loring *et al.*, 1990; Baxendale, 2002; Rabin *et al.*, 2004; Lineweaver *et al.*, 2006; Binder *et al.*, 2008). Severity of hippocampal sclerosis has also been used as a predictor for memory outcome, with less severe hippocampal sclerosis carrying a greater risk of postoperative memory decline (Hermann *et al.*, 1992; Trenerry *et al.*, 1993). Other epilepsy-related factors such as age of epilepsy onset and duration of epilepsy have been identified as useful predictors of postoperative outcome (Baxendale *et al.*, 2008).

fMRI is an attractive clinical tool to evaluate cognitive function as it is non-invasive and repeatable. A number of small studies have investigated the role of fMRI in the prediction of the effects of ATR on memory (Rabin *et al.*, 2004; Richardson *et al.*, 2004, 2006; Janszky *et al.*, 2005; Binder *et al.*, 2008; Powell *et al.*, 2008). Most previous studies have focused on the prediction of verbal memory decline; only a few have investigated visual memory decline after non-dominant ATR (Rabin *et al.*, 2004; Janszky *et al.*, 2005; Powell *et al.*, 2008).

Memory fMRI in the medial temporal lobe is challenging due to limits on resolution and the possibility of geometric distortions and signal drop out caused by susceptibility effects associated with the use of echo planar imaging (Robinson *et al.*, 2004).

We previously developed a material specific memory encoding paradigm that allowed testing of verbal and visual memory in one scanning session (Powell *et al.*, 2005). In the current study, we applied a similar paradigm to a large number of patients with medial temporal lobe epilepsy, who were candidates for either right or left ATR. We also studied a group of age and gender matched healthy controls. We tested the hypotheses that there will be: (i) evidence of material specific lateralization of memory encoding in controls; (ii) evidence of reorganization of memory encoding in patients with temporal lobe epilepsy compared to controls, due to the underlying pathology or ongoing epilepsy; and (iii) a relationship between activations on a memory fMRI

task and neuropsychological scores for verbal and visual memory in controls and patients with temporal lobe epilepsy with increased activation being associated with better verbal or visual memory competence.

Subsequently, in patients who underwent left or right ATR we determined whether preoperative memory fMRI was able to predict postoperative verbal and visual memory decline. From a clinical perspective, the predictive power of a diagnostic method for individual patients is most relevant. We therefore used a step-wise linear regression model to test the predictive power of memory encoding fMRI compared to other epilepsy related predictors. Finally, we established an algorithm to predict postoperative verbal and visual memory outcome on an individual subject level.

Materials and methods

Subjects

We studied 72 patients with medically refractory temporal lobe epilepsy [41 left (21 females): median age 43 years, range 17–63; 31 right (20 females): median age 37 years, range 23–52] who underwent presurgical evaluation at the National Hospital for Neurology and Neurosurgery, London. All patients had undergone structural MRI at 3T, including qualitative assessment by expert neuroradiologists and quantification of hippocampal volumes and T₂ relaxation times (Woermann *et al.*, 1998; Bartlett *et al.*, 2007) showing unilateral hippocampal sclerosis in 40 patients with left temporal lobe epilepsy and 28 patients with right temporal lobe epilepsy; of the remaining patients, one had a left, one had a right anterior temporal cavernoma, one had right anterior temporal focal cortical dysplasia and one patient showed right medial temporal dysembryoplastic neuroepithelial tumour. All patients had normal contralateral medial temporal lobe structures on qualitative and quantitative MRI. Prolonged interictal and ictal video-EEG confirmed that seizures arose from the ipsilateral temporal lobe in all 72 patients. All patients' first language was English. During presurgical evaluation all patients underwent standardized neuropsychological assessment. Handedness was determined using a standardized questionnaire (Oldfield, 1971); language dominance was assessed using a range of fMRI tasks (Powell *et al.*, 2006), revealing left hemisphere dominance in 39 patients, atypical, bilateral language representation in 31 patients and 2 patients with atypical, right hemisphere dominance. In addition, we calculated a lateralization index using the Bootstrap method of the Statistical Parametric Mapping toolbox (Wilke and Lidzba, 2007) for the contrast 'verbal fluency' for each subject in the middle and inferior frontal gyri. A lateralization index of <−0.65 or >0.65 was considered as strongly lateralized to the left/right hemisphere. These lateralization indices were used as covariates for the second level analysis. In patients IQ was measured using the Wechsler Adult Intelligence Scale-III. The mean verbal IQ was 98.72 (SD = 17.66) in right temporal lobe epilepsy and 92.03 (SD = 12.59) in patients with left temporal lobe epilepsy; the mean performance IQ was 95.91 (SD = 15.51) in patients with right

temporal lobe epilepsy and 95.78 (SD=19.41) in those with left temporal lobe epilepsy.

All patients were treated with anti-epileptic medication at the time of their assessment, which mostly remained unchanged at the time of postoperative neuropsychological testing.

Twenty-nine of 41 left and 25 of 31 patients with right temporal lobe epilepsy underwent an ATR. The standard neurosurgical procedure was removal of the temporal pole, opening of the temporal horn, followed by *en bloc* resection of the hippocampus with a posterior resection margin at the mid brainstem level. The International League Against Epilepsy classification of postoperative seizure outcome following epilepsy surgery was used (Wieser *et al.*, 2001), revealing a seizure outcome grade of one or two in 25 left and 17 patients with right temporal lobe epilepsy and a seizure outcome grade of three to five in four left and eight patients with right temporal lobe epilepsy. For the 54 operated patients seizure outcome is given at one year following surgery for 42 subjects and 6–12 months for 12 subjects.

All patients underwent preoperative language- and memory-fMRI and standard neuropsychological assessment preoperatively and 4 months after ATR. All tests were performed at least 24 hours after a secondarily generalized and at least 6 hours after a complex partial seizure.

We also studied 20 right-handed native English-speaking healthy volunteers (median age 50 years, range 22–70; 10 females) with no history of neurological and psychiatric disease. Seventeen controls were left language dominant, three showed atypical, bilateral language representation as assessed by the fMRI language tasks. In controls, IQ was estimated using the Nelson Adult Reading Test (Nelson and Willison, 1991). The mean score in controls was 106.3 (SD=14.12).

This study was approved by the National Hospital for Neurology and Neurosurgery and the Institute of Neurology Joint Research Ethics Committee, and written informed consent was obtained from all subjects.

Neuropsychological tests

Neuropsychological testing is an integral part of our standard presurgical assessment. We selected two learning tests, one verbal and one visual, from the memory tests employed that have been demonstrated to be good indicators of postoperative memory decline (Baxendale *et al.*, 2006).

In the verbal learning task, subjects are read a list of 15 words five times and on each presentation they recall as many words as possible. The total number of words correct, expressed as a percentage, was used as the indicator of verbal memory performance. In the design learning test, subjects are presented with a design five times with recall being tested after each presentation. The percentage of correct responses over the five trials was used as the measure of visual memory performance.

Patients completed these tests before and 4 months after ATR. In those patients who underwent an ATR, measures of verbal and visual memory change following surgery were calculated as postoperative–preoperative scores. Preoperative scores as well as changes in verbal and visual memory scores from baseline following left/right ATR were then correlated with preoperative fMRI activation patterns. A clinically significant postoperative change was defined using reliable change indices (Baxendale and Thompson, 2005). The reliable change indices (90% confidence interval) were 16% for verbal learning and 28% for design learning.

Magnetic resonance data acquisition

MRI studies were performed on a 3T General Electric Excite HD_x scanner. Standard imaging gradients with a maximum strength of 40 mTm⁻¹ and slew rate 150 Tm⁻¹s⁻¹ were used. All data were acquired using an 8-channel array head coil for reception and the body coil for transmission. In addition to the fMRI data, for each subject we acquired a high resolution echo planar image covering the whole brain with the following parameters: two shots, echo time=30 ms, repetition time=4500 ms, matrix 256 × 256, 88 contiguous 1.5 mm slices. The geometric distortions were matched by introducing an additional delay to increase the echo spacing (Boulby *et al.*, 2005).

For the fMRI task, gradient-echo planar T₂*-weighted images were acquired, providing blood oxygenation level dependent contrast. Each volume comprised 44 contiguous 1.5 mm oblique axial slices through the temporal and frontal lobes, with a 24 cm field of view, 128 × 128 matrix and in-plane resolution of 1.88 × 1.88 mm; echo time=30 ms and repetition time=4.5 s. The field of view was positioned to cover the temporal lobe with the anterior–posterior axis aligned with the long axis of the hippocampus on sagittal views, and with the body of the hippocampus in the centre.

Memory fMRI paradigm and data analysis

Memory paradigm

Stimuli of three different material types [Pictures (P), Words (W) and Faces (F)] were visually presented to the subjects during a single scanning session, after explanation of what was required. This paradigm was used to investigate verbal and visual memory encoding, as described previously (Powell *et al.*, 2007). In brief, a total of 210 stimuli were presented, one every 4 s, in 7 cycles. Each cycle consisted of a block of 10 pictures (black and white nameable line drawn objects), 10 words (single concrete nouns) and 10 faces (partly black and white, partly coloured photographs unfamiliar to the subjects), followed by 20 s of crosshair fixation. During scanning, subjects were instructed to perform a deep encoding task which involved making a judgement on whether each stimulus was pleasant or unpleasant, and to indicate this using a button press. This task was employed in order to encourage stimulus encoding, but was not used in any subsequent parts of the fMRI analysis. Sixty minutes after scanning, subjects performed a recognition test outside the scanner; this comprised three separate blocks (one for pictures, one for words and one for faces). For the recognition task each of the 70 stimuli of each material type presented during scanning were randomly mixed with 35 foils and presented in an identical way to that used during scanning. Subjects were instructed to indicate whether they could remember seeing the stimulus during scanning or whether it was new to them. The 210 encoding stimuli presented during scanning were classified according to the responses made during the recognition test. A correctly remembered (R) response indicated the stimulus was subsequently remembered. An incorrect response indicated the stimulus was subsequently forgotten (F). Thus, for each of the three stimulus types (P, W and F) R and F responses were identified, giving a total of six event types: PR, WR, FR and PF, WF and FF, in which R denoted a remembered item and F denoted a forgotten item. These were then entered as regressors in the design matrix.

Data analysis

Imaging data were analysed using Statistical Parametric Mapping (SPM5) (Friston *et al.*, 1995) (Wellcome Trust Centre for Imaging Neuroscience; <http://www.fil.ion.ucl.ac.uk/spm/>). The imaging time series of each subject was realigned using the mean image as a reference, spatially normalized into standard anatomical space (using a scanner specific template created from 30 healthy controls, 15 patients with left hippocampal sclerosis and 15 patients with right hippocampal sclerosis) using the high resolution whole brain echo planar image and smoothed with a Gaussian kernel of 10 mm full-width at half maximum.

Event-related design

In order to test for subsequent memory effect an event-related analysis was used to compare encoding-related responses to individual stimuli that were subsequently remembered versus stimuli that were forgotten (Friston *et al.*, 1998). A two-level event-related random-effects analysis was employed.

At the first level, for each subject trial specific responses were modelled by convolving a delta function that indicated each event onset with the canonical haemodynamic response function to create regressors of interest, one regressor for each of the six event types (PR, PF, WR, WF, FR and FF). Each subject's movement parameters were included as confounds and parameter estimates pertaining to the height of the haemodynamic response function for each regressor of interest were calculated for each voxel. Three contrast images were created for each subject corresponding to the subsequent memory effect for each material type (picture encoding defined by PR–PF, word encoding defined by WR–WF and face encoding defined by FR–FF). All these images were then used for the second-level analysis.

At the second level of the random effects analysis, we divided the subjects into three groups: healthy volunteers, left temporal lobe epilepsy and right temporal lobe epilepsy patients. Each subject's contrast images were entered into a second level one sample *t*-test, which modelled the group effect (i.e. control subjects or patients) on the various contrasts of interest; two sample *t*-tests were used to highlight brain regions demonstrating more or less activation in one group compared with another.

In order to test for correlations between areas of fMRI activation and subject's performance on verbal learning and design learning pre and postoperatively, simple and multiple regression analyses were performed over the whole brain. For each subject the verbal learning score and the design learning score were entered as covariates separately for control subjects and left and right temporal lobe epilepsy patients. The measures of change of verbal learning and design learning scores were used to test for correlations between preoperative fMRI activation and change in verbal and visual memory test scores, from before to four months after epilepsy surgery in those patients who had an ATLR and postoperative neuropsychological assessment.

The language lateralization index derived from language fMRI as described above, the ratio of hippocampal volumes and duration of epilepsy (in years) were entered as additional covariates.

'Asymmetry image' analysis

In order to investigate the relationship between the asymmetry of medial temporal encoding activation and memory change after ATLR, we created 'asymmetry images' by rotating the normalized contrast images by 180° in the x-axis and subtracting these flipped images from the original contrast image (Richardson *et al.*, 2004). The created images represent encoding asymmetry for each stimulus type showing left minus right activation in the left and right minus left activation in

the right hemisphere. At the second level of the random effects analysis, we used a simple regression model for each group to look for brain regions showing correlations between preoperative encoding asymmetry and verbal and visual memory change following ATLR.

Second level of analysis

We tested for: (i) main effects of verbal and visual memory encoding in patients and controls; (ii) evidence of material specific lateralization of memory function by group comparison of subsequent verbal and visual memory effects in patients versus controls; (iii) efficiency of (re)organization of verbal memory functions by correlating effects for encoding pictures and words with verbal learning in controls and temporal lobe epilepsy patients and (iv) efficiency of (re)organization of visual memory functions by correlating effects for encoding pictures and faces with design learning in controls and temporal lobe epilepsy patients.

In order to evaluate whether preoperative memory fMRI is a useful predictor of postoperative verbal and visual memory deficits we then tested whether: (i) change in verbal learning scores was related to fMRI activation for encoding words in patients with left and right temporal lobe epilepsy; (ii) change in design learning scores was related to fMRI activation for encoding faces in patients with right and left temporal lobe epilepsy; (iii) encoding asymmetry for words predicted change in verbal learning scores in patients with left temporal lobe epilepsy and (iv) encoding asymmetry for faces predicted change in design learning scores in patients with right temporal lobe epilepsy.

Unless otherwise stated, we report all medial temporal lobe activations at a threshold of $P < 0.01$, corrected for multiple comparisons (family-wise error in a small volume of interest). In view of our *a priori* hypothesis we performed the small volume correction using a sphere of 10 mm diameter for the left and right hippocampi based on the peak activation. Medial temporal lobe regions of activation were labelled with reference to Duvernoy's *The Human Hippocampus* (Duvernoy, 1998).

Prediction of verbal and visual memory outcome in individual subjects

In order to identify a robust fMRI method that would be useful in a clinical setting to predict verbal and visual memory decline in individual subjects we applied the following method.

Region of interest analysis: memory asymmetry index

Based on the 'Asymmetry image analysis' we defined two spherical regions of interest of 6 mm diameter centred on the coordinates of the peak activation for encoding words or faces in the left (representing left minus right activation) and right (representing right minus left activation) anterior and posterior medial temporal lobes, in order to quantify this activation in the single subjects. In this way we obtained a memory asymmetry index within these regions for each subject. We then tested for correlations between each subject's memory asymmetry index within these regions and their change in performance on the verbal learning and design learning tests (after left/right ATLR) outside the scanner.

Stepwise linear regression

To identify the most important predictive variable(s) for postoperative verbal and visual memory decline, memory asymmetry indices were

then entered into a stepwise linear regression together with variables that have been found to be predictive in previous studies.

We tested the following hypotheses.

Preoperative neuropsychology

We tested whether preoperative verbal learning and design learning scores would correlate with and therefore be predictive of change in verbal and visual memory.

Pathology

We looked for correlations between severity of pathology and change in verbal learning and design learning scores. We used left hippocampal volume as covariate for the left temporal lobe epilepsy group and right hippocampal volume as covariate for the right temporal lobe epilepsy group.

Language lateralization

We tested whether language lateralization to the left hemisphere would predict postoperative change in verbal memory after left and visual memory after right ATLR.

Lastly, we considered whether memory asymmetry indices, language lateralization and preoperative learning test performance were predictive of postoperative decline in individual subjects.

Results

Neuropsychological performance and hippocampal volumes

Patients with left temporal lobe epilepsy had significantly lower scores (mean=55.83, SD=11.34) than controls (mean=66.53, SD=10.85) on the verbal learning test ($P=0.004$, ANOVA). There was no significant difference between controls and patients with right temporal lobe epilepsy (mean=59.26, SD=12.12) or between patients with left and right temporal lobe epilepsy on the verbal learning test.

Patients with right temporal lobe epilepsy (mean=62.23, SD=17.54) demonstrated significantly lower scores for design learning than controls (mean=77.42, SD=16.60) ($P<0.013$, ANOVA). There was no significant difference in design learning scores between controls and patients with left temporal lobe epilepsy (mean=71.49, SD=18.53) or between patients with left and right temporal lobe epilepsy.

Postoperative memory change

Twenty-five out of 29 patients undergoing a left ATLR had a postoperative decline in verbal learning scores, and for seven, this was classified as clinically significant; three patients showed a non-significant improvement in verbal learning scores and one patient's score remained unchanged. The mean change between pre and postoperative verbal learning scores was -12 , ranging from -48 to $+10$. In patients with right temporal lobe epilepsy, the mean change score for verbal learning after right ATLR was -3 , ranging from -45 to $+12$.

Twelve out of 25 patients undergoing a right ATLR had a postoperative decline in design learning scores (two clinically significant), 13 patients showed a clinically non-significant

postoperative improvement in design learning. The mean change between pre and postoperative design learning scores was -2 , ranging from -61 to $+26$. In patients with left temporal lobe epilepsy, the mean change score for design learning after left ATLR was -3 , ranging from -54 to $+36$.

Hippocampal volumes

Left and right hippocampal volumes were significantly different in both left and right temporal lobe epilepsy patients. In the left temporal lobe epilepsy group mean (SD) right hippocampal volume was 2.78 (0.30) cm³, mean left hippocampal volume 1.80 (0.54) cm³ (paired t -test $P<0.0001$, two-tailed). In the right temporal lobe epilepsy group mean (SD) right hippocampal volume was 1.78 (0.47) cm³, mean left hippocampal volume 2.60 (0.34) cm³ (paired t -test $P<0.0001$, two-tailed).

There was no significant difference between left hippocampal volume in the left temporal lobe epilepsy group and right hippocampal volume in the right temporal lobe epilepsy group, or between left and right hippocampal volume in controls. Controls' hippocampal volumes did not differ significantly from contralateral hippocampal volumes in patients with right and left temporal lobe epilepsy.

Preoperative fMRI activations and material specific memory lateralization

Main effects on fMRI activation for encoding words, faces and pictures

Controls demonstrated significant left hippocampal activation for encoding words ($P<0.0001$, family-wise error corrected) (Table 1). For encoding faces there was a significant activation in the right hippocampus ($P=0.050$, family-wise error corrected) (Fig. 1A and B). There was no significant hippocampal activation for encoding pictures in controls.

In patients with left temporal lobe epilepsy, there was significant left hippocampal activation for encoding words ($P=0.031$, family-wise error corrected) and significant right hippocampal activation for encoding faces ($P=0.005$, family-wise error corrected), while there was no significant hippocampal activation for encoding pictures. Patients with right temporal lobe epilepsy did not reveal any significant hippocampal activation for encoding pictures, words or faces at the group level.

Group comparisons for main effects

Patients with left temporal lobe epilepsy demonstrated significantly less left hippocampal activation for encoding words ($P=0.010$, family-wise error corrected) than controls (Fig. 1C). Patients with right temporal lobe epilepsy revealed significantly less left hippocampal activation for encoding words ($P=0.022$, family-wise error corrected) than controls. There was a trend for patients with right temporal lobe epilepsy to have less right hippocampal activation for encoding faces ($P=0.058$, family-wise error corrected) than controls (Fig. 1D). There was no significant difference in fMRI activation for encoding pictures between patients with left or right temporal lobe epilepsy and controls.

Table 1 fMRI activation peaks in the hippocampus for the main effects of encoding words and faces

Subjects	fMRI contrast	Z-score	Corrected P-value (family-wise error)	Coordinates (x, y, z) in MNI space	Lateralization of hippocampal activation
Controls	Word encoding	4.49	$P < 0.0001$	−22, 2, −16	Left
	Face encoding	2.47	$P = 0.050$	28, −18, −20	Right
Left temporal lobe epilepsy patients	Word encoding	2.63	$P = 0.031$	−12, −8, −18	Left
	Face encoding	3.33	$P = 0.005$	26, −20, −8	Right
Right temporal lobe epilepsy patients	Word encoding	–	NS	–	–
	Face encoding	–	NS	–	–
Group comparisons between patients and controls for the main effects of encoding words and faces					
Left temporal lobe epilepsy < controls	Word encoding	3.05	$P = 0.010$	−28, 4, −24	Left
Right temporal lobe epilepsy < controls	Word encoding	2.82	$P = 0.022$	−22, −2, −22	Left
Right temporal lobe epilepsy < controls	Face encoding	2.34	$P = 0.058$	32, −6, −18	Right

MNI space = coordinates related to a standard brain defined by the Montreal Neurological Institute (MNI); NS = not significant.

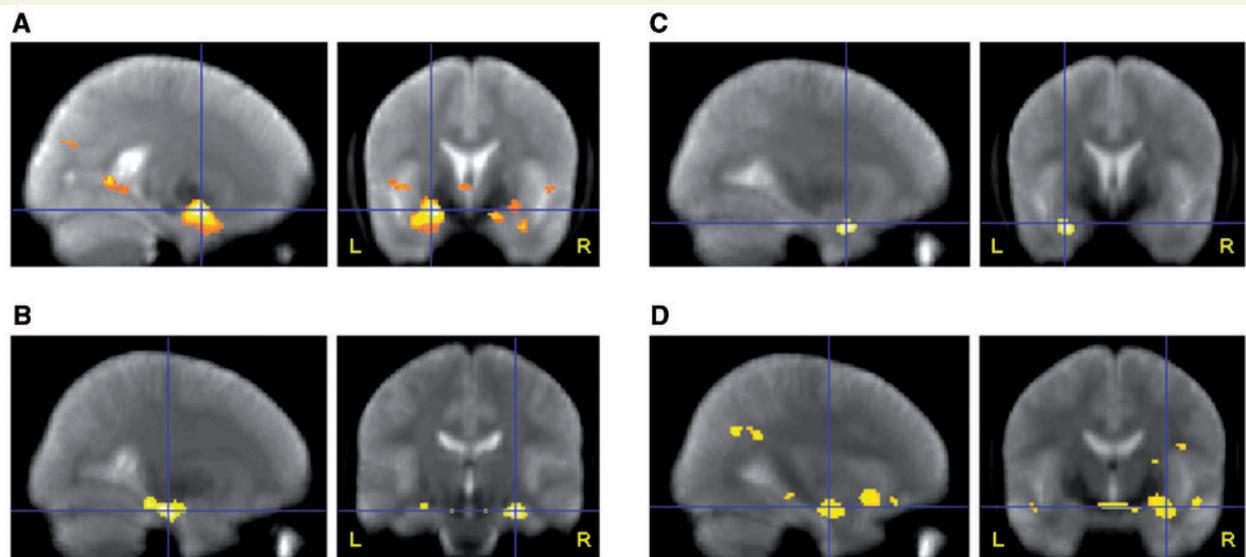


Figure 1 Group results in controls, and patients with left or right temporal lobe epilepsy. Main effects in controls are shown in **A** and **B**. (**A**) Word encoding: left hippocampal activation and (**B**) face encoding: right hippocampal activation. **C** and **D** show group comparison between controls, left and right temporal lobe epilepsy patients. (**C**) Less left hippocampal activation for encoding words in left temporal lobe epilepsy compared with controls. (**D**) Less right hippocampal activation for encoding faces in right temporal lobe epilepsy compared with controls. Threshold $P < 0.01$, uncorrected. Significant regions are superimposed onto an averaged normalized mean echo planar image from 30 healthy controls, 15 patients with left and 15 patients with right hippocampal sclerosis.

Correlation between fMRI activations and neuropsychological performance

A multiple regression analysis was performed to assess the relationship between left and right hippocampal fMRI activation for encoding pictures, words and faces and performance on preoperative tests for verbal and visual memory (Table 2). In controls, there was no significant correlation between memory fMRI for encoding pictures or words and verbal learning or between memory fMRI for encoding pictures or faces and design learning.

In patients with left temporal lobe epilepsy, there was a significant correlation in the left hippocampus ($P = 0.008$, family-wise error corrected), characterized by greater fMRI activation for

encoding words being correlated with better verbal learning scores. There was no correlation in the contralateral hippocampus.

There was a significant positive correlation between left hippocampal fMRI activation for encoding pictures and verbal learning scores ($P = 0.017$, family-wise error corrected).

We also found a significant positive correlation in the left hippocampus between preoperative fMRI activation for encoding faces and design learning scores ($P = 0.011$, family-wise error corrected). At a lower threshold, there was also a positive correlation in the right hippocampus, but this was not significant.

In right temporal lobe epilepsy patients, there was a significant positive correlation in the left hippocampus ($P = 0.042$, family-wise

Table 2 Association of verbal learning/design learning scores with memory fMRI activation

Subjects	fMRI contrast: neuropsychology task	Z-score	Corrected P-value (family-wise error)	Coordinates (x, y, z) in MNI space	Lateralization of hippocampal activation
Controls	Word encoding: VL	–	NS	–	–
	Face encoding: DL	–	NS	–	–
Left TLE	Word encoding: VL	3.15	$P=0.008$	–18, –6, –18	Left
Left TLE	Face encoding: DL	3.02	$P=0.011$	–24, –8, –10	Left
Right TLE	Word encoding: VL	2.60	$P=0.042$	–22, –28, –6	Left
Right TLE	Word encoding: 1/VL	2.68	$P=0.036$	22, –8, –14	Right
Right TLE	Face encoding: DL	3.53	$P=0.003$	34, –16, –14	Right

DL = design learning; MNI space = coordinates related to a standard brain defined by the Montreal Neurological Institute (MNI); NS = not significant; TLE = temporal lobe epilepsy; VL = verbal learning.

Table 3 Association of change of verbal learning/design learning scores with preoperative memory fMRI activation

Subjects	fMRI contrast: change in neuropsychology task	Z-score	Corrected P-value (family-wise error)	Coordinates (x, y, z) in MNI space	Lateralization of hippocampal activation
Left TLE	Word encoding: 1/VL	2.72	$P=0.028$	–24, –20, –6	Left
Left TLE	Face encoding: DL	–	NS	–	–
Right TLE	Word encoding: VL	–	NS	–	–
Right TLE	Face encoding: 1/DL	2.60	$P=0.050$	16, –14, –16	Right

DL = design learning; NS = not significant; TLE = temporal lobe epilepsy; VL = verbal learning.

error corrected), with greater fMRI activation for encoding words being correlated with better verbal learning scores. The inverse contrast revealed a significant negative correlation in the right hippocampus ($P=0.036$, family-wise error corrected), with greater fMRI activation for encoding words in the right hippocampus being correlated with worse verbal learning scores. There was also a significant positive correlation in the right hippocampus characterized by greater fMRI activation for encoding faces being correlated with better design learning scores ($P=0.003$, family-wise error corrected). There was no correlation in the contralateral hippocampus.

There was no significant correlation in the medial temporal structures between fMRI activation for encoding pictures and design learning scores.

Relation of hippocampal fMRI activation to hippocampal volumes

There was no significant correlation between hippocampal volume and fMRI activation for encoding words in patients with left temporal lobe epilepsy and no significant correlation between hippocampal volume and fMRI activation for encoding faces in patients with right temporal lobe epilepsy.

Preoperative fMRI and prediction of memory decline

A multiple regression analysis was performed to assess the relationship between preoperative fMRI activation for encoding words

and faces and changes in performance on tests for verbal and visual memory after left and right ATLR (Table 3). Encoding pictures with more bilateral activations provided weaker correlations with neuropsychological performance on tests for verbal and visual memory and so was not considered further.

There was a significant correlation in the left anterior hippocampus between preoperative fMRI activation for encoding words and change in verbal learning scores after left ATLR ($P=0.028$, family-wise error corrected), characterized by greater preoperative fMRI activation for encoding words being correlated with greater postoperative decline in verbal learning (Fig. 2A). No correlations were seen between preoperative memory fMRI for encoding faces and change in design learning scores after left ATLR.

There was no significant correlation between preoperative fMRI activation for encoding words and postoperative change in verbal learning scores in patients with right temporal lobe epilepsy. There was a significant correlation between change in design learning after right ATLR and preoperative fMRI activation for encoding faces in the right anterior hippocampus ($P=0.05$, family-wise error corrected), characterized by greater preoperative fMRI activation for encoding faces being correlated with greater postoperative decline in design learning (Fig. 2B).

Asymmetry of encoding-related fMRI activations and correlation with postoperative change in neuropsychological performance

Having identified that hippocampal activation, particularly for word and face encoding, was related to changes in material

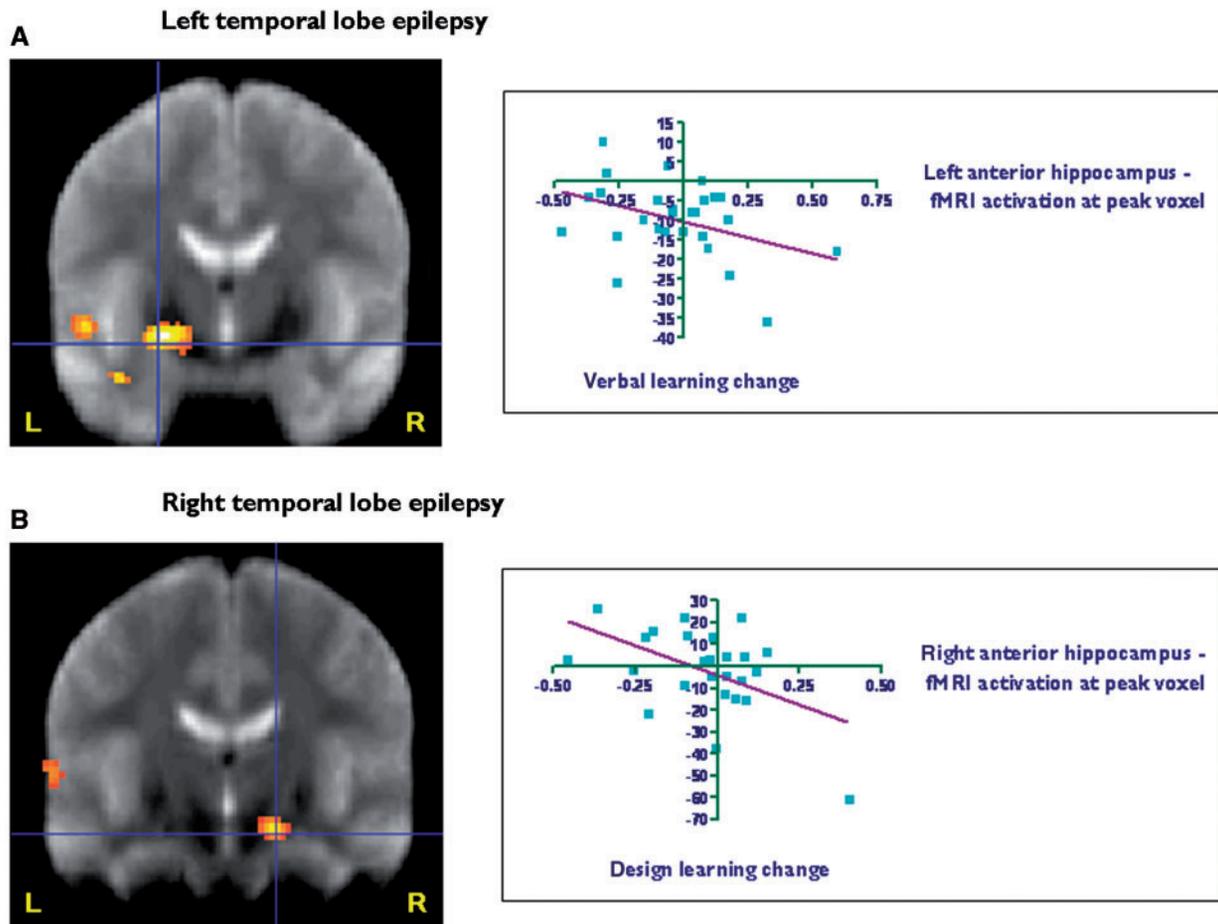


Figure 2 Prediction of verbal and visual memory decline using memory fMRI. (A) Left anterior hippocampal activation for encoding words correlates with change in verbal learning scores after left ATLR, characterized by greater verbal memory decline in subjects with greater fMRI activation. (B) Right anterior hippocampal activation for encoding faces correlates with change in design learning scores after right ATLR, characterized by greater visual memory decline in subjects with greater fMRI activation. Threshold $P < 0.01$, uncorrected. The correlations at the peak voxel are illustrated on the right. Significant regions are superimposed onto an averaged normalized mean echo planar image from 30 healthy controls, 15 patients with left and 15 patients with right hippocampal sclerosis.

specific memory after ATLR, a simple regression analysis was performed to assess the relationship between preoperative fMRI encoding asymmetry for words and faces and change in performance on tests for verbal and visual memory after ATLR (Table 4).

Preoperatively, greater left than right anterior hippocampal activation asymmetry for encoding words was correlated with greater verbal memory decline after left ATLR ($P = 0.028$, family-wise error corrected). There was a positive correlation in the left posterior hippocampus, that did not reach statistical significance for the voxel-wise analysis ($P = 0.076$, family-wise error corrected) with greater left than right posterior hippocampal activation being associated with better verbal memory outcome after left ATLR.

Greater right than left anterior hippocampal activation asymmetry for encoding faces was correlated with greater visual memory decline after right ATLR ($P = 0.063$, family-wise error corrected).

Region of interest analysis: memory asymmetry index in individual subjects

In order to determine whether memory fMRI may be applied as a robust clinical tool for predicting effects of ATLR on memory, we calculated a memory asymmetry index in the anterior and posterior medial temporal lobe to encode words and faces for each individual subject for correlation with each patient's change in verbal and visual memory scores.

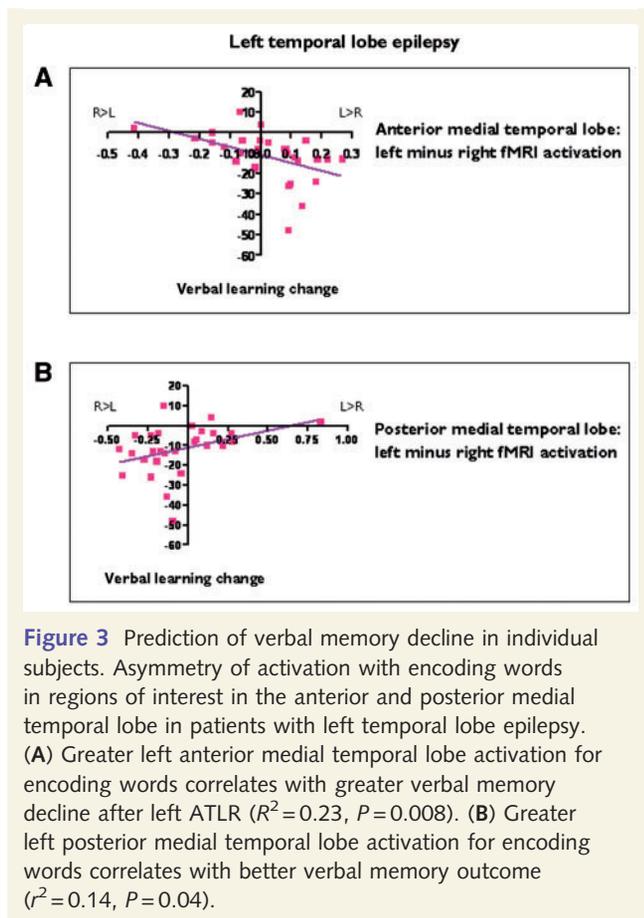
There was a significant negative correlation between memory asymmetry indices for encoding words and change in verbal learning scores, characterized by greater left than right anterior medial temporal lobe fMRI activation for encoding words being correlated with greater verbal memory decline after left ATLR ($R^2 = 0.23$, $P = 0.008$).

In the posterior medial temporal lobe there was a significant positive correlation, characterized by greater left than right posterior medial temporal lobe activation being correlated with better verbal memory outcome after left ATLR ($R^2 = 0.14$, $P = 0.04$) (Fig. 3).

Table 4 Preoperative memory encoding asymmetry for words and faces and changes of verbal learning and design learning scores

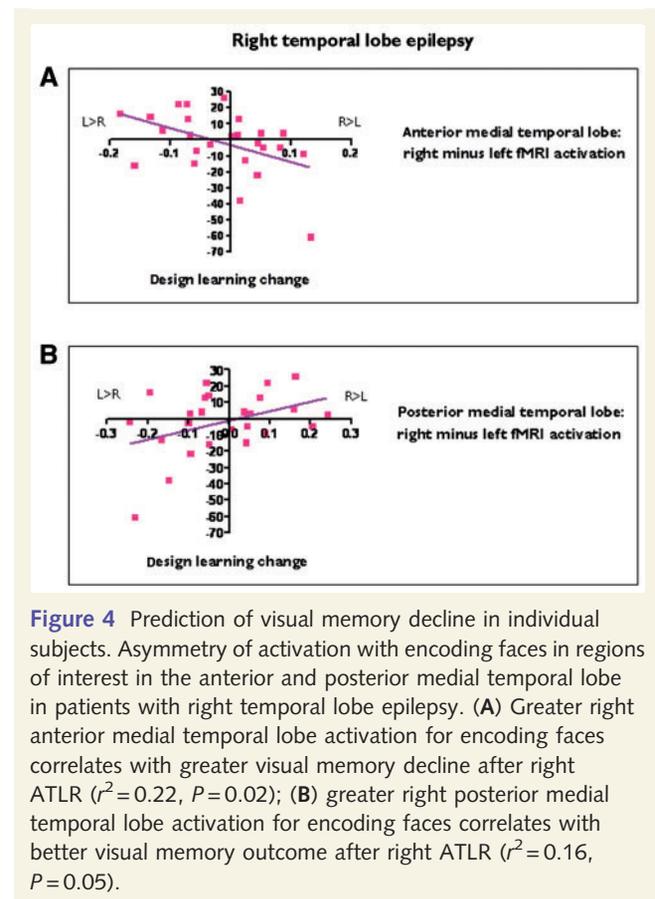
Subjects	fMRI encoding asymmetry: change in neuropsychology task	Z-score	Corrected P-value (family-wise error)	Coordinates (x, y, z) in MNI space	Anatomical region
Left TLE	Encoding words: 1/VL	2.96	$P=0.028$	-16, -4, -4	Left anterior HC
Left TLE	Encoding words: VL	2.70	$P=0.076$	-34, -38, -10	Left posterior HC
Right TLE	Encoding faces: 1/DL	2.63	$P=0.063$	32, -6, -10	Right anterior HC
Right TLE	Encoding faces: DL	2.12	NS	38, -26, -8	Right posterior HC

DL = design learning; HC = hippocampus; MNI space = coordinates related to a standard brain defined by the Montreal Neurological Institute (MNI); NS = not significant; TLE = temporal lobe epilepsy; VL = verbal learning.



Greater right than left fMRI activation for encoding faces in the right anterior medial temporal lobe was correlated with greater visual memory decline ($R^2=0.22$, $P=0.02$) after right ATLR.

In the posterior medial temporal lobe there was a significant positive correlation between memory asymmetry indices for encoding faces and change in design learning scores after right ATLR, characterized by greater right than left posterior medial temporal lobe activation being correlated with better visual memory outcome ($R^2=0.16$, $P=0.05$) (Fig. 4).



Epilepsy-related factors and memory decline

There were no statistically significant correlations between left hippocampal volume and postoperative verbal memory decline in patients with left temporal lobe epilepsy or between right hippocampal volume and postoperative visual memory decline in patients with right temporal lobe epilepsy.

In patients with left temporal lobe epilepsy there was no significant correlation between preoperative verbal learning scores and verbal memory decline after left ATLR (Pearson's correlation

coefficient, $r = -0.037$; $P = 0.42$) (one-tailed). In patients with right temporal lobe epilepsy there was a significant correlation between preoperative design learning scores and visual memory decline after right ATLR, characterized by a greater decline in patients with better preoperative performance (Pearson's correlation coefficient $r = -0.381$; $P = 0.03$) (one-tailed).

There was a significant correlation between language lateralization index and verbal memory decline (Pearson's correlation coefficient $r = 0.331$; $P = 0.04$) (one-tailed), characterized by greater language lateralization to the left being correlated with greater verbal memory decline after left ATLR. There was no significant correlation between language lateralization index and visual memory decline after right ATLR.

No significant correlations were seen between duration of epilepsy and verbal or visual memory decline in patients with left or right temporal lobe epilepsy.

0.1% ($R^2 = 0.001$) of the variance of verbal memory decline were explained by preoperative verbal learning scores, 0.1% ($R^2 = 0.001$) by left hippocampal volumes and 11% ($R^2 = 0.109$) by language lateralization.

14.5% ($R^2 = 0.145$) of the variance of visual memory decline were explained by preoperative design learning scores, 7.2% ($R^2 = 0.072$) by right hippocampal volumes and 4.1% ($R^2 = 0.041$) by language lateralization.

Stepwise linear regression to identify variables predictive of memory decline

Four variables were entered into stepwise linear regression models with postoperative verbal and visual memory change as the dependent variables in order to test for the strongest predictor. These were (i) for verbal memory: preoperative verbal learning scores, left hippocampal volume, language lateralization index, memory asymmetry index for encoding words (in the left anterior medial temporal lobe); and (ii) for visual memory: preoperative design learning scores, right hippocampal volume, language lateralization index, memory asymmetry index for encoding faces (in the right anterior medial temporal lobe).

Verbal memory: In this model, which was predictive of postoperative verbal memory change ($R^2 = 0.23$, $P < 0.008$), memory asymmetry for encoding words in the anterior medial temporal lobe was the only and strongest predictor; no other variables made a significant contribution ($P > 0.1$) to the model.

Visual memory: This model predicted postoperative visual memory change ($R^2 = 0.395$, $P < 0.004$). Stepwise linear regression demonstrated that memory asymmetry for encoding faces in the anterior medial temporal lobe (beta weights: -0.502) and preoperative design learning scores (beta weights: -0.425) made a significant contribution to this model with memory asymmetry for encoding faces being the strongest predictor.

Prediction of memory decline in individual subjects

From a clinical perspective, the sensitivity, specificity and positive predictive value of a diagnostic method are the most important

measures, with the latter reflecting the probability that a positive test reflects the underlying condition that is being tested for. Being able to advise patients on the possible risk for a clinically significant verbal or visual memory decline is most relevant.

A clinical significant verbal memory change was defined as a decline of $>16\%$ and a significant visual memory change as a decline of $>28\%$. We first calculated the positive predictive value, sensitivity and specificity of memory fMRI alone (Table 5). Greater activation on word encoding in the left, than the right anterior medial temporal lobe identified all seven patients who subsequently experienced a clinically significant decline of verbal memory after left ATLR. Of the two who experienced a clinically significant decline of visual memory after right ATLR, one had greater activation during face encoding in the right, than the left anterior medial temporal lobe.

With a relatively large number of false positives, memory fMRI alone provides only average power to predict postoperative decline (positive predictive value for verbal memory change: 35%; positive predictive value for visual memory change: 20%). We therefore also considered language lateralization (< -0.65 = strongly left lateralized) and performance on preoperative psychology tests ($>50\%$ = high preoperative verbal learning score; $>65\%$ = high preoperative design learning score) in addition to the memory asymmetry index (either predominantly left or right anterior medial temporal lobe activation) to calculate the risk on an individual subject level (positive predictive value of all three tests) as these variables have been previously reported to be predictive (Baxendale *et al.*, 2006; Binder *et al.*, 2008; Saling, 2009). In this way, anterior medial temporal lobe encoding asymmetry for words with greater left than right activation, combined with higher preoperative verbal memory scores on neuropsychological testing and language lateralization to the left hemisphere identified all left temporal lobe epilepsy cases with a clinically significant verbal memory decline after left ATLR with 100% sensitivity and 86% specificity.

Table 5 Positive predictive value, sensitivity and specificity of memory fMRI in a region of interest in the anterior medial temporal lobe

Verbal memory change (left TLE)	Sensitivity 100%	Specificity 40.91%	PPV 35%
Visual memory change (right TLE)	Sensitivity 50%	Specificity 82.61%	PPV 20%

PPV = positive predictive value; TLE = temporal lobe epilepsy.

Table 6 Positive predictive value, sensitivity and specificity of memory asymmetry indices, language lateralization and preoperative verbal learning/design learning scores

Verbal memory change (left TLE)	Sensitivity 100%	Specificity 86.36%	PPV 70%
Visual memory change (right TLE)	Sensitivity 50%	Specificity 100%	PPV 100%

PPV = positive predictive value; TLE = temporal lobe epilepsy.

In the same way, visual memory decline after right ATRL was predicted with 50% sensitivity and 100% specificity in right temporal lobe epilepsy, but only two patients had a clinically significant visual memory decline (Table 6). When used without fMRI data, preoperative verbal learning and hippocampal volumes did not discriminate between the seven who did, and the 22 patients who did not have a significant decline in verbal memory.

Discussion

We report a series of investigations of memory fMRI in temporal lobe epilepsy, and the ability of the method to predict memory decline after ATRL. First, we demonstrated that left hippocampal activation in a verbal memory task was associated with out of scanner verbal learning proficiency in patients with left temporal lobe epilepsy, while right hippocampal activation in a visual memory task was associated with performance on design learning in patients with right temporal lobe epilepsy, highlighting the role of the hippocampus during material specific memory encoding. Secondly, we demonstrated that memory fMRI activation in the hippocampal regions was predictive of both verbal and visual memory outcome after left or right ATRL. We showed that memory fMRI was the strongest predictor for postoperative verbal and visual memory decline compared to other related factors such as language lateralization, preoperative performance on neuropsychological tasks and duration of epilepsy. Finally, we devised an algorithm to predict a clinically significant postoperative decline in individual patients.

Memory fMRI in temporal lobe epilepsy

A number of studies have used fMRI for prediction purposes (Rabin *et al.*, 2004; Richardson *et al.*, 2004, 2006; Janszky *et al.*, 2005; Binder *et al.*, 2008; Powell *et al.*, 2008); however, nearly all of these studies are based on small patient numbers, mostly reporting group results or are limited by imaging techniques. Most studies used block designs which have the advantage of greater sensitivity detecting activation in individual subjects and of being less vulnerable to alterations in the haemodynamic response function than event-related analyses. Rabin *et al.* (2004), for example, used a complex visual scene-encoding task to show symmetrical medial temporal lobe activation in controls while patients with temporal lobe epilepsy showed greater asymmetry. This was also related to postsurgical memory outcome with greater ipsilateral activation correlating with greater memory decline using change in recognition performance during the tasks rather than out of scanner tests of verbal and visual memory as a covariate (Rabin *et al.*, 2004). Using Roland's Hometown Walking task (Roland *et al.*, 1987) Janszky *et al.* (2005) found that reduced activation of the medial temporal lobe region ipsilateral to the seizure focus correlated with a favourable memory outcome after right ATRL (Janszky *et al.*, 2005). Binder and co-workers found that left language dominance assessed by preoperative language fMRI was useful in addition to other factors such as late age of epilepsy onset and preoperative neuropsychological performance to predict postoperative

memory decline in patients with left temporal lobe epilepsy compared to intracarotid amygdala testing for both language and memory lateralization (Binder *et al.*, 2008).

Previous studies by our group have demonstrated the advantages of an event-related analysis for evaluating verbal and/or visual memory decline after ATRL (Richardson *et al.*, 2004; Powell *et al.*, 2008). Although less powerful than blocked designs, event-related designs allow detection of activations that arise specifically during successful encoding. Another advantage is the possibility of capturing anterior hippocampal activation during an encoding task, which is therefore in an area that will be removed by ATRL; while studies based on blocked designs are more likely to show areas of activation in more posterior hippocampal and parahippocampal regions, which occur during cognitive processes other than memory encoding. Richardson *et al.* (2003, 2004) used an event-related design to assess verbal memory encoding in 10 patients with temporal lobe epilepsy who subsequently underwent left ATRL, demonstrating that greater left than right hippocampal activation was strongly related to greater postoperative verbal memory decline (Richardson *et al.*, 2003, 2004).

Powell *et al.* (2005) used a material specific memory encoding paradigm that tested verbal and visual memory in one scanning session. They demonstrated that patients with relatively greater ipsilateral compared to contralateral medial temporal lobe activation suffered greater verbal or visual memory decline after dominant/non-dominant ATRL in an initial pilot study of 15 patients with temporal lobe epilepsy (Powell *et al.*, 2008). Using a similar paradigm with a 3T rather than a 1.5T MRI scanner, our study assessed the predictive power of memory fMRI in a large cohort of patients that resulted in the development of an algorithm to predict clinical significant verbal and visual memory decline in individual subjects. We demonstrated that relatively greater ipsilateral than contralateral preoperative anterior hippocampal activation for word or face encoding predicted greater verbal or visual memory decline in a large series of patients with temporal lobe epilepsy who underwent left or right ATRL. In addition, absolute activation within the left or right anterior hippocampus was also predictive of both postoperative verbal and visual memory decline.

Neurobiological implications

To explain memory deficits following ATRL two different models of hippocampal function have been put forward (Chelune *et al.*, 1991). The hippocampal reserve theory suggests that it is the reserve or capacity of the contralateral hippocampus that supports memory function after surgery and therefore determines the decline in memory function. The functional adequacy model on the other hand suggests that it is the capacity of the ipsilateral hippocampus, which is to be resected, that determines whether changes in memory function will be observed. Other studies assessing baseline neuropsychology (Chelune *et al.*, 1991; Helmstaedter and Elger, 1996), intracarotid amygdala testing (Kneebone *et al.*, 1995) and MRI volumetry (Trenerry *et al.*, 1993) have provided support for the functional adequacy model of the ipsilateral hippocampus rather than the functional reserve of the contralateral hippocampus supporting memory function. Our findings that

greater left/right anterior hippocampal activation was associated with greater verbal/visual memory decline after ATR while no significant correlations were observed in the contralateral hippocampus strongly support the functional adequacy theory in keeping with findings of other studies that employed regions of interest in the medial temporal lobe to evaluate the risk of postoperative memory decline (Rabin *et al.*, 2004; Richardson *et al.*, 2006). The fact that there was some bitemporal involvement of some verbal and visual memory function with the paradigms used suggests that the paradigms were not 'pure' in terms of being material specific, or that there may have been some bilaterality of specific memory encoding functions. This may provide some evidence for the hippocampal reserve model. Several post-resection studies challenge the model of pure material specificity as summarized by Saling (2009), suggesting that cerebral organization of verbal and visual memory are neither opposites nor fully lateralized. Recent fMRI studies also concluded that contralateral reorganization was not efficient but rather a marker of network disruption due to underlying pathology (Powell *et al.*, 2007).

A novel finding of our study was that while ipsilateral anterior hippocampal activation was associated with greater verbal and visual memory decline following left and right ATR, respectively, relatively greater activation in the posterior part of the ipsilateral hippocampus (which is likely to be spared during an ATR) was correlated with better verbal or visual memory outcome. Together with our results of the voxel-based analysis, these findings provide strong support for the functional adequacy model suggesting that ipsilateral recruitment of posterior hippocampal networks is more efficient than recruitment of the contralateral hippocampus supporting memory function after surgery.

Clinical implications

Prediction of postoperative neuropsychological deficits is the ultimate goal of clinical neuroimaging as part of presurgical investigations in patients with temporal lobe epilepsy. We demonstrated that the prediction of both verbal and visual memory decline was possible using memory fMRI in patients with both left and right temporal lobe epilepsy.

From a clinical perspective it is the prediction of verbal memory decline in individual subjects which is most relevant, particularly in those individuals who are high functioning preoperatively and therefore have most to lose. We devised an algorithm using asymmetry indices of preoperative memory encoding activation in the anterior medial temporal lobe, language lateralization and performance on preoperative neuropsychological assessment to predict clinically significant postoperative verbal and visual memory outcome in individual subjects. We identified a region of interest in individual patients, in the anterior medial temporal lobe and calculated an asymmetry index of fMRI activation for memory encoding for each subject. Individuals with greater left than right activation in this region were at greater risk of suffering a clinically significant verbal memory decline after left ATR, while those with greater right than left activation were found to be at risk of suffering a clinically significant visual memory decline following right ATR. This methodology is straight forward to apply, robust, and could be readily adopted in clinical practice. Using memory

asymmetry indices, language lateralization indices and preoperative performance on neuropsychological tests, we were then able to predict a clinically significant postoperative verbal decline in all of our patients who underwent left ATR. The algorithm was less predictive of visual memory decline, but this was much less common and is usually of less clinical importance; yet may be relevant for some roles, such as remembering routes and architectural designs. Having devised this algorithm, it now needs to be tested prospectively in a further large series of patients.

Methodological aspects and limitations

This study has several strengths and limitations.

- (i) Using an event-related memory design is time consuming and demanding on patients and personnel. In patients and controls with excellent performance on the postscanning memory test the contrast 'items remembered' versus 'items forgotten' might not result in strong activation. Introducing a third contrast such as 'familiar' and therefore more variety, could be a solution for this problem. On the other hand, the event-related analysis has the great advantage of showing activation in the anterior hippocampus, which is the part of the hippocampus that will be removed during an ATR. By using an event-related design one only takes into account successfully encoded items. Localizing the part of the brain at which fMRI activation correlates with out of scanner performance on neuropsychological tests provides the biological basis for (postoperative) neuropsychological findings. In 10 further patients with temporal lobe epilepsy scanned over the time frame of this study, no activation was seen in the single subjects, or the subjects could not manage to carry out the scanning protocol, which is therefore not universally applicable.
- (ii) In this study, imaging parameters were optimized for capturing activation in the temporal lobes and nearby structures. Accordingly our field of view was limited to coverage of the temporal lobes so that we cannot comment on any possible compensatory mechanisms involving other brain areas, such as the orbito-frontal cortex as described by Dupont *et al.* (2000) for example. Furthermore, our results may be influenced by the effect of volume averaging on the extent and magnitude of hippocampal signal, given that most of the patients had hippocampal sclerosis. We also experienced the usual technical difficulties of fMRI studies tailored to the temporal lobes such as low resolution, distortions and signal dropout. Future studies will benefit from improved fMRI techniques with whole brain coverage and improved fMRI paradigms to obtain strong and reliable activations in each subject.
- (iii) Finally memory was tested only 4 months after surgery, which might be too early for any contralateral hippocampal reserve to become fully functional; prospective follow-up studies are underway evaluating memory outcome after one year.

Conclusion and future studies

We have shown that memory fMRI is the strongest predictor for postoperative verbal and visual memory decline in individual subjects using a material specific memory encoding paradigm compared to other previously suggested predictors. Our results support the functional adequacy theory, suggesting that it is the capacity of the ipsilateral hippocampus, most likely the remaining posterior part, which preserves verbal and visual memory encoding function after ATR. We are carrying out postoperative fMRI memory studies correlating postoperative fMRI activation with postoperative performance on neuropsychological tests to address this important issue. This may lead to a re-evaluation of the role of tailored hippocampal resections to minimize the risk of memory impairment. Future work is needed to optimize imaging parameters in order to obtain whole brain coverage and gain information on possible reorganization in brain areas other than the temporal lobe. Development of additional cognitive fMRI tasks will be required in order to assess other aspects of memory function that might be impaired in patients with temporal lobe epilepsy, in addition to verbal and visual memory encoding (i.e. working memory). Memory fMRI studies and correlation with postoperative performance at intervals after ATR are needed for comparison with preoperative activation patterns and to elucidate the nature of postoperative recovery and plasticity. The algorithm we devised to predict memory decline in individual patients now needs to be tested in a further prospective cohort.

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