Memory fMRI predicts verbal memory decline after anterior temporal lobe resection

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Objective: To develop a clinically applicable memory fMRI method of predicting post-surgical memory outcome in individual patients.

Methods: A prospective cohort study where 50 patients with temporal lobe epilepsy (23 left) and 26 controls performed an fMRI memory encoding paradigm of words with a subsequent out of scanner recognition assessment was performed. Neuropsychological assessment was performed pre-operatively 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 pre-operative activations. Individual lateralisation indices were calculated within a medial temporal and frontal region and compared with other clinical parameters (hippocampal volume, pre-operative verbal memory, age at onset of epilepsy and language lateralisation) 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 whilst bilateral posterior hippocampal activation correlated with less verbal memory decline post-operatively. In a multivariate regression model, left lateralised memory lateralisation 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 non-dominant temporal lobe resection.
Conclusion: We propose a clinically applicable memory fMRI paradigm to predict post-operative verbal memory decline after surgery in the language dominant hemisphere in individual patients.

Key words: prediction, memory fMRI, anterior temporal lobe resection, verbal memory
Introduction

Anterior temporal lobe resection (ATLR) brings remission in 80% of patients with refractory temporal lobe epilepsy (TLE). Significant verbal memory loss occurs after 30% of speech dominant hemisphere ATLR and less commonly after non-dominant 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.

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 pre-operative list learning scores and fMRI language lateralisation index. Several studies have investigated absolute activations rather than asymmetry images to predict post-surgical verbal memory decline using a lateralisati within the MTL with mixed results. To date, lateralisation of absolute activations to predict memory decline has only been investigated within the medial temporal lobe. Using a verbal memory encoding paradigm we showed that frontal and temporal activations were involved in successful verbal memory formation suggesting that pre-operative extra-temporal activations may play a role in predicting post-operative verbal memory decline.

We aimed to develop a clinically applicable memory fMRI method for predicting post-surgical memory decline in individual patients. We:
1) Investigated which temporal and extra-temporal brain activations were predictive of post-surgical 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 post-surgical verbal memory decline in individual patients.

3) Compared memory fMRI to language fMRI and standard clinical parameters including age at onset of epilepsy, pre-operative hippocampal volume and pre-operative memory score for predicting post-surgical memory outcome.

Methods

Subjects

57 patients (27 left) with medically refractory TLE undergoing epilepsy surgery at the National Hospital for Neurology and Neurosurgery, London were prospectively studied. Prolonged inter-ictal 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. 4 patients (3 left (LTLE)) were excluded as resection did not include the hippocampus. 1 right TLE (RTLE) patient was excluded as a previous lesionectomy included part of the anterior MTL. 2 patients with IQ <70 (1 LTLE) were excluded. In total, 50 patients (23 LTLE) were included (Table 1, Table e-1).
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. 26 healthy native English speaking controls were also studied (Table 1, Table e- 4). Handedness and language dominance were determined using a standardized questionnaire and language fMRI tasks. Asymmetry of expressive language activation was calculated within an inferior and middle frontal gyrus mask created using the WFU PickAtlas in SPM8. A bootstrap method was used to calculate language LI using SPM8. A LI of ≥ 0.5 or ≤-0.5 was deemed strongly left or right lateralised respectively. 46 patients (21 LTLE) were left lateralised, 2 bilateral (1 LTLE) and 2 (1 LTLE) right lateralised (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 standardised cognitive assessments including intellectual functioning. Verbal learning (VL) was assessed using the BIRT Memory and Information Processing Battery (BMIPB) List Learning subtest. Participants were read a list of 15 words over five trials with recall tested after each trial. The score was the sum of recalled words. This was performed preoperatively and 4 months post-operatively. 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 was defined as a ≥ 10 point decline at 4 months after surgery.

**Magnetic Resonance data acquisition**

We used a 3T GE Excite HDx MRI scanner. Gradient-echo echoplanar images provided blood oxygen level dependent contrast (BOLD). Each volume comprised 36 contiguous oblique axial slices, slice thickness 2.5mm (0.3 mm gap), field of view 24cm, matrix 96 x 96 interpolated to 128 x 128 during image reconstruction, in-plane resolution 2.5mmx2.5mm, SENSE factor 2.5, Echo time (TE) 25ms, TR 2.75s. The field of view covered the temporal and frontal lobes with the slices aligned with the long axis of the hippocampus.

**Memory encoding paradigm**

Concrete nouns were presented visually. Each word was presented for 3s in 30 second blocks. Each block consisted of 10 words followed by 15s cross hair fixation. 10 blocks (100 words) were presented in total. An inter-stimulus interval of 3s differed to the TR of 2.75 s to introduce jitter and ensure random sampling. Participants were instructed to memorise items for subsequent recall testing. A subjective pleasant/unpleasant decision was indicated using an MR compatible joystick as a deep encoding task. After scanning, subjects were shown the same 100 words intermixed with 50 novel words in a recognition task. 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/](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 8mm full-width at half maximum Gaussian kernel.

**Event related analysis**

We compared the encoding-related responses for stimuli that were subsequently remembered, with a two-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 (ANOVA). We determined the relevance of fMRI memory activations using a simple regression model of WR activations with pre-operative list learning scores. Preoperative brain activations associated with greater / less post-surgical 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, 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, 12mm diameter sphere unless otherwise stated.

**Individual patient memory Lateralisation Index Calculation**

An anatomical mask incorporating frontal and medial temporal lobes (amygdala, parahippocampal gyrus, hippocampus, middle and inferior frontal gyri) was created using the WFU PickAtlas in SPM8. A bootstrap method was used to calculate LI within the fronto-temporal mask in all patients using the SPM 8 LI toolbox. LI of ≥ 0.5 was deemed strongly left lateralised.

**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) in predicting post-operative verbal memory decline.

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

**Results**

**Behavioural**

LTLE and RTLE patients performed worse than controls in the recognition test pre and post-operatively (p<0.005). LTLE patients showed a significant decline whilst RTLE patients showed a non-significant 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, pre and post-operatively (two-tailed t-test p<0.005 (Table 1)). Left and right TLE patients did not differ significantly in age, age at onset of epilepsy, epilepsy duration, or verbal learning (two-tailed t-test p>0.1), (Table 1).

Of the 23 LTLE patients assessed 4 months post-operatively, 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). 18 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, pre and post central, inferior frontal, middle occipital gyri and orbitofrontal cortex, left hippocampus and parahippocampal gyrus (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 (Fig 1, Table e-2).

**Correlation of fMRI word remembered (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 successful verbal memory formation was associated with activation of these structures pre-operatively. In RTLE patients, no correlation between WR activations and preoperative list learning was seen (Table e-3).

**Prediction of post-operative Verbal Memory**

**Clinical parameters and verbal memory decline**

**LTLE**

Verbal memory decline correlated significantly with language lateralisation (R=0.44, p=0.037); implying greater verbal memory decline with increasing left language LI. Pre-operative verbal memory, age at onset of epilepsy and hippocampal volumes did not correlate with post-operative memory change (p> 0.1).

**RTLE**
Pre-operative verbal memory, age at onset of epilepsy, hippocampal volume and language lateralisation did not correlate with post-operative verbal memory change (p> 0.1).

**Correlation of fMRI WR activations with post-operative 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 (Fig 2, Table e-4).

Less verbal memory decline after left ATLR correlated with posterior MTL activations within the right 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 fronto-temporal 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) (Fig 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 post-operative 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 fronto-temporal 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. 7 out of 8 significant decliners had a fronto-temporal memory LI of ≥0.5, conferring a test sensitivity of 87.5%. Specificity was 80% (Fig 3, Table 2). Left lateralised 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**

22 (21 LTLE) patients had dominant and 28 (2 LTLE) patients had non-dominant ATLR. Although the mean change in memory post-operatively in LTLE and RTLE patients did not differ, more patients with dominant ATLR (9/22) had significant verbal memory decline than did patients after non dominant resection (6/28), consistent with previous literature 22, 23.
In the LTLE group, left lateralised activation within the medial temporal and frontal lobes were involved in successful memory formation and predicted significant post-operative verbal memory decline.

Retrospective studies showed earlier age at onset of epilepsy and better pre-operative memory to predict post-operative verbal memory outcome\textsuperscript{5,20}. We did not replicate this, likely due to small numbers. The crucial point is that in the current study, despite small numbers, fronto-temporal memory LI $\geq 0.5$ indicating greater left than right activation correlated significantly with post-operative change in memory, and was the strongest independent predictor of post-operative verbal memory decline.

With an LI $\geq 0.5$ 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 PPV of 35\%, 100\% sensitivity and 41\% specificity based on greater left than right MTL activations\textsuperscript{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 post-operative 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, early age at onset of epilepsy and was seizure free one year after surgery, so verbal memory decline was surprising. Three LTLE patients with a memory LI of $\geq 0.5$ did not have significant memory decline (LTLE 2, 11, 13, table e-1). All three had relatively small preoperative hippocampi and
younger age at onset of epilepsy; both factors that have been associated with memory preservation post-operatively.

One RTLE patient was right lateralised for language and showed significant decline in verbal memory after right ATLR. Fronto-temporal memory LI was right lateralised 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\textsuperscript{24-27}. We showed that pre-operative 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 pre-operative risk assessment of post-surgical memory decline. The functional adequacy model suggests that post-surgical memory decline is inversely proportional to the function of the ‘to-be-resected’ tissue, whilst the hippocampal reserve model suggests it is the ability of the contralateral hippocampus to sustain memory function that determines post-surgical memory outcome\textsuperscript{28}. Previously, event-related analyses supported the functional adequacy model, with greater activation in the ‘to be resected’ anterior hippocampus predicting verbal memory decline\textsuperscript{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\textsuperscript{29}. We showed that activations within the left anterior MTL and frontal lobe, involved in successful memory formation pre-operatively, predicted decline post-operatively. We therefore propose extending
Chelunes’ model whereby functional adequacy is not just the function of the ‘to-be-resected’ hippocampus but also the pre-operative 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 extra-temporally in all patients, a crucial pre-requisite for individual memory prediction paradigms. This contrast differed from the subtraction contrast we used previously (words remembered minus words familiar/forgotten). The latter contrast, whilst 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 inter-test 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 post-operatively. Patients with significant memory decline at 4 months remain with this decline at 12 months follow up. 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 extra-temporal areas to memory prediction, and that greater pre-operative 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 now needs evaluation in larger patient groups and is applicable at centres that already utilise language fMRI in their pre-surgical protocol.

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Table 1: Age, age at onset of epilepsy and duration of epilepsy as median (interquartile range). Hippocampal volume, NART IQ, preoperative (preop VL), postoperative (Postop VL) verbal learning, preoperative recognition accuracy (Preop RA) and postoperative recognition accuracy (postop RA) as mean (standard deviation). Controls (C). *C>patient group indicated, 2-tailed t-test p<0.005.

Table 2: Memory fronto-temporal lateralisation index (LI) in relation to changes in verbal memory after left anterior temporal lobe resection.
Figure Legends

Title: Memory encoding activations in controls, left TLE and right TLE patients

Figure 1: Surface rendered whole brain and coronal images showing medial temporal lobe (MTL) words remembered (WR) activations in controls, CTR (upper panel), left TLE patients, LTLE (middle panel) and right TLE patients, RTLE (lower panel). LTLE patients showed less left frontal and MTL activations (LTLE<CTR) and greater right frontal activation compared to controls (LTLE>CTR).

Title: Correlations of words remembered activations with postoperative verbal memory decline

Figure 2: Correlation of words remembered activations with post-operative verbal memory decline in left TLE (LTLE (upper panel)) and right TLE patients (RTLE (lower panel)). In both LTLE and RTLE patients, the rendered images show left frontal activations correlated with greater post-operative verbal memory decline. The sliced images showed that predominantly left medial temporal lobe activations correlated with greater post-operative verbal memory decline in LTLE patients. Activations within the medial temporal lobe did not correlate with verbal memory decline in RTLE patients.
Title: Scatter plot of fronto-temporal memory lateralisation index and post-operative change in verbal memory

**Figure 3:** Correlation of individual Lateralisation Indices 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 lateralization index of 0.5 (Left>Right). 7 of 8 patients who experienced a significant verbal memory decline had LI $\geq0.5$.

**Individual Author Contribution**

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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