decline after anterior temporal lobe resection

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ABSTRACT

Objective: To develop a clinically applicable memory functional MRI (fMRI) method of predicting postsurgical memory outcome in individual patients.

Methods: In this prospective cohort study, 50 patients with temporal lobe epilepsy (23 left) and 26 controls underwent an fMRI memory encoding paradigm of words with a subsequent out-of-scanner recognition assessment. Neuropsychological assessment was performed preoperatively and 4 months after anterior temporal lobe resection, and at equal time intervals in controls. An event-related analysis was used to explore brain activations for words remembered and change in verbal memory scores 4 months after surgery was correlated with preoperative activations. Individual lateralization indices were calculated within a medial temporal and frontal region and compared with other clinical parameters (hippocampal volume, preoperative verbal memory, age at onset of epilepsy, and language lateralization) as a predictor of verbal memory outcome.

Results: In left temporal lobe epilepsy patients, left frontal and anterior medial temporal activations correlated significantly with greater verbal memory decline, while bilateral posterior hippocampal activation correlated with less verbal memory decline postoperatively. In a multivariate regression model, left lateralized memory lateralization index (≥ 0.5) within a medial temporal and frontal mask was the best predictor of verbal memory outcome after surgery in the dominant hemisphere in individual patients. Neither clinical nor functional MRI parameters predicted verbal memory decline after nondominant temporal lobe resection.

Conclusion: We propose a clinically applicable memory fMRI paradigm to predict postoperative verbal memory decline after surgery in the language-dominant hemisphere in individual patients. *Neurology®* 2015;84:1512–1519

GLOSSARY

ATLR = anterior temporal lobe resection; **CI** = confidence interval; **fMRI** = functional MRI; **FWE** = family-wise error; **LI** = lateralization index; **LTLE** = left temporal lobe epilepsy; **MTL** = medial temporal lobe; **PHG** = parahippocampal gyrus; **PPV** = positive predictive value; **RCI** = reliable change index; **RTLE** = right temporal lobe epilepsy; **TLE** = temporal lobe epilepsy; **WR** = words remembered.

Anterior temporal lobe resection (ATLR) brings remission in 80% of patients with refractory temporal lobe epilepsy (TLE).[1] Significant verbal memory loss occurs after 30% of speech dominant hemisphere ATLR[2–5] and less commonly after nondominant ATLR.

Material specific memory encoding paradigms that predominantly activate the left (verbal) and right (visual) hemispheres have been investigated to predict memory decline after ATLR.[6–8]

During a verbal encoding task, greater left than right activation within the anterior medial temporal lobe (MTL) was a better predictor of verbal memory decline than preoperative list learning scores and functional MRI (fMRI) language lateralization index (LI).[8] Several studies have investigated absolute activations rather than asymmetry images to predict postsurgical verbal memory decline using a LI within the MTL with mixed results.[9,10] To date, lateralization of absolute activations to predict memory decline has only been investigated within the medial

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temporal lobe.[11–13] Using a verbal memory encoding paradigm, we showed that frontal and temporal activations were involved in successful verbal memory formation,[14] suggesting that preoperative extratemporal activations may play a role in predicting postoperative verbal memory decline.

To develop a clinically applicable memory fMRI method for predicting postsurgical memory decline in individual patients, we preformed the following:

1. Investigated which temporal and extratemporal brain activations were predictive of postsurgical verbal memory outcome after ATLR, using an event-related word encoding task
2. Devised a clinically applicable algorithm using objective fMRI LI parameters from an MTL and frontal region of interest to predict postsurgical verbal memory decline in individual patients
3. Compared memory fMRI to language fMRI and standard clinical parameters including age at onset of epilepsy, preoperative hippocampal volume, and preoperative memory score for predicting postsurgical memory outcome

METHODS **Subjects.** Fifty-seven patients (27 left) with medically refractory TLE undergoing epilepsy surgery at the National Hospital for Neurology and Neurosurgery, London, UK, were prospectively studied. Prolonged interictal and ictal EEG-video telemetry confirmed ipsilateral seizure onset zones in all patients.

Inclusion criteria included patients who underwent standard en bloc ATLR with resection of the hippocampus extending to mid brainstem level. Four patients (3 left TLE [LTLE]) were excluded as resection did not include the hippocampus. One right TLE (RTLE) patient was excluded as a previous lesionectomy included part of the anterior MTL. Two patients with IQ <70 (1 LTLE) were excluded. In total, 50 patients (23 LTLE) were included (table 1, table e-1 on the *Neurology*® Web site at Neurology.org).

All patients had structural MRI at 3T including hippocampal volume quantification (table 1). All patients received antiepileptic medication and spoke fluent English. Detailed neuropsychometry was performed before and 4 months after ATLR.

Twenty-six healthy native English-speaking controls were also studied (table 1). Handedness and language dominance were determined using a standardized questionnaire[15] and language fMRI tasks.[16] Asymmetry of expressive language activation was calculated within an inferior and middle frontal gyrus mask created using the WFU PickAtlas in SPM8.[17] A bootstrap method was used to calculate language LI using SPM8.[8] A LI of ≥0.5 or ≤0.5 was deemed strongly left or right lateralized, respectively. Forty-six patients (21 LTLE) were left lateralized, 2 bilateral (1 LTLE) and 2 (1 LTLE) right lateralized (table e-1).

Standard protocol approvals, registrations, and patient consents. This study was approved by the National Hospital for Neurology and Neurosurgery and UCL Institute of Neurology Joint Research Ethics Committee. Written informed consent was obtained from all participants.

Neuropsychological testing. All patients underwent standardized cognitive assessments including intellectual functioning.[18] Verbal learning was assessed using the BIRT Memory and Information Processing Battery List Learning subtest.[19,20] Participants were read a list of 15 words over 5 trials with recall tested after each trial. The score was the sum of recalled words. This was performed preoperatively and 4 months postoperatively. A reliable change index (RCI) was used to assess cognitive change after surgery. We calculated RCIs for the list learning task, based on data from the controls tested at baseline and 6–10 months later. Using these RCI, significant decline with 90% confidence interval (CI)[8] was defined as a ≥10-point decline at 4 months after surgery.

Magnetic resonance data acquisition. We used a 3T GE (Cleveland, OH) Excite HDx MRI scanner. Gradient-echo echoplanar images provided blood oxygen level–dependent contrast. Each volume comprised 36 contiguous oblique axial slices, slice thickness 2.5 mm (0.3-mm gap), field of view 24 cm, matrix 96 × 96 interpolated to 128 × 128 during image reconstruction, in-plane resolution 2.5 mm × 2.5 mm, SENSE factor 2.5, echo time 25 ms, repetition time 2.75 seconds. The field of view covered the temporal and frontal lobes with the slices aligned with the long axis of the hippocampus.[14]

Memory encoding paradigm. Concrete nouns were presented visually. Each word was presented for 3 seconds in 30-second blocks. Each block consisted of 10 words followed by 15-second crosshair fixation.

Ten blocks (100 words) were presented in total. An interstimulus interval of 3 seconds differed from the repetition time of 2.75 seconds to introduce jitter and ensure random sampling.[14] Participants were instructed to memorize items for subsequent recall testing. A subjective pleasant/unpleasant decision was indicated using a magnetic resonance–compatible joystick as a deep encoding task.[21] After scanning, subjects were shown the same 100 words intermixed with 50 novel words in a recognition task.

Table 1	Age, age at onset of epilepsy, and duration of epilepsy								
	Age, y, median (IQR)	Age at onset, y, median (IQR)	Duration of epilepsy, y, median (IQR)	HV, cm³, mean (SD)	NART IQ, mean (SD)	Preop VL, mean (SD)	Postop VL, mean (SD)	Preop RA, %, mean (SD)	Postop RA, %, mean (SD)
Controls	37 (24)	NA	NA	2.15 (1.1)	111.5 (11)	57.4 (8.9)	57.3 (5.5) (retest)	76 (5.1)	75.2 (19.5) (retest)
LTLE	34 (17)	11 (21)	18 (27)	1.9ª (0.7)	93.1ª (10.3)	43.1ª (10.7)	39.3ª (14.6)	54.1 (24.0)	47.4ª (22.5)
RTLE	35 (22)	17 (12)	17 (24)	2.4 (0.5)	100.2ª (11.1)	48.4ª (8.9)	44.3ª (11.6)	55 (24.1)	59.7ª (19.2)

Abbreviations: HV = hippocampal volume; IQR = interquartile range; NART = National Adult Reading Test; RA = recognition accuracy; VL = verbal learning.
ª Controls > patient group indicated, 2-tailed *t* test *p* < 0.005.

A button box was used to indicate if items were remembered, familiar, or novel. Words previously presented in the scanner were sorted as remembered, familiar, or forgotten. Recognition accuracy (%) was calculated as true positive − false positive.

Data analysis. Analysis used SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). Imaging time series were realigned, normalized into standard anatomical space (using a scanner-specific template created from 30 controls, and 30 left and right hippocampal sclerosis patients), and smoothed with an 8-mm full-width at half maximum Gaussian kernel.[14]

Event-related analysis. We compared the encoding-related responses for stimuli that were subsequently remembered with a 2-level event-related random-effects analysis.

First level. For each subject, delta functions of words remembered (WR) were convolved with the canonical hemodynamic response and its temporal derivative. The generated WR contrast image for each subject was used in the second-level analysis.

Second level. One-sample t tests were used to examine the group effect of each contrast. Differences between groups were explored with analysis of variance. We determined the relevance of fMRI memory activations using a simple regression model of WR activations with preoperative list learning scores.[14]

Preoperative brain activations associated with greater/less postsurgical verbal memory decline were investigated using a simple regression model of change in list learning scores against WR activations. Language LIs were used as a covariate in second-level analyses.

Group activations were corrected for multiple comparisons family-wise error (FWE), $p < 0.05$. Group differences and correlations are reported at $p < 0.001$, uncorrected. All activations within the MTL are corrected for multiple comparisons FWE within a 12-mm diameter sphere[14] unless otherwise stated.

Individual patient memory LI calculation. An anatomical mask incorporating frontal and medial temporal lobes (amygdala, parahippocampal gyrus [PHG], hippocampus, middle and inferior frontal gyri) was created using the WFU PickAtlas in SPM8.[17] A bootstrap method was used to calculate LI within the frontotemporal mask in all patients using the SPM8 LI toolbox. LI of ≥0.5 was deemed strongly left lateralized.

Linear regression. Linear regression was used to investigate the utility of memory LI, language LI, and predictive clinical variables (preoperative hippocampal volume, preoperative list learning, and age at onset of epilepsy)[8] in predicting postoperative verbal memory decline.

Statistical analyses used PASW Statistics 18.0 (IBM, Armonk, NY).

RESULTS **Behavioral.** LTLE and RTLE patients performed worse than controls in the recognition test preoperatively and postoperatively ($p < 0.005$). LTLE patients showed a significant decline while RTLE patients showed a nonsignificant improvement in recognition accuracy ($p > 0.1$) (table 1).

Neuropsychological performance and clinical parameters. Both LTLE and RTLE patients had lower IQs and performed significantly less well than controls on the verbal learning task, preoperatively and postoperatively (2-tailed t test $p < 0.005$; table 1). LTLE and RTLE patients did not differ significantly in age, age at onset of epilepsy, epilepsy duration, or verbal learning (2-tailed t test $p > 0.1$; table 1).

Of the 23 LTLE patients assessed 4 months postoperatively, 14 showed verbal memory decline (8 significant), 1 showed no change, and 8 improved (3 significant). The mean change in verbal learning was −3.7 (SD 13.7) (range −32 to +27). Eighteen RTLE patients showed verbal memory decline (7 significant) and 9 improved (2 significant). Mean change in verbal learning was −4.2 (SD 9.4). One RTLE patient was right dominant for language and verbal memory declined significantly after right ATLR (table e-1).

Main effects and group comparisons. Controls activated the left fusiform, precentral and postcentral, inferior frontal, and middle occipital gyri, orbitofrontal cortex, left hippocampus, and PHG. LTLE patients activated the left fusiform, inferior frontal, precentral, and inferior temporal gyri, inferior parietal lobule, hippocampus, and PHG. Activations were seen in the right superior frontal gyrus, inferior parietal lobule, and hippocampus.

RTLE patients activated left hippocampus, precentral, inferior temporal, and inferior frontal gyri, orbitofrontal cortex, and supplementary motor area. LTLE patients showed significantly less activation in the left fusiform gyrus, anterior PHG, body of hippocampus, middle temporal gyrus, and medial frontal lobe, and greater right inferior frontal gyrus activation than controls. No quantitative activation differences were seen between RTLE patients and controls (figure 1, table e-2).

Correlation of fMRI WR activations with list learning scores. WR activations did not correlate with list learning in controls. In LTLE patients, left PHG, body and posterior hippocampus, amygdala ($p = 0.01$), right hippocampus ($p = 0.009$), left orbitofrontal cortex, and anterior cingulum activations correlated significantly with higher preoperative list learning scores. This implied that successful verbal memory formation was associated with activation of these structures preoperatively. In RTLE patients, no correlation between WR activations and preoperative list learning was seen (table e-3).

Prediction of postoperative verbal memory. *Clinical parameters and verbal memory decline.* *LTLE.* Verbal memory decline correlated significantly with language lateralization ($R = 0.44$, $p = 0.037$), implying greater verbal memory decline with increasing left language LI. Preoperative verbal memory, age at onset of epilepsy, and hippocampal volumes did not correlate with postoperative memory change ($p > 0.1$).

RTLE. Preoperative verbal memory, age at onset of epilepsy, hippocampal volume, and language lateralization did not correlate with postoperative verbal memory change ($p > 0.1$).

Figure 1   Memory encoding activations in controls, left temporal lobe epilepsy patients, and right temporal lobe epilepsy patients
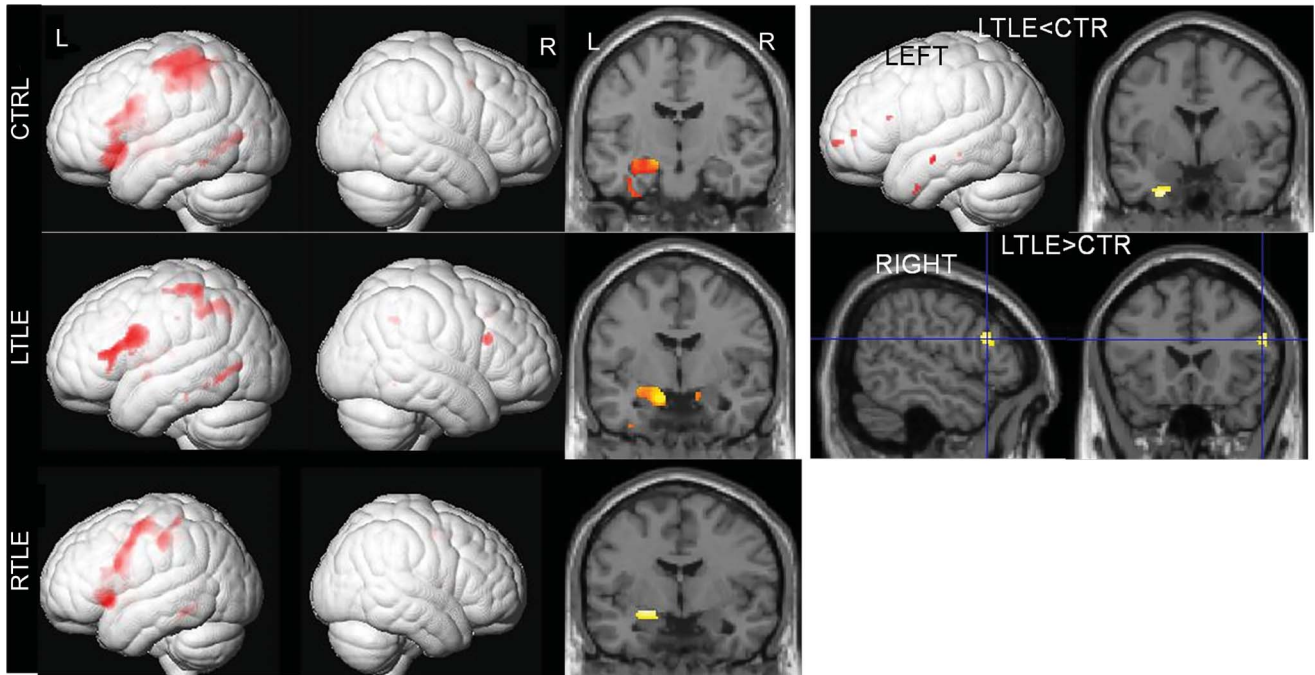

Surface-rendered whole brain and coronal images show medial temporal lobe (MTL) words remembered activations in controls (CTR; upper panel), left temporal lobe epilepsy (TLE) patients (LTLE; middle panel), and right TLE patients (RTLE; lower panel). LTLE patients show less left frontal and MTL activations (LTLE < CTR) and greater right frontal activation compared to controls (LTLE > CTR).

Correlation of fMRI WR activations with postoperative change in list learning. In LTLE patients, predominantly left-sided WR activations within the amygdala, hippocampus, orbitofrontal cortex, inferior and middle frontal gyri, and anterior cingulate cortex correlated significantly with verbal memory decline after left ATLR. In RTLE patients, left inferior frontal gyrus activations correlated with verbal memory decline after right ATLR (figure 2, table e-4).

Less verbal memory decline after left ATLR correlated with posterior MTL activations within the right

Figure 2   Correlations of words remembered activations with postoperative verbal memory decline
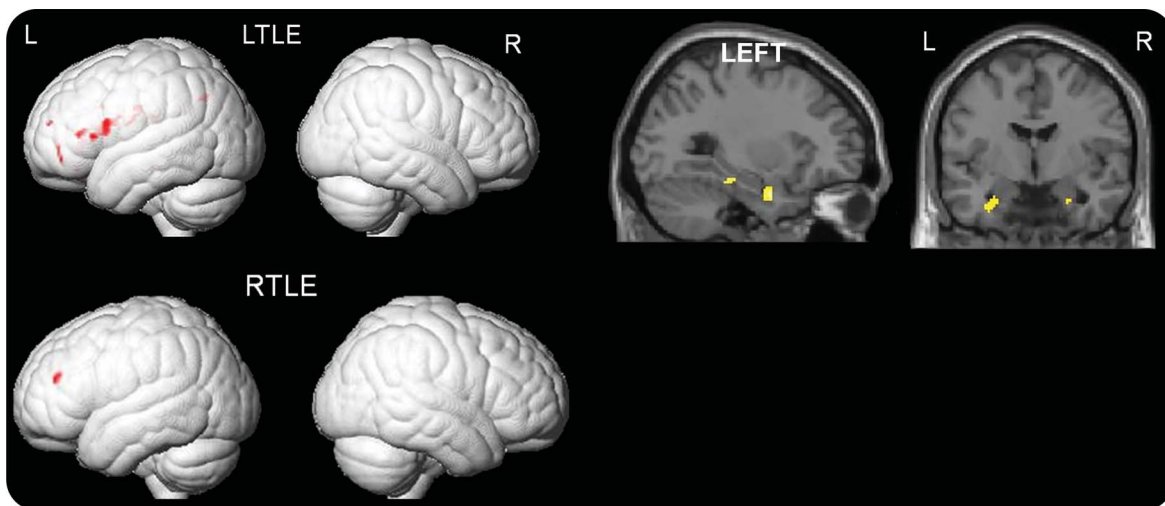
Correlation of words remembered activations with postoperative verbal memory decline in left temporal lobe epilepsy (TLE) (LTLE; upper panel) and right TLE (RTLE; lower panel) patients. In both LTLE and RTLE patients, the rendered images show left frontal activations correlated with greater postoperative verbal memory decline. The sliced images show that predominantly left medial temporal lobe activations correlated with greater postoperative verbal memory decline in LTLE patients. Activations within the medial temporal lobe did not correlate with verbal memory decline in RTLE patients.

Figure 3   Scatterplot of frontotemporal memory lateralization index and postoperative change in verbal memory
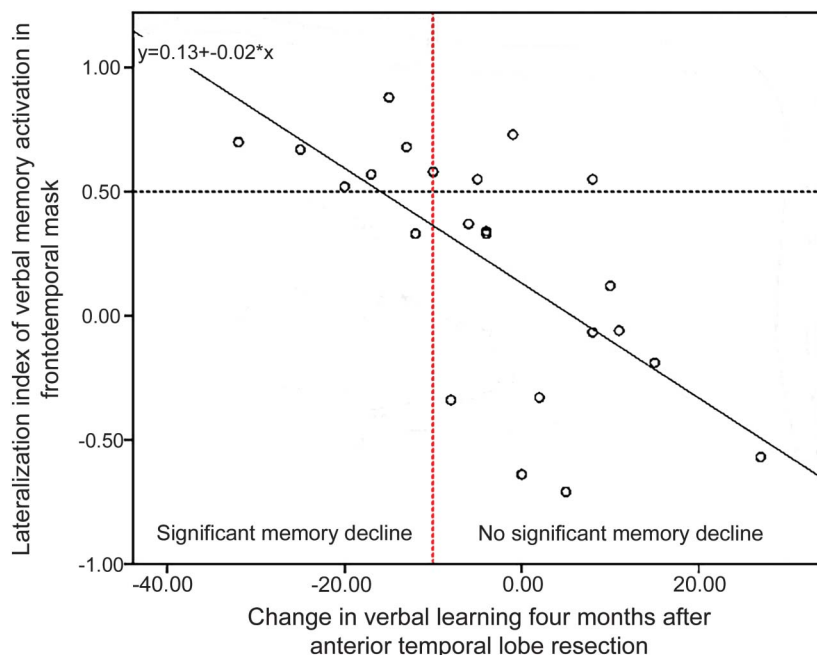
Correlation of individual lateralization indices (LIs) for words remembered in an anatomical front temporal mask with change in list learning 4 months following left anterior temporal lobe resection (R^2 = 0.432). The dotted vertical red line indicates the level of significant decline calculated by reliable change index using control data. The horizontal black dotted line indicates a LI of 0.5 (left > right). Seven of 8 patients who experienced a significant verbal memory decline had LI ≥0.5.

posterior hippocampus and PHG and less significantly with left posterior hippocampal activation (p = 0.038) (table e-4).

Individual memory fMRI parameters predictive of verbal memory decline. The activation LI associated with words remembered in the frontotemporal mask correlated significantly with change in memory scores, with greater left-sided activation predictive of greater verbal memory decline in LTLE patients (R = 0.66, p = 0.001) (figure 3). Memory LI did not correlate with verbal memory change in RTLE patients (R = 0.14, p > 0.1).

Linear regression. Linear regression showed that language and memory LI predicted postoperative verbal memory decline in LTLE patients. Memory LI was

the best predictor of verbal memory outcome compared to other parameters in the multivariable adjusted analysis (β coefficient −16.1, 95% CI −28.4 to −3.9, p = 0.01) (table e-5).

No parameter investigated (language LI, memory LI, age at onset of epilepsy, preoperative hippocampal volume, preoperative verbal learning) predicted verbal memory decline in RTLE patients (p > 0.1).

Memory prediction for individual LTLE patients. Greater left than right activation within the frontotemporal mask was the best independent predictor of verbal memory decline. For use as a predictive tool, an objective measure of LI of ≥0.5 was chosen as a predictive threshold. Seven out of 8 significant decliners had a frontotemporal memory LI of ≥0.5, conferring a test sensitivity of 87.5%. Specificity was 80% (figure 3, table 2). Left lateralized language LI ≥0.5 had 100% sensitivity in predicting verbal memory decline in LTLE patients but specificity was low at 13.3% as 21 of the 23 LTLE patients had a language LI of ≥0.5.

Using verbal memory fMRI alone, if a patient had a LI of ≥0.5 there was 70% (7/10) risk of significant verbal memory decline after surgery. If LI was <0.5, the risk of significant memory decline was 7.7% (1/13) (table 2).

DISCUSSION Twenty-two (21 LTLE) patients had dominant and 28 (2 LTLE) patients had nondominant ATLR. Although the mean change in memory postoperatively in LTLE and RTLE patients did not differ, more patients with dominant ATLR (9/22) had significant verbal memory decline than did patients after nondominant resection (6/28), consistent with previous literature.[22,23]

In the LTLE group, left lateralized activation within the medial temporal and frontal lobes was involved in successful memory formation and predicted significant postoperative verbal memory decline.

Retrospective studies showed earlier age at onset of epilepsy and better preoperative memory to predict postoperative verbal memory outcome.[5,20] We did not replicate this, likely due to small numbers. The crucial point is that in the current study, despite small numbers, frontotemporal memory LI ≥0.5 indicating greater left than right activation correlated significantly with postoperative change in memory, and was the strongest independent predictor of postoperative verbal memory decline.

With an LI ≥0.5 memory fMRI alone had a positive predictive value (PPV) of 70%, sensitivity of 87.5%, and 80% specificity for predicting significant memory decline after left ATLR. Previous memory fMRI prediction algorithms using asymmetry image analysis reported

Table 2   Memory frontotemporal lateralization index (LI) in relation to changes in verbal memory after left anterior temporal lobe resection

Frontotemporal L LI	Significant verbal memory decline, number of patients	Nonsignificant decline/improvement in verbal memory, number of patients	Total
LI ≥ 0.5	7	3	10
LI < 0.5	1	12	13
Total	8	15	23

PPV of 35%, 100% sensitivity, and 41% specificity based on greater left than right MTL activations.[8]

Outcome after surgery may be affected by several factors including age at surgery, age at onset of epilepsy, preoperative memory, underlying pathology and its extent, surgical variables, and postoperative seizure outcome. These will contribute to the scatter seen in figure 3. In one LTLE patient, memory LI failed to predict significant decline. This patient (patient LTLE 17, table e-1) had impaired preoperative verbal memory, small left hippocampus, and early age at onset of epilepsy, and was seizure-free 1 year after surgery, so verbal memory decline was surprising. Three LTLE patients with a memory LI of ≥0.5 did not have significant memory decline (LTLE 2, 11, 13, table e-1). All 3 had relatively small preoperative hippocampi and younger age at onset of epilepsy; both factors have been associated with memory preservation postoperatively.

One RTLE patient was right lateralized for language and showed significant decline in verbal memory after right ATLR. Frontotemporal memory LI was right lateralized in this patient and would have predicted decline in this patient. Otherwise, neither memory LI, language LI, nor clinical parameters predicted verbal memory decline in RTLE patients.

Epilepsy affects networks and widespread structural and functional disruption including the contralateral temporal lobe has been described in unilateral TLE.[24–27] We showed that preoperative left frontal activation correlated with verbal memory decline in RTLE patients, exemplifying the network disruption that occurs with epilepsy and surgery.

Two models have been proposed in the preoperative risk assessment of postsurgical memory decline. The functional adequacy model suggests that postsurgical memory decline is inversely proportional to the function of the to-be-resected tissue, while the hippocampal reserve model suggests it is the ability of the contralateral hippocampus to sustain memory function that determines postsurgical memory outcome.[28] Previously, event-related analyses supported the functional adequacy model, with greater activation in the to-be-resected anterior hippocampus predicting verbal memory decline.[6–8] Using asymmetry images, these studies were unable to comment on the hippocampal reserve model as activations in asymmetry images represent either left > right activations or vice versa.[29] We showed that activations within the left anterior MTL and frontal lobe, involved in successful memory formation preoperatively, predicted decline postoperatively. We therefore propose extending Chelunes' model whereby functional adequacy is not just the function of the to-be-resected hippocampus but also the preoperative network, encompassing the to-be-resected MTL.

Our study has several strengths. First, we used a sensitive verbal memory contrast (words remembered) that showed significant activations in the MTL and extratemporally in all patients, a crucial prerequisite for individual memory prediction paradigms. This contrast differed from the subtraction contrast we used previously (words remembered minus words familiar/forgotten).[9] The latter contrast, while more specific for successful verbal memory encoding network, was less sensitive and not every patient had significant MTL activations. For the purpose of clinical prediction, a sensitive contrast was required. We acknowledge that the words remembered contrast is less specific and incorporates components of a language network. Second, we created a prediction algorithm based on an objective LI measure that was calculated within SPM and is applicable to a newly encountered patient. Third, medication was not changed in the interval between the assessments.

Our study has limitations. Although reliable change was calculated from our control population at equivalent intertest intervals to patients, it may have been better to calculate these data using TLE patients who did not have surgery, but this would add further variables such as medication changes.

Our algorithm was based on memory outcome 4 months postoperatively. Patients with significant memory decline at 4 months remain with this decline at 12 months follow-up.[30] Further, 12 months after surgery, other factors such as medication and mood change may complicate interpretation.

Asymmetry of verbal memory fMRI activation was the strongest predictor of verbal memory outcome after dominant ATLR, compared to language fMRI and clinical parameters. We demonstrate the contribution of extratemporal areas to memory prediction, and that greater preoperative activation of the memory encoding network that incorporates the to-be-resected hippocampus is inversely related to memory outcome.

This memory fMRI prediction algorithm is applicable to temporal lobe surgery and needs evaluation in larger patient groups and is applicable at centers that already utilize language fMRI in their presurgical protocol.

AUTHOR CONTRIBUTIONS

Meneka K. Sidhu: study concept, design, data acquisition, analysis, interpretation, and drafting of manuscript. Jason Stretton: study concept, data acquisition, data interpretation, and revision for intellectual content. Gavin P. Winston: data acquisition, interpretation, and revision for intellectual content. Mark Symms: data quality, MR physics support, revision for intellectual content. Pamela J. Thompson: data interpretation, revision for intellectual content. Matthias J. Koepp: study concept, supervision, data interpretation, and revision for intellectual content. John S. Duncan: study concept, supervision, analysis, and revision for intellectual content.

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