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Activations in temporal areas using visual and auditory naming stimuli: A language fMRI study in temporal lobe epilepsy

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Highlights

- Word finding difficulty is a complication of anterior temporal lobe resection
- fMRI verbal fluency paradigms primarily activate language areas in the frontal lobe
- We used Auditory and Picture naming fMRI, which activated temporal language networks
- Auditory and Picture naming may better predict impaired word finding after temporal lobe resection

ABSTRACT

Objective: Verbal fluency functional MRI (fMRI) is used for predicting language deficits after anterior temporal lobe resection (ATLR) for temporal lobe epilepsy (TLE), but primarily engages frontal lobe areas. In this observational study we investigated fMRI paradigms using visual and auditory stimuli, which predominately involve language areas resected during ATLR.

Methods: Twenty-three controls and 33 patients (20 left (LTLE), 13 right (RTLE)) were assessed using three fMRI paradigms: verbal fluency, auditory naming with a contrast of auditory reversed speech; picture naming with a contrast of scrambled pictures and blurred faces.

Results:

Group analysis showed bilateral temporal activations for auditory naming and picture naming. Correcting for auditory and visual input (by subtracting activations resulting from auditory reversed speech and blurred pictures/scrambled faces respectively) resulted in left-lateralised activations for patients and controls, which was more pronounced for LTLE compared to RTLE patients.

Individual subject activations at a threshold of T > 2.5, extent > 10 voxels, showed that verbal fluency activated predominantly the left inferior frontal gyrus (IFG**)** in 90% of LTLE, 92% of RTLE, and 65% of controls, compared to right IFG activations in only 15% of LTLE and RTLE and 26% of controls.

Middle temporal (MTG) or superior temporal gyrus (STG) activations were seen on the left in 30% of LTLE, 23% of RTLE, and 52% of controls, and on the right in 15% of LTLE, 15% of RTLE, and 35% of controls.

Auditory naming activated temporal areas more frequently than did verbal fluency (LTLE: 93%/73%; RTLE: 92%/58%; controls: 82%/70% (left/right)). Controlling for auditory input resulted in predominantly left-sided temporal activations.

Picture naming resulted in temporal lobe activations less frequently than did auditory naming (LTLE 65%/55%; RTLE 53%/46%; controls 52%/35% (left/right)). Controlling for visual input had left-lateralising effects.

Conclusion: Auditory and picture naming activated temporal lobe structures, which are resected during ATLR, more frequently than did verbal fluency. Controlling for auditory and visual input resulted in more left-lateralised activations. We hypothesise that these paradigms may be more predictive of postoperative language decline than verbal fluency fMRI.

ABBREVIATIONS

AED = Antiepileptic drug; AN = Auditory naming; AN–AR = Auditory naming – Auditory reversed; ATLR = Anterior temporal lobe resection, BOLD = Blood oxygenation level dependent; CPS = Complex partial seizure; fMRI = Functional magnetic resonance imaging; FuG = Fusiform gyrus; HC = Hippocampus; HS = Hippocampal sclerosis; IFG = Inferior frontal gyrus; ITG = Inferior temporal gyrus; LTLE = Left temporal lobe epilepsy; MFG = Middle frontal gyrus; MTG = Middle temporal gyrus; NART = National adult reading test; PHG = Parahippocampal gyrus, PN = Picture naming; PN–(SPc+F) =Picture naming – (scrambled pictures + blurred faces); RTLE = Right temporal lobe epilepsy; SFG = Superior

frontal gyrus; SGS = Secondary generalised seizure; STG = Superior temporal gyrus; TLE = Temporal lobe epilepsy; VF = Verbal fluency

Keywords: Temporal lobe epilepsy, functional MRI, auditory and visual naming tasks, verbal fluency, word finding difficulties, language, anterior temporal lobe.

1. INTRODUCTION

Many individuals with medically intractable temporal lobe epilepsy (TLE) have word finding difficulties, particularly when seizure onset is lateralised to the speech-dominant hemisphere (Bell et al., 2003; Bonelli et al., 2011; Hamberger, 2015).

Anterior temporal lobe resection (ATLR) results in seizure remission in up to 80% of individuals with well-characterized TLE (de Tisi et al., 2011). Between 30% and 50% of individuals experience a significant reduction in naming abilities after resection of the speech-dominant temporal lobe (Bonelli et al., 2012; Davies et al., 1998). Left TLE patients with hippocampal sclerosis (HS) and left language dominance show increased recruitment of homologous right hemisphere areas, in addition to wider left hemisphere language areas for language processing, suggesting widespread language representation (Jensen et al., 2011).

Functional magnetic resonance imaging (fMRI) has a useful role in the pre-surgical assessment as a non-invasive predictor of language decline after an ATLR (Duncan, 2009). Most fMRI studies in epilepsy patients focus on expressive language tasks such as the verb generation or verbal fluency task, which primarily activate frontal lobe language areas (Bonelli et al., 2012; Centeno et al., 2014; Szaflarski et al., 2008; Woermann et al., 2003). Stronger preoperative activation in the left middle frontal region on a verbal fluency

paradigm was predictive of greater decline in naming after left ATLR (Bonelli et al., 2012). Although sensitive to the occurrence of significant decline, this activation pattern lacked specificity, with activation in the ipsilateral frontal lobe not always being associated with naming decline following temporal lobe resection (Bonelli et al., 2012).

Reorganisation of language networks occurs in both temporal and frontal networks in chronic epilepsy, and thus, it could be of value to include language tasks that primarily affect temporal lobe language networks (Thivard et al., 2005). Language paradigms that cause consistent activation in the to-be-resected anterior temporal lobe are less well established (Binder et al., 2011; Duncan, 2009), although semantic decision tasks developed by Binder et al. have been used to show temporal lobe language function (Binder et al., 2011; Janecek et al., 2013; Sabsevitz et al., 2003). Object naming paradigms involving visual (Hermann and Wyler, 1988) and auditory stimuli (Hamberger et al., 2001; Specht et al., 2009) may provide more specific predictions of naming difficulties after ATLR (Bookheimer et al., 1997; Rosazza et al., 2013; Schlosser et al., 1998; Schlosser et al., 1999).

We aimed to investigate language activation patterns using fMRI language tasks employing visual and auditory stimuli to identify language areas in the temporal lobes, which could be better predictors for postoperative word finding difficulties than verbal fluency fMRI.

2. MATERIAL AND METHODS

2.1. Subjects

We studied 23 healthy controls and 33 patients with medically refractory TLE (20 left TLE (LTLE), 13 right TLE (RTLE)). These were sequential patients with a confirmed diagnosis of TLE undergoing presurgical assessment at the National Hospital for Neurology and Neurosurgery (NHNN). The age range for all subjects was 18–65 years. Control subjects had no history of epilepsy or any other chronic neurological or psychiatric disease. Exclusion

criteria for all subjects were non-fluency in written and spoken English, pregnancy, any contraindication to MRI (e.g. metallic implants, pacemakers), and inability to give informed consent. An additional exclusion criterion for patients was history of a secondary generalised tonic-clonic seizure within 24h prior to the study. Demographic and clinical data are summarized in Table 1.

Prolonged interictal and ictal EEG-video telemetry confirmed ipsilateral seizure onset zones in all patients. All patients underwent structural MRI at 3.0 T, including quantification of hippocampal volumes and T_2 relaxation times (Woermann et al., 1998). MRI identified hippocampal sclerosis (HS) in nine patients (8 left/1 right), dysembryoplastic neuroepithelial tumour (DNET) in five (1 left/ 4 right), cavernoma in five (4 left/ 1 right), focal cortical dysplasia and ganglioglioma in one patient each, both on the right, and 12 normal MRI (7 left/ 5 right).

All patients were native English speakers, English was the first language in 21 controls with the remaining two being fluent English speakers from before the age of five years (Centeno et al., 2014).

Handedness was determined using the Edinburgh Hand Preference Inventory (Oldfield, 1971). Four of 20 left TLE, one of 13 right TLE and one of 23 controls were left handed.

Controls (7 high school, eight undergraduates and eight postgraduates) had a higher education level than TLE patients (20 high school, nine undergraduates and four postgraduates; $F=3.88$, $p=0.03$). There was no difference between the groups in estimated intellectual level, as derived from performance on the National Adult Reading Test (NART (Nelson and Wilson, 1991); $F=0.74$, $p=0.5$).

The study was approved by the National Hospital for Neurology and Neurosurgery and the UCL Institute of Neurology Joint Research Ethics Committee. Written informed consent was obtained from all participants.

2.2. Neuropsychological tests

All subjects underwent neuropsychological testing prior to scanning to provide a measure of their linguistic proficiency. The measures employed were standardised clinical tests that form part of the pre and post-surgical neuropsychological evaluations of TLE patients. Naming was assessed using the McKenna Graded Naming Test (McKenna et al., 1983). This measure consists of thirty line drawings of objects and animals, placed in order of difficulty. The performance indicator is the number of items correctly named. In addition participants completed a phonemic fluency test during which they had to say as many words beginning with the letter "S" in 60 seconds, followed by a semantic fluency test, which required subjects to name as many members of the category "animals" also in 60 seconds (Bird et al., 2004).

2.3. MR data acquisition

MRI studies were performed using a 3T General Electric Excite HDx scanner (GE, Wisconsin), using standard imaging gradients with a maximum strength of $40mTm^{-1}$ and slew rate 150 TM^{-1} s^{-1}. All data were acquired using the standard eight-channel RF receive head array coil and the body RF coil for transmission.

For fMRI, gradient-echo planar T2*-weighted images were acquired (TE= 25 ms, TR=2000 ms), providing blood oxygenation level dependent (BOLD) contrast. Each volume comprised 40 contiguous 2.5 mm slices with a 24 cm field of view, 64x64 matrix, giving an in-plane pixel size of 3.75 x 3.75 mm. The field of view was positioned to maximise coverage of the

frontal and temporal lobes and minimise signal drop-out from the temporal and orbitofrontal lobes. To mitigate geometric distortions, ASSET (The GE implementation of parallel imaging) was used.

All subjects underwent a standard structural MRI scanning protocol on the same scanner, which included a coronal 3D volumetric T1-weighted Inversion Recovery-Prepared Spoiled Gradient Recalled (IR-SPGR) sequence for coregistration as well as an oblique coronal 2D dual-echo proton density and T2-weighted image sequence and an oblique coronal 2D fast fluid-attenuated inversion recovery (Fast-FLAIR) and axial T2-weighted sequence.

2.4. Language fMRI tasks and data analysis

2.4.1. Language paradigms

All subjects performed a covert verbal fluency (VF) paradigm, with a blocked experimental design with alternating 30-s activation blocks (one letter per block; total of 5 blocks) and 30-s of cross-hair fixation over 5 min (Bonelli et al., 2011; Powell et al., 2006). During the activation phase, subjects were asked to covertly generate different words beginning with a visually presented letter (A, S, W, D, E).

Two overt language tasks were employed. Subjects responded to visual and auditory stimuli via a magnetic-resonance compatible screen viewed through a mirror (Bonelli et al., 2012) and a compatible audio-system (headphone and microphone devices).

Prior to scanning, each subject was given detailed explanations with examples to ensure test instructions were fully understood. All tasks were recorded with an external microphone outside the scanner. The naming tasks were extensively piloted in TLE patients and controls prior to this study.

- Auditory naming (AN) consisted of five cycles of alternating 30-s activation blocks (AN) and two control blocks of 15-s each, comprising reversed speech (AR) and cross-hair fixation over 5 min. During the activation phase (AN), subjects were asked to name aloud objects and animals from their auditory description (e.g. “body part you think with”). The AR condition comprised reversed recordings of the AN stimuli and participants were instructed to count aloud “one, two” upon presentation with reversed speech and to rest during cross-hair fixation.

- Picture naming (PN) involved five cycles of visually presented stimuli, each cycle consisting of alternating 30-s activation blocks (PN), and three control blocks of 15-s each, comprising scrambled pictures (SPc), blurred cartoon faces (F), and crosshair fixation over 6.15 min. During the activation phase (PN), participants were instructed to name aloud black and white line drawings of everyday objects and animals. The control condition SPc comprised distorted versions of the black and white drawings. Additionally, blurred drawings of black and white cartoon faces (F) were used as a second control condition to overcome a possible lack of object recognition effort that might be associated with scrambled pictures. Subjects were instructed to count aloud “one, two” in response to SPc and F, and to rest during crosshair fixation.

2.4.2. Data analysis

Imaging data were analysed using Statistical Parametric Mapping 8 (http://www.fil.ion.ucl.ac.uk/spm/). The imaging time series of each subject was realigned, normalised 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 8 mm full-width at half-maximum.

A two level random effects analysis was employed. In the first level, condition-specific effects were estimated according to the general linear model (Friston et al., 1995) for each subject. Regressors of interest were formed by convolving blocks of stimuli with the canonical hemodynamic response function for each of the conditions of interest. Parameter estimates for regressors were calculated for each voxel. Five contrast images were generated for each subject within the three groups (controls, LTLE, RTLE), which were VF, AN, PN (all contrasted by crosshair fixation as rest condition), auditory naming minus auditory reverse (AN–AR), and picture naming minus scrambled pictures and faces (PN–(SPc+F)).

At the first level analysis, we assessed all the areas of activation for each contrast across the whole brain, highlighting those areas located in the frontal and temporal lobes (Supplementary Tables 2 A–C). As we focused on activations in the to-be-resected areas of temporal lobe, we report activations in individual subjects at a more liberal threshold of $T>2.5$, extent 10 voxels, which we considered appropriate for interpreting activations in individual subjects.

These contrast images were used for the second-level analysis. A one-sample t-test was used to examine the group effect of each contrast. To assess statistically different temporal lobe activations between all three groups, we performed a two-sample t-test.

At this second level, we tested for main effects within and differences between the three groups for: VF, AN, AN–AR, PN, and PN–(SPc+F). To test for correlations between areas of fMRI activation and naming outside the scanner, one-sample t-tests were performed over the whole brain using the McKenna score as a covariate. Results for the main effects and group comparisons are shown at threshold $p<0.001$ uncorrected, as we focused on differences

within the to-be-resected temporal lobes. Family-wise error (FWE)-corrected ($p<0.05$) activations are additionally reported for main effects and group comparisons.

2.4.3. Language dominance

Lateralisation indices (LIs) of statistic parametric maps (spmT) were calculated to quantitatively assess hemispheric dominance for language (Adcock et al., 2003). LIs were calculated for each subject's three spmT maps (corresponding to AN-AR, PN-(SPc+F) and VF tasks) by applying the bootstrap method of the lateralisation index toolbox implemented in SPM8 (Wilke and Lidzba, 2007) using an anatomical mask incorporating temporal and mesial temporal lobe structures created from the WFU PickAtlas in SPM8 (Maldjian et al., 2003). According to the formula [$LI = (L – R)/(L + R)$], a positive LI indicates left hemispheric dominance and a negative index indicates right hemispheric lateralisation. LIs were subsequently defined as left-hemisphere dominant ($LI > +0.2$) and atypical dominance, comprising both bilateral distribution ($-0.2 \leq LI \leq +0.2$) and right-hemisphere dominant ($LI < -0.2$).

3. RESULTS

3.1. Neuropsychological test results

3.1.1. Naming test scores

Patients scored at a significantly lower level on the McKenna Graded Naming Test (McKenna et al., 1983); LTLE: mean 16.15, SD 6.19; RTLE: mean 17.07, SD 5.48) than controls (mean 20.04, SD 2.99; $F = 3.6$; $p = 0.03$). Scores were within the impaired range for 4 people in the LTLE (20%) and 2 in the RTLE group (15%); no control scores were impaired although one participant scored just below the average range. There was no

significant correlation between age of epilepsy onset and naming test scores in left or right TLE patients ($F = 1.07$, $p = 0.48$).

3.1.2. Verbal fluency scores

The phonemic fluency scores for LTLE (mean 16.20, SD 5.72) and RTLE (mean 14.84, SD 7.32) were lower than in controls (mean 19.43, SD 6.94), but the difference did not reach statistical significance ($F = 2.35$, $p = 0.10$). In the semantic fluency test, LTLE (mean 18.35, SD 5.32) and RTLE patients (mean 17.92, SD 4.53) scored significantly lower than controls (mean 25.08, SD 4.77; $F = 13.33$, $p < 0.001$).

3.2. Language fMRI results

3.2.1. Individual subject results

3.2.1.1. Performance recording and monitoring

All subjects performed the tasks successfully (90% correct answers with prior explanation, monitoring and recording the complete process). Five LTLE patients and one RTLE patient did not complete the AN task because of technical problems with the audio system.

3.2.1.2. Verbal fluency

For VF, activations occurred predominantly in the left frontal lobe with significant activations in the left inferior frontal gyrus (IFG) in 90% of LTLE 92% of RTLE, and 65% of controls, compared to right-sided IFG activations in 15% of LTLE, 15% of RTLE, and 26% of controls (Supplementary Tables 2 A–C).

Activations in either middle temporal (MTG) or superior temporal gyrus (STG) were seen on the left in 30% of LTLE, 23% of RTLE, and 52% of controls, and on the right in 15% of LTLE, 15% of RTLE, and 35% of controls.

3.2.1.3. Auditory naming

AN activated the left MTG or STG in 93% of LTLE and 92% of RTLE, and in 87% of controls. Right-sided MTG or STG activations were detected in 73% of LTLE patients and 70% of controls, but were less frequent in RTLE patients (58%). (Figure 1 (**A**), (**B**)).

Removing the effects of auditory input (AN–AR; Figure 1**C**) resulted in predominantly left-sided temporal activations for LTLE (73% left- vs. 20% right-sided STG or MTG) and controls (83% left-sided vs. 22% right-sided STG or MTG) and in exclusively left-sided activations in RTLE (83% left-sided vs. 0% right-sided STG or MTG). Activations were generally more frequent in MTG compared to STG (Table 2; Supplementary Tables 2A–2C)

3.2.1.4. Picture naming

For PN, left-sided STG or MTG activations were observed in 65% of LTLE, 53% of RTLE, and 52% of controls, whereas right/sided STG or MTG activations were slightly less frequent (55% LTLE, 46% RTLE, 35% controls). Controlling for visual input (PN–(SPc+F); Fig. 1 (D)) led to more left-lateralised temporal activations in LTLE (50% left-sided vs. 25% right-sided STG or MTG activations). There were less frequent but more left-sided activations in RTLE (46% left-sided vs. 23% right-sided STG or MTG activations) and in controls (43% left-sided vs. 17% right-sided STG or MTG activations).

All the individual results with the frequency distribution of activations within temporal lobe regions (STG and MTG) for all contrasts in the three groups are listed in Table 2. See Supplementary Tables 2A–2C for activations in additional regions.

3.2.1.5. Combined activation frequencies of auditory and visual naming and group comparisons

4. We further investigated the frequencies of individual activations in temporal lobe regions (STG or MTG) when looking at a combination of auditory and visual naming after correcting for auditory and visual input, i.e. for the contrasts AN-AR and PN-(Sc+F). To

investigate group differences, Chi^2 tests were performed to compare the number of individuals in each group who had suprathreshold activations in *either* AN-AR *or* PN-(ScF) as well as the number of subjects with activations in AN-AR *and* PN-(ScF). The only statistically siginificant difference between the three groups was found for activations in right temporal regions for combined activations in AN-AR and PN-(Sc+F), which was more frequent in LTLE patients compared to RTLE and controls ($p=0.02$). See

Table ***3*** for detailed statistics.

4.1.1.1. Lateralisation indices for temporal lobe regions

Left-sided lateralisation was found in the majority of subjects in all three language tasks analysed (AN-AR, PN-(SPc+F), VF). For AN-AR, there was atypical (either bilateral or right-sided) language dominance in 3 LTLE patients and 3 controls. For PN-(SPc+F), there was atypical dominance in 8 LTLE patients, 3 RTLE patients and 9 controls. For VF, 2 LTLE patients, 1 RTLE patient and 7 controls had atypical lateralisation (Fig).

Kruskal-Wallis test for independent samples did not indicate a statistically significant difference in distribution of LIs across the three groups for the AN-AR ($p=0.34$) and PN-(SPc+F) condition ($p=0.06$). For VF, there was a significant difference between groups ($p=0.02$), and post hoc testing indicated stronger left-sided lateralisation in RTLE patients compared to controls ($p=0.02$).

4.1.2. Group results

Main effects in temporal lobe areas are listed in Table 4 and Fig for each contrast and across the three groups (Left TLE, right TLE and controls).

For VF, temporal lobe activations were only seen in left STG for RTLE patients, but not for LTLE patients or controls.

AN showed left-sided activation in STG and/or MTG for all three groups, and included left-sided activation of hippocampus (HC) after correcting for auditory input using AN-AR. LTLE patients also activated right STG and parahippocampal gyrus (PHG) for AN, and right HC for AN–AR.

PN showed bilateral activation in STG as well as left MTG in LTLE patients, whereas no significant temporal activations were observed in RTLE patients or controls. Controlling for

visual input using the contrast PN – (SPc+Fc) resulted in activations in left FuG and HC in LTLE patients as well as in right FuG in RTLE patients.

After correcting for multiple comparisons (FWE), there were significant left-sided activations in STG or MTG for the AN task in LTLE patients and controls. LTLE patients furthermore had significant left-sided activations in PHG in the AN-AR condition as well as in FuG in the PN and PN-(SPc+F) conditions. There were no suprathreshold activations in RTLE patients. The VF paradigm did not show significant activations in temporal regions in either of the three groups.

4.1.3. Correlation with McKenna naming score:

There was no significant correlation of fMRI activation ($p<0.001$, extent 20 voxels) with McKenna score for any of the tasks in the temporal lobe in any group.

4.1.4. Group comparisons

Correcting for multiple comparisons (FWE), no significant group differences were observed between LTLE or RTLE patients and controls. The following results refer to the uncorrected threshold $p <0.001$, extent cluster 20 voxels.

4.1.4.1. Verbal fluency

The only significant group difference in the temporal lobe was observed within left PHG, where LTLE showed higher activations than controls.

4.1.4.2. Auditory naming

There were significantly greater activations in the right HC and left MTG in LTLE patients compared to controls. Controlling for auditory input, LTLE patients showed greater activations in left HC, right PHG, and left MTG than controls.

4.1.4.3. Picture naming

LTLE patients had significantly greater activations than controls within left STG and amygdala as well as right HC. Controlling for visual input, LTLE patients showed significantly greater activations within bilateral STG, right MTG, and right FuG compared to controls. There were no significant group differences between RTLE patients and controls for all three tasks.

The differences in activations in the temporal lobe between the three groups are shown in Table 5 and Figure 4.

5. DISCUSSION

We used two overt language fMRI paradigms involving visual and auditory stimuli and a covert verbal fluency fMRI task in a typical population of patients with TLE referred for preoperative evaluation. The objective was to identify which paradigms gave reliable language activation patterns in the temporal lobe, which is resected in ATLR, anticipating that such a paradigm would be useful for predicting word-finding deficits after ATLR.

The main findings were:

1. Auditory and visual naming paradigms activated temporal lobe regions more reliably than verbal fluency, with a more pronounced effect for auditory than visual naming.

2. Auditory and visual naming paradigms resulted in temporal lobe activations more frequently in patients than controls.

3. Correcting for auditory and visual input resulted in left-lateralised activations for patients and controls.

Our findings concur with previous studies (Carpentier et al., 2001), which showed bilateral activation of both MTG and STG for an auditory fMRI task. Naming functions have been shown to involve the perisylvian cortex in the language-dominant hemisphere (Hamberger

and Seidel, 2009). Visual confrontation has been an essential tool in the assessment of naming ability and visual naming has been used to demonstrate naming difficulties (Bonelli et al., 2011; Hermann et al., 1999). In our study, both MTG and STG were activated in auditory and picture naming tasks. Picture naming showed a more bilateral pattern than auditory naming, specifically in the LTLE group, which was also reflected by the lateralisation indices of temporal regions. The LTLE group also showed more frequent combined activations of auditory and picture naming tasks in right temporal regions compared to RTLE patients and controls. There was no correlation of fMRI activations in the temporal lobe with McKenna naming score, which might be attributable to the modest sample size.

Recent studies have demonstrated the important role of auditory naming in assessing word finding difficulties in TLE patients (Hamberger and Seidel, 2003; Hamberger and Tamny, 1999; Specht et al., 2009). In addition, auditory naming has been suggested to be an accurate indicator of subjective word finding difficulties (Hamberger and Seidel, 2009). Our results suggest that both auditory and visual naming tasks involve the temporal lobe and the combination of both paradigms may better predict naming decline after ATLR than verbal fluency (Rosazza et al., 2013).

Visual and auditory naming tasks are sensitive tools to assess naming difficulties in TLE patients (Hamberger and Tamny, 1999). Cortical stimulation studies using both visual naming (naming colour photographs of common objects) and auditory naming (naming items from their auditory description) measures have shown the involvement of anterior and posterior lateral temporal language regions during these tests (Hamberger et al., 2001; Malow et al., 1996), including Positron Emission Tomography studies (Bookheimer et al., 1997; Trebuchon-Da Fonseca et al., 2009). In our study, as expected, in all three groups, verbal fluency activations were predominantly left frontal, in contrast to auditory and picture

naming tasks, which activated the anterior part of both STG and MTG (Figures 1 and 3), in keeping with previous experiments (Bonelli et al., 2012; Rosazza et al., 2013). Future work will need to determine if LIs derived from auditory and visual naming are reliable predictors for naming difficulties following ATLR. The additional use of further paradigms, such as semantic language tasks, might also highlight temporal language areas beyond naming/word finding.

In our study, left TLE patients showed significantly greater auditory naming activations within left MTG and right hippocampus than controls. We previously reported right hippocampal involvement in reading proficiency in patients who had undergone left ATLR and remained seizure-free (Noppeney et al., 2005). These preoperative findings suggest involvement of a bilateral language network in those with left TLE (Hamberger and Cole, 2011; Janszky et al., 2006).

The important role of the dominant hippocampus in naming ability in controls and patients with TLE has been described (Bonelli et al., 2011). It is of note that patients showed overall more frequent activations than controls despite worse performance on neuropsychological tests. We showed previously that failure to segregate task-positive and task-negative networks, with increased hippocampal activation during working memory paradigms, was associated with poor performance (Stretton et al., 2014). Our finding that LTLE patients appear to have greater activations in left temporal regions compared to controls is in contrast to some previous investigations that found reduced activations in these areas with different paradigms (Adcock et al., 2003; Thivard et al., 2005), and this will need to be replicated in larger groups. We speculate that LTLE patients might be recruiting broader areas to execute the naming tasks and suggest that increased temporal lobe activations during language tasks ipsilateral to the epileptogenic focus could result from disrupted integration in functional networks.

5.1. Methodological strengths and limitations

We used tasks that integrate everyday language skills such as talking, reading, listening to sentences, and naming in a patient sample comprising a typical presurgical TLE population including a wide range of ages and different causes. Using an overt speech design ensured the tasks were being carried out. As noted previously (Gartus et al., 2009; Leuthardt et al., 2012), overt word production elicits substantial perisylvian cortical activations, which is negated by creating appropriate contrasts essentially subtracting motor activity (AN-AR; PN-(SPc+F)).

Although we used performance on neuropsychological tests prior to scanning to determine general motivation and ability, and explained and practised the fMRI tasks prior to scanning, some subjects did not manage to accomplish all the tasks the first time. As responses were monitored continuously, if the task was not being performed we were able to interrupt and repeat the specific paradigms after further instructions. Overt language paradigms are technically challenging, in six patients we were not able to obtain audio recordings to assess performance for the auditory naming paradigm. This study was focused on the temporal lobes and, as anticipated, correcting for multiple comparisons (FWE) resulted in a lower number of significant activations.

5.2. Conclusion and Future work

The motivation of the present work was to investigate language paradigms that consistently activate anterior temporal lobe structures, which are resected in ATLR, with the hypothesis that lateralisation indices of activation in this part will be sensitive and specific to predicting language decline after ATLR.

ATLR is an effective surgical procedure for treating drug-resistant TLE, consisting of resection of lateral and mesial temporal structures. A posterior cortical incision at the lateral temporal gyri begins approximately 5 cm from the temporal tip, which is slanted anteriorly across superior gyrus to avoid the primary auditory cortex (Al-Otaibi et al., 2012; Hermann et

al., 1999). This surgery carries risks for verbal memory (Bonelli et al., 2010) and language impairment, particularly naming deficits after left temporal resections (Bonelli et al., 2012; Hamberger et al., 2001; Hermann et al., 1999; Sabsevitz et al., 2003).

Language fMRI is helpful to determine language lateralisation and estimate the risk of decline after ATLR (Berl et al., 2005; Carpentier et al., 2001; Rosazza et al., 2013; Wood et al., 2011) in order to help patients in the surgical decision making process. Whilst the lateralisation of verbal fluency activation in frontal lobe language areas as a measure of expressive language function has been shown to be sensitive to predicting post-operative naming difficulties, it was not very specific, with false positive predictions of decline (Bonelli et al., 2012). We have implemented naming tasks that involve language areas in temporal structures to primarily measure naming functions. We suggest that these may be better predictors of word finding difficulties after ATLR than verbal fluency. Future work will investigate the sensitivity and specificity of LIs derived from overt naming tasks to predict naming decline after ATLR.

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COMPETING INTERESTS

None.

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FIGURE LEGENDS

Figure 1. (A) Auditory naming (AN) activation in left TLE patient in left superior temporal gyrus (STG) and left middle temporal gyrus (MTG). **(B)** AN activation in left TLE patient in right MTG. **(C)** Auditory naming–auditory reversed (AN–AR) activation in left TLE patient in left MTG**. (D)** PN activation in right TLE patient in left STG. **(**Height threshold T>2.5. Extent threshold k=10 voxels).

Figure 2. Upper row: Box-Whisker-Plots of LIs for the contrasts AN-AR (left column), PN-(SPc+F; center column), and VF (right column) for the three groups (LTLE, RTLE, CTR). Boxes represent IQR, horizontal lines across boxes represent median, whiskers represent 1.5×IQR , circles represent outliers and asterisks represent extreme values (>3×IQR). **Lower row:** Dotplots of LIs for the contrasts AN-AR (left column), PN-(SPc+F; center column), and VF (right column) for the three groups (LTLE, RTLE, CTR). Blue outlined circles represent right-handed subjects, red filled circles represent left-handed subjects. LI=lateralisation index; AN–AR=auditory naming–auditory reversed; PN–(SPc+F)=picture naming–(scrambled pictures + faces); VF=verbal fluency; IQR=interquartile range; LTLE=left temporal lobe epilepsy; RTLE=right temporal lobe epilepsy; CTR=controls.

Figure 3. fMRI activations rendered and superimposed on coronal views of MRI template images for control subjects (C), patients with left temporal lobe epilepsy (LTLE) and right temporal lobe epilepsy (RTLE). All activations are shown at a threshold of P<0.001 uncorrected with an extent threshold of k=20 voxels. AN= auditory naming; AN–AR= auditory naming–auditory reversed; PN= picture naming; PN–SPc+F= picture naming–scrambled pictures+faces; VF= verbal fluency.

Figure 4. Group comparisons are shown on a coronal image at threshold P<0.001 uncorrected with an extent threshold of k=20 voxels. Top row on the left for AN, top row on the right for AN–AR, middle row on the left for PN, middle row on the right for PN–SPc+F and lower row for VF. LTLE= left temporal lobe epilepsy; RTLE= right temporal lobe epilepsy; C= controls; AN= auditory naming; AN–AR= auditory naming–auditory reverse; PN= picture naming; PN–SPc+F= picture naming–scrambled pictures+faces; VF= verbal fluency.

FIGURES

Individual activations for auditory and picture naming

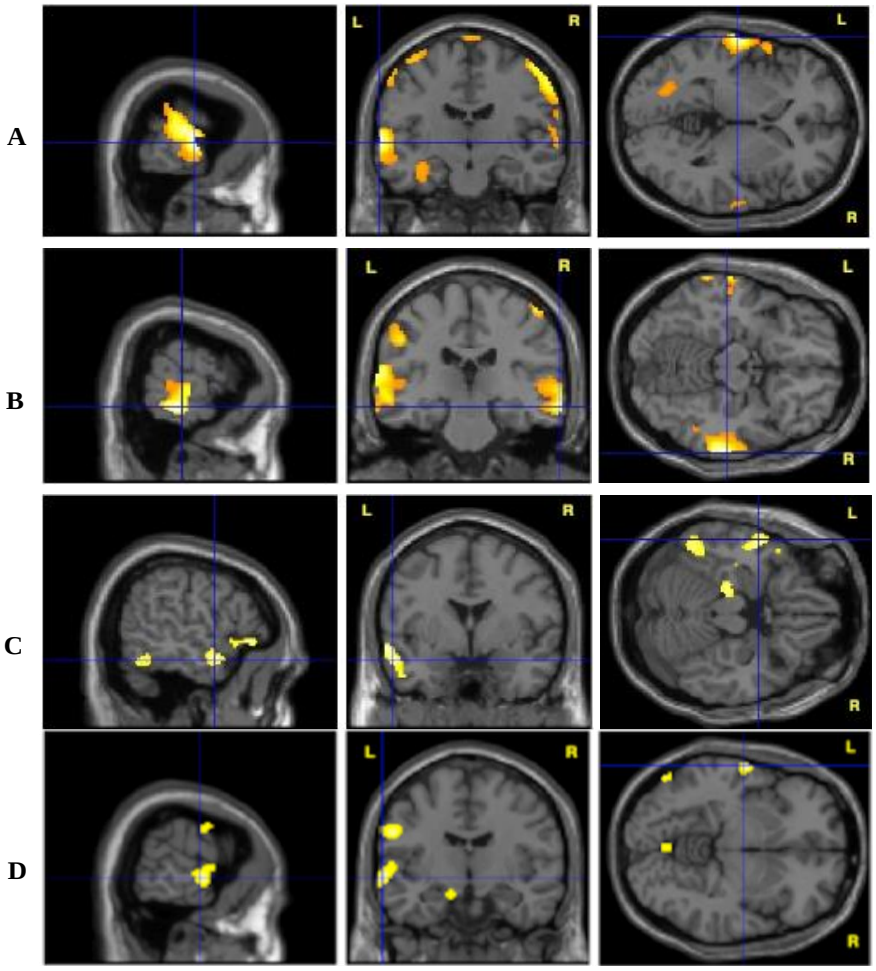

Fig 1

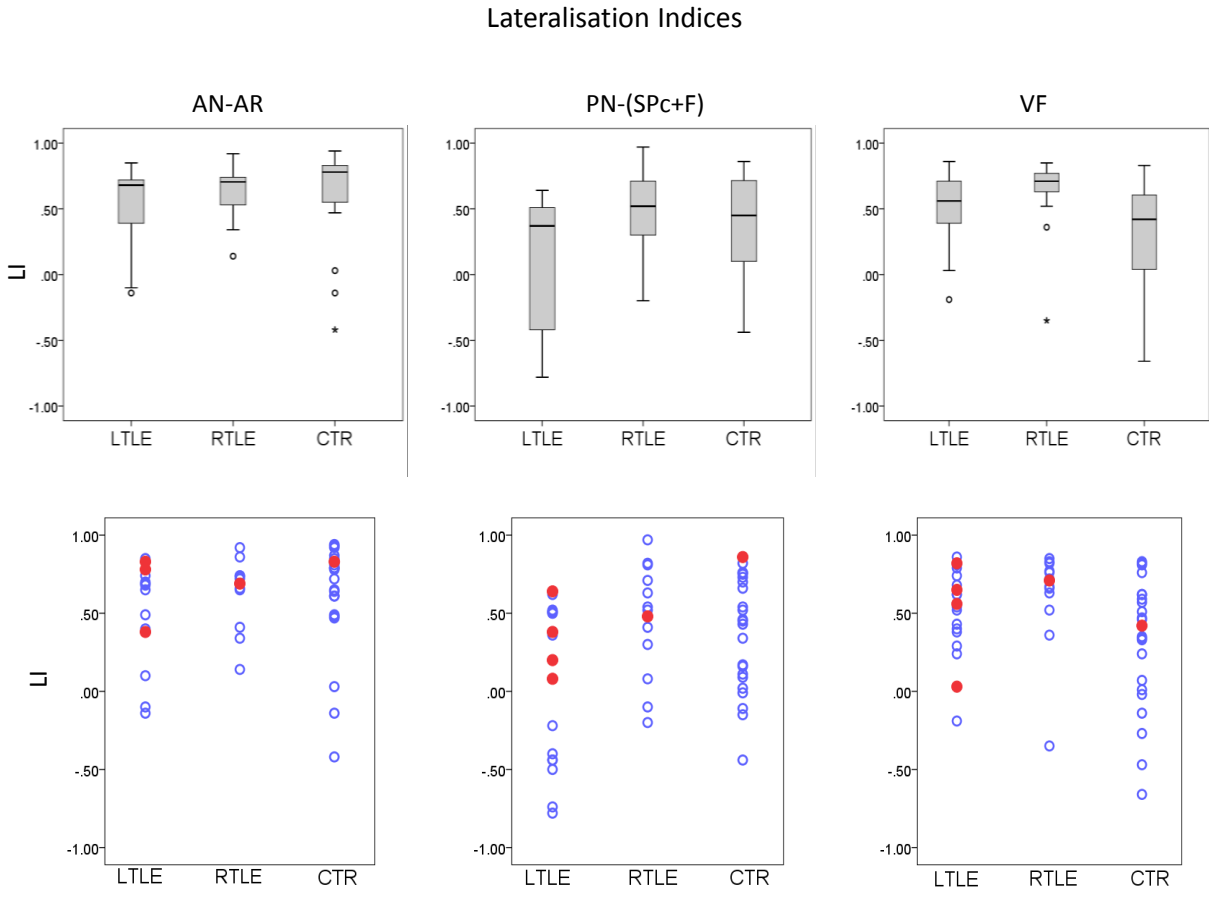
Lateralisation Indices
AN-AR
PN-(SPc+F)
VF
LI
1.00
.50
.00
-.50
-1.00
LTLE
RTLE
CTR

Fig 2

Main effects for five different contrasts

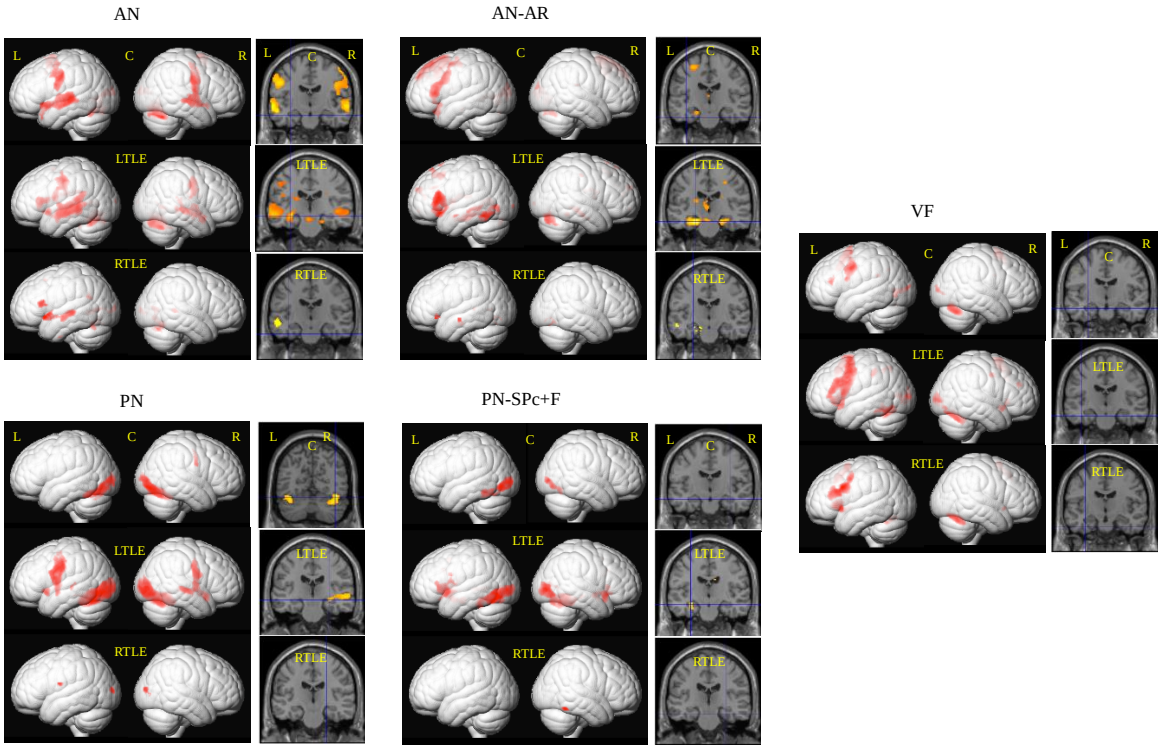

Fig 3

Group activation differences of LTLE patients > controls for the five contrasts (AN, AN-AR, VF, PN, PN-(SPc+Fc))

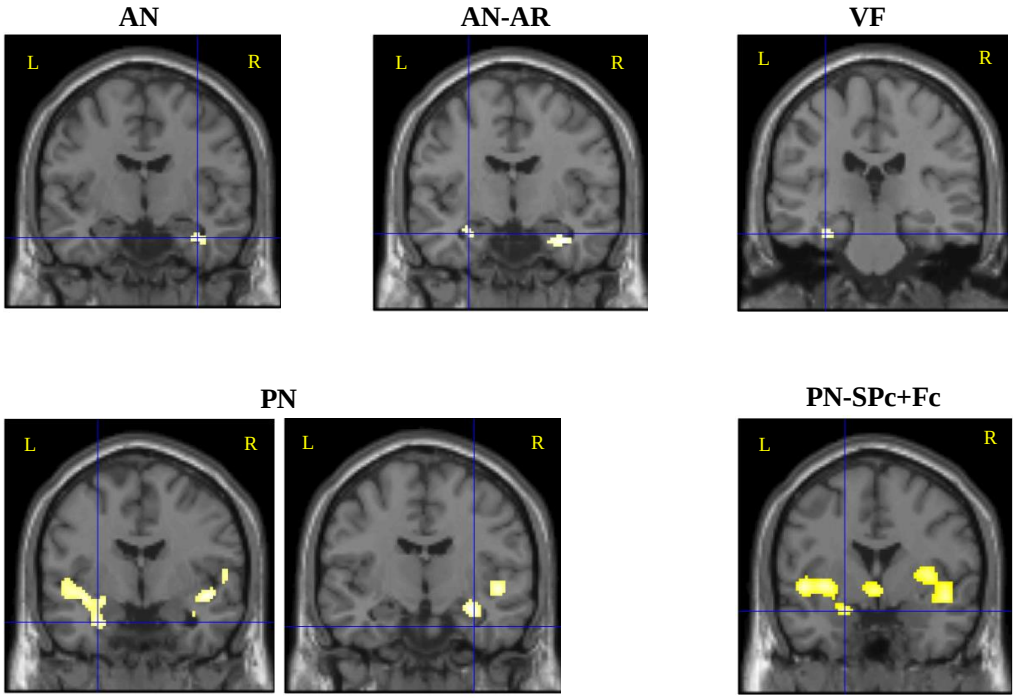

Figure 4

Table 1. Demographic and clinical data in control subjects and patients. Age, seizure frequency and number of AEDs are shown as median and range, NART IQ is shown as mean and SD.

	Age (years)	Gender female/ male	Age onset (years)	CPS monthly	SGS monthly	Number AEDs	Native English speaker	Handedness right /left	NART IQ
Controls	39 (18–61)	13/10	n/a	n/a	n/a	n/a	21/23	22/1	108 (7.2)
Left TLE	40 (26–59)	10/10	15 (1–52)	4 (0–130)	0 (0–3)	2 (0–4)	20/20	16/4	105 (10.7)
Right TLE	33 (19–47)	7/6	9 (1–32)	4 (0–100)	0.08 (0–4)	2 (0–4)	13/13	12/1	105 (142)

NART = National Adult Reading Test; TLE = temporal lobe epilepsy; CPS = complex partial seizures; SGS = secondary generalised seizures; AEDs = antiepileptic drugs; SD = standard deviation.

Table 2. Frequency distribution of activations (T>2.5, extent >10 voxels) within temporal lobe regions for the five contrasts (VF, AN, AN-AR, PN, PN-(SPc+F)) in left TLE patients, right TLE patients, and controls.

		VF	AN	AN–AR	PN	PN–(SPc+F)
Left TLE		**N=20**	**N=15**		**N=20**	
STG	Left	5 (25%)	11 (73%)	5 (33%)	9 (45%)	7 (35%)
	Right	1 (5%)	10 (67%)	2 (13%)	8 (40%)	5 (25%)
MTG	Left	4 (20%)	14 (93%)	10 (67%)	11 (55%)	7 (35%)
	Right	2 (10%)	9 (63%)	1 (7%)	11 (55%)	3 (15%)
STG/MTG	Left	6 (30%)	14 (93%)	11 (73%)	13 (65%)	10 (50%)
	Right	3 (15%)	11 (73%)	3(20%)	11 (55%)	5 (25%)
Right TLE		**N=13**	**N=12**		**N=13**	
STG	Left	3 (23%)	6 (50%)	3 (25%)	6 (46%)	4 (31%)
	Right	2 (15%)	6 (50%)	0	5 (38%)	1 (8%)
MTG	Left	2 (15%)	10 (83%)	8 (66%)	5 (38%)	5 (38%)
	Right	1 (8%)	2 (16%)	0	3 (23%)	2 (15%)
STG/MTG	Left	3 (23%)	11 (92%)	10 (83%)	7 (53%)	6 (46%)
	Right	2 (15%)	7 (58%)	0	6 (46%)	3 (23%)
Controls		**N=23**	**N=23**		**N=23**	
STG	Left	9 (39%)	17 (74%)	11 (48%)	11 (48%)	4 (17%)
	Right	5 (22%)	13 (57%)	4 (17%)	6 (26%)	1 (4%)
MTG	Left	10 (43%)	20 (87%)	15 (65%)	5 (22%)	9 (39%)
	Right	7 (30%)	13 (57%)	2 (9%)	4 (17%)	3 (13%)
STG/MTG	Left	12 (52%)	20 (87%)	19 (83%)	12 (52%)	10 (43%)
	Right	8 (35%)	16 (70%)	5 (22%)	8 (35%)	4 (17%)

VF= verbal fluency; AN= auditory naming; AN–AR= auditory naming–auditory reversed; PN= picture naming; PN–(SPc+F)= picture naming–(scrambled pictures+ blurred faces), (see also supplementary tables 2 A–C); TLE= temporal lobe epilepsy; STG= superior temporal gyrus; MTG= middle temporal gyrus; STG/MTG= superior and middle temporal gyri.

Table 3. Frequency distribution of activations (T>2.5, extent >10 voxels) within temporal lobe regions for the contrasts AN-AR and PN-(SPc+F) as well as their combination in left TLE patients, right TLE patients, and controls. P values of Chi² test are reported for group comparisons.

Left STG/MTG	LTLE (n=15)	RTLE (n=12)	CTR (n=23)	p
AN–AR	11 (73%)	10 (77%)	19 (83%)	0.74
PN–(SPc+F)	8 (53%)	6 (46%)	10 (43%)	0.83
Either AN–AR or PN–(SPc+F)	12 (80%)	10 (77%)	19 (83%)	0.97
Both AN–AR and PN–(SPc+F)	7 (47%)	6 (46%)	10 (43%)	0.93
Right STG/MTG				
AN–AR	3 (20%)	0	5 (22%)	0.22
PN– (Sc+F)	4 (27%)	3 (23%)	4 (17%)	0.76
Either AN–AR or PN–(Sc+F)	4 (27%)	3 (23%)	9 (39%)	0.61
Both AN–AR and PN–(Sc+F)	3 (20%)	0	0	**0.02**

AN–AR= auditory naming–auditory reversed; PN–(SPc+F)= picture naming–(scrambled pictures+ blurred faces); LTLE=left temporal lobe epilepsy; RTLE=right temporal lobe epilepsy; CTR=controls; STG/MTG= superior and middle temporal gyri.

NB: Only subjects who had undergone both the AN and PN tasks were included in the analysis (LTLE: 15/20, RTLE: 12/13; CTR: 23/23).

Table 4. Whole-brain cluster level activations (citing temporal activations only) are shown at threshold P< 0.001 uncorrected with an extent threshold of 20 voxels.

	VF	**AN**	**AN–AR**	**PN**	**PN–(SPc+F)**
Left TLE	**N=20**	**N=15**		**N=20**	
STG Left				-48 24 -6 (3.91)	
Right		52 10-22 (3.86)		50 14 -20 (3.48)	
MTG Left		-58 -38 -2 (5.36)			
Right			-58 -4 -18 (3.29)	-58 -30 0 (3.47)	
FuG Left					-32 -48 -16 (4.11)
Right					32 -56- 14 (4.47)
PHG Left					
Right		20 -20 -22 (3.71)			
Amyg Left					
Right					
HC Left			-22 -20 -20 (4.75)		
Right			34 -28 -12 (4.15)		-28 -16 -24 (4.35)
Right TLE	**N=13**	**N=12**		**N=13**	
STG Left	-56 16 -8 (3.53)	-58 10 -8 (4.18)			
Right					
MTG Left		-48 -32 -2 (4.03)	-54-16-16 (3.61)		
Right					
ITG Left		-34 -8 -44 (3.81)			
Right					
FuG Left					
Right					40-54-22 (3.71)
PHG Left					
Right					
HC Left			-26-16-20 (3.84)		
Right					
Controls	**N=23**	**N=23**		**N=23**	
STG Left		-54 14 -14 (4.87)			
Right					
PHG Left			-22 -18 -20 (3.77)		
Right					

TLE= temporal lobe epilepsy; STG= superior temporal gyrus; MTG= middle temporal gyrus; ITG= inferior temporal gyrus; FuG= Fusiform Gyrus; PHG= parahippocampal gyrus; HC= hippocampus. VF= verbal fluency; AN=auditory naming; AN–AR= auditory naming – reverse speech; PN= picture naming; PN–(SPc+F)= picture naming – (scrambled pictures+cartoon faces).

Table 5. Activation differences (coordinates and z–scores) between left TLE patients and controls

	VF	AN	AN–AR	PN	PN–(SPc+F)
Left TLE> controls					
STG Left				-46 -20 -2 (3.47)	-46 -4 -2 (4.11)
Right					44 -16 0 (3.76)
MTG Left		-56-64 12 (3.54)	-52 0 -18 (3.47)		
Right					68 -38 2 (3.56)
FuG Left					
Right					26 -54 -14 (3.81)
PHG Left	-32 -24 -22 (3.61)				
Right			24 –4 –28 (3.47)		
Amyg Left				-26 -2 28 (3.49)	
Right					
HC Left			-28 -8 -22 (3.28)	32 -10 -18 (3.66)	
Right		36 -8 -26 (3.43)			

Whole-brain cluster-level activations (citing temporal activations only) are shown at threshold P< 0.001 uncorrected with an extent threshold of 20 voxels. LTLE= left temporal lobe epilepsy; STG= superior temporal gyrus; MTG= middle temporal gyrus; FuG= Fusiform Gyrus; PHG= parahippocampal gyrus; Amyg = amygdala; HC= hippocampus