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Left temporal lobe language network connectivity in temporal lobe epilepsy

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Abstract

Impairment of naming function is a critical problem for temporal lobe epilepsy (TLE) patients, yet the neural correlates of the disruption of temporal lobe language networks are poorly understood. Using functional magnetic resonance imaging (fMRI), we investigated the activation and task-related functional connectivity of left temporal lobe language networks and their relation to clinical naming performance and disease characteristics.

We studied 59 adult patients with TLE (35 left TLE) and 32 healthy controls with auditory and visual naming fMRI tasks. Time series of activation maxima in the left posterior inferior temporal lobe were extracted to create a psychophysiological interaction (PPI) regressor for subsequent seed-based whole-brain task-related functional connectivity analyses.

Correlational analyses were performed to assess the association of fMRI activation and functional connectivity with clinical naming scores, age of onset of epilepsy, and duration of epilepsy.

Auditory naming elicited activation in the left posterior inferior temporal gyrus and visual naming in the left fusiform gyrus across all groups. Activations in the left inferior temporal gyrus, left thalamus and left supplementary motor region during auditory naming as well as left fusiform activations during picture naming correlated with better clinical naming performance. Functional connectivity analyses indicated coupling of left posterior inferior temporal regions to bilateral anterior and posterior temporal lobe regions and the bilateral inferior precentral gyrus as well as contralateral occipital cortex. Stronger functional connectivity was associated with better clinical naming performance in all groups.

In left TLE patients only, functional connectivity increased with later age of onset of epilepsy and shorter disease duration. This suggests that onset of seizures early in life and prolonged

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disease duration lead to disrupted recruitment of temporal lobe networks ipsilateral to the seizure focus, which might account for naming deficits in TLE.

Keywords: Temporal lobe epilepsy, language networks, functional connectivity, psychophysiological interaction, disease characteristics

Abbreviations

AED - antiepileptic drugs

AN - auditory naming

ANOVA - analysis of variance

ASSET - Array Spatial Sensitivity Encoding Technique

BOLD - blood oxygenation level dependent

CPS - complex partial seizure

CTR - controls

DMN - default mode network

DNET - dysembryoplastic neuroepithelial tumour

DTI - diffusion tensor imaging

F - blurred faces

fMRI - functional MRI

FWE - family-wise error

IQR - interquartile range

L - left

NART - National Adult Reading Test

NHNN - National Hospital for Neurology and Neurosurgery

PN - picture naming

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PPI - psychophysiological interaction

R - right

ROI - region of interest

SD - standard deviation

SGS - secondary generalised seizure

SMA - supplementary motor area

SPc - scrambled pictures

SPM - statistical parametric mapping

spmT - statistical parametric maps

TLE - temporal lobe epilepsy

1. Introduction

Temporal lobe epilepsy (TLE) is often associated with deficits in language function (Davey and Thompson, 1991). Disruption of normal functioning and organization of brain networks has been postulated to contribute to language impairment in TLE (Powell *et al.*, 2007; Protzner and McAndrews, 2011) and an early age of onset of epilepsy has been associated with poorer language performance (Schoenfeld *et al.*, 1999).

Impairment of naming function is a quintessential feature of language deficits in TLE and both auditory and visual naming tasks are clinically applied to assess naming performance (Hamberger, 2015). Performance on auditory naming tasks seems to be particularly related to word finding difficulties in conversational speech with its multiple neuropsychological demands (Bell *et al.*, 2003). Naming decline is also a concern for TLE patients following anterior temporal lobe resection (Bell *et al.*, 2002) and language fMRI has a useful role in the pre-surgical assessment as a non-invasive predictor of a reduction in naming capacity (Duncan, 2009; Bonelli *et al.*, 2012).

Temporal lobe language areas, particularly in the posterior and basal temporal regions, have been shown to be majorly involved in clinical naming performance in TLE (Trebuchon-Da Fonseca *et al.*, 2009), highlighting the importance of assessing temporal lobe language networks in this epilepsy syndrome. Currently, however, most clinically applied fMRI paradigms in presurgical epilepsy evaluation employ verbal fluency or verb generation tasks, which mainly activate frontal lobe language regions (Woermann *et al.*, 2003; Szaflarski *et al.*, 2008; Bonelli *et al.*, 2012; Centeno *et al.*, 2014). Recently, novel auditory and visual naming fMRI paradigms have been shown to reliably activate temporal lobe regions in presurgical TLE patients and controls (González *et al.*, 2016).

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Advances in structural and functional imaging techniques over recent years have shifted our understanding from discrete brain regions being responsible for language comprehension and production to the recognition of a distributed network of functionally coupled brain regions subserving language. The functional connections between cortical regions may be investigated by functional connectivity analyses derived from fMRI data (Friston, 1994) and are defined as the temporal correlation of the time series of spatially remote areas, indicating that the haemodynamic responses in these regions show a comparable pattern over time (Friston *et al.*, 1993; Friston, 1994).

Few studies have investigated language networks and reorganization in TLE using functional connectivity analyses. Resting state fMRI data indicate impaired connectivity between language-related regions in the inferior frontal gyrus and also between the inferior frontal gyrus and the default mode network (DMN) in TLE patients, especially in those with left hemisphere seizure onset (Waites *et al.*, 2006; Pravata *et al.*, 2011). Investigations on task-related functional connectivity of language networks in TLE are very scarce; poor language functions correlated with reduced functional connectivity between left hemisphere frontal lobe language regions (Vlooswijk *et al.*, 2010; Pravata *et al.*, 2011) but connectivity patterns of temporal lobe language regions remain poorly understood.

The aim of this study was to investigate the functional anatomy of naming in the temporal lobe. We used auditory and visual naming fMRI in TLE patients implementing a seed-based whole-brain functional connectivity approach, to explore how these activations and their functional connections were related to clinical naming performance and disease duration. We hypothesized that:

1. Temporal lobe activations during naming tasks would be functionally coupled to brain regions consistent with language networks proposed in theoretical models.

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2. The strength of connectivity from temporal lobe regions would depend on clinical naming performance and disease duration.

2. Methods

2.1. Subjects

Ninety-six participants were enrolled in the study, comprising 63 patients with medically refractory TLE (37 left TLE (L-TLE), 26 right TLE (R-TLE)) and 33 healthy controls. We excluded two L-TLE, two R-TLE patients, and one control subject from the analysis due to poor fMRI data quality, leaving a total of 91 participants (48% males, age range 18–63 years). Patients with a confirmed diagnosis of TLE were consecutively recruited from those undergoing presurgical assessment at the National Hospital for Neurology and Neurosurgery (NHNN). Control subjects were age- and gender-matched to the overall patient group, and 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, and inability to give informed consent. An additional exclusion criterion for patients was history of a secondarily generalised tonic-clonic seizure within 24h prior to the study. Demographic and clinical data are summarized in Table 1.

Table 1. Demographic and clinical data in controls and patients. Age and age of onset of epilepsy are shown as mean \pm SD. Seizure frequency (CPS, SGS) and number of AED are shown as median and IQR.

	Age (years)	Gender female/male	Age onset (years)	CPS monthly	SGS monthly	Number AED	Handedness right /left
<i>Controls (n=32)</i>	38.5 \pm 11.4	19/13	n/a	n/a	n/a	n/a	29/3
<i>L-TLE (n=35)</i>	35.4 \pm 10.9	17/18	17.1 \pm 9.3	5 (8)	0 (0)	2 (1)	31/4
<i>R-TLE (n=24)</i>	37.0 \pm 10.8	11/13	22.3 \pm 12.9	6 (11)	0 (0)	2 (0.8)	21/3

Note: AED = antiepileptic drugs; CPS = complex partial seizures; IQR = interquartile range; LTLE = left temporal lobe epilepsy; RTLE = right temporal lobe epilepsy; SD = standard deviation; SGS = secondarily generalised seizures.

Prolonged interictal and ictal EEG video telemetry confirmed and lateralised temporal seizure onset zones (ipsilateral in patients with structural brain lesions) in all patients. All patients underwent structural MRI at 3.0 T, including quantification of hippocampal volumes and T₂ relaxation times (Woermann *et al.*, 1998). MRI identified hippocampal sclerosis (HS) in 28 patients (17 left/11 right), dysembryoplastic neuroepithelial tumour (DNET) in 12 (8 left/ 4 right), cavernoma in three (2 left/ 1 right), focal cortical dysplasia in two (1 left/1 right), low grade glioma in three (1 left/2 right), and 11 normal MRI (6 left/ 5 right).

All participants were fluent in written and spoken English. Handedness was determined using the Edinburgh Hand Preference Inventory (Oldfield, 1971).

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). Intellectual level was derived from performance on the National Adult Reading Test (NART; Nelson and Wilson, 1991).

2.3. MR data acquisition

MRI studies were performed using a 3T General Electric Signa MR750 scanner (GE, Wisconsin), using standard imaging gradients with a maximum strength of 50 mTm^{-1} and slew rate $200 \text{ TM}^{-1} \text{ s}^{-1}$. All data were acquired using the standard 32-channel RF receive head array coil and the body RF coil for transmission.

For fMRI, we acquired gradient-echo planar T2*-weighted images (TE = 22 ms, TR = 2500 ms), providing blood oxygenation level dependent (BOLD) contrast. Each volume comprised 50 contiguous 2.4 mm slices (0.1-mm gap) with a 24 cm field of view, 64×64 matrix, giving an in-plane pixel size of 3.75×3.75 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, the Array Spatial Sensitivity Encoding Technique (ASSET; the GE implementation of parallel imaging) was used.

All subjects underwent a structural MRI scanning protocol on the same scanner, which included an axial T1 Bravo sequence as well as a diffusion sequence. Patients additionally underwent a standard clinical imaging protocol including an axial and coronal T2-weighted sequence, an

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axial susceptibility-weighted sequence, and an oblique coronal 2D dual-echo proton density and T2-weighted image sequence.

2.4. Language paradigms

We employed two overt language tasks, auditory naming (AN) and picture naming (PN) as described previously (González *et al.*, 2016). Subjects responded to visual and auditory stimuli presented via a magnetic-resonance compatible screen viewed through a mirror (Bonelli *et al.*, 2012) and a compatible audio-system (headphone and microphone devices).

AN sessions consisted of five cycles of alternating 30-s activation blocks and two control blocks of 15-s each, comprising auditory reversed speech (AR) and cross-hair fixation. During the activation phase, subjects were asked to name aloud objects and animals from their auditory description. Participants were instructed to count aloud “one, two” during AR and to rest with eyes open during cross-hair fixation.

PN sessions involved five cycles of visually presented stimuli, each consisting of alternating 30-s activation blocks and three control blocks of 15-s each, comprising scrambled pictures (SPc), blurred cartoon faces (F), and crosshair fixation. During the activation phase, participants were instructed to name aloud black and white line drawings of everyday objects and animals. Subjects were instructed to count aloud “one, two” in response to SPc and F, and to rest with eyes open during crosshair fixation. Further details on the acquisition paradigms can be found in the Supplementary Information.

Prior to scanning, each subject was given detailed explanations with examples to ensure test instructions were fully understood. We recorded all tasks with an external microphone outside the scanner. All study participants successfully performed >80% on both fMRI tasks and there was no statistically significant difference in task performance among the three groups

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($p > 0.05$). Due to technical problems with the audio and visual presentation systems, auditory naming could not be acquired in one L-TLE patient and one control subject.

2.5. 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 high resolution whole brain echo planar images of 30 healthy controls, 15 patients with left hippocampal sclerosis, and 15 patients with right hippocampal sclerosis) 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 haemodynamic response function for each of the conditions of interest. Parameter estimates for regressors were calculated for each voxel. Two contrast images were generated for each subject within the three groups (controls, L-TLE, R-TLE), comprising auditory naming minus reversed speech (AN-AR), and picture naming minus scrambled pictures and faces (PN-(SPc+F)).

These contrast images were used for the second-level analysis. One-sample t-tests were used to examine the main effect of each task across groups. One-way analyses of variance (ANOVA) were used to quantitatively assess statistical differences among the three groups (L-TLE, R-TLE, controls). Unless otherwise stated, we report activations at a threshold of $p < 0.05$, corrected voxel-wise for multiple comparisons (family-wise error rate [FWE]) across the whole brain.

2.5.1. Functional connectivity (psychophysiological interaction, PPI)

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We employed a psychophysiological interaction (PPI) analysis to assess task-related functional connectivity between activated areas. To identify the seed region for the PPI analysis, we located each subject's individual peak response to the contrasts AN–AR and PN–(SPc+F) within a region of interest (ROI) in the left posterior inferior temporal lobe, defined from group activation maps of each contrast, and the time series of a sphere of 8mm radius around this peak voxel was extracted from the normalized, smoothed echo planar imaging (EPI) images (Bonelli *et al.*, 2012). The PPI model included 3 regressors: (1) The main effect of the seed region (i.e. the functional connectivity), (2) the main effect of the task (AN–AR and PN–(SPc+F), respectively) and (3) the interaction between the two, representing a task-modulated change in functional connectivity, or PPI (Friston, 1994). Areas functionally coupled to the left temporal lobe seed region were examined across groups by one-sample t-tests for each task and were compared across groups by using one-way ANOVA. All PPI activations are reported at a threshold of $p < 0.05$, corrected voxel-wise for multiple comparisons (family-wise error rate [FWE]) across the whole brain unless otherwise stated.

For the convenience of the reader, for the contrast AN–AR we refer to as "auditory naming" and for the contrast PN–(SPc+F) as "picture naming".

2.5.2. Correlations with clinical factors

We assessed correlations of areas of auditory and picture naming fMRI activation and functional connectivity with naming performance outside the scanner in all subjects. In patients, we additionally investigated correlations of fMRI activations with age of onset of epilepsy and disease duration.

Positive and negative correlations were explored using McKenna naming scores (McKenna *et al.*, 1983) as well as age of onset and disease duration as covariates in one-sample t-tests. In accordance with previous investigations using auditory and picture naming fMRI paradigms, activations were expected to encompass the bilateral superior, middle and inferior temporal

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gyrus and fusiform gyrus as well as the left middle and inferior frontal gyrus (Gonzalvez *et al.*, 2016; Croft *et al.*, 2014). Using the group activation maps, masks were created to identify the activation maximum within these regions of interest. All correlational activations are shown masked for the group effects at a threshold of $p < 0.001$ uncorrected, extent threshold 10 voxels, corrected for multiple comparisons using a small volume correction within a sphere of 8 mm radius (FWE; $p < 0.05$), centered at the location of activation maximum in the frontal and temporal lobe regions of interest (Bonelli *et al.*, 2012; Sidhu *et al.*, 2013). Estimated verbal IQ derived from performance on the NART (Nelson and Wilson, 1991) was used as a covariate of no interest for all analyses.

3. Results

3.1. Demographic data

The three groups did not differ in age ($F = 5.14$; $p = 0.08$) and the distribution of gender (Pearson $\chi^2 = 1.22$; $p = 0.54$) and handedness (Pearson $\chi^2 = 0.15$; $p = 0.93$) was comparable across all groups. The two patient groups did not differ in frequency of complex partial (Mann-Whitney-U = 443.5; $p = 0.72$) and generalised seizures (Mann-Whitney-U = 398.0; $p = 0.63$) or number of antiepileptic drugs (AED) taken (Mann-Whitney-U = 358.5; $p = 0.31$).

3.2. Neuropsychological results

There was a significant difference in intellectual level (estimated IQ) derived from performance on the NART (Nelson and Wilson, 1991) between the three groups ($H(2) = 19.1$; $p < 0.001$; Table 2). Post-hoc analysis indicated that estimated IQ was lower in L-TLE patients ($p < 0.001$) and R-TLE patients ($p = 0.03$) than in controls. There was no significant difference in IQ between L-TLE and R-TLE patients ($p = 0.49$).

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Clinical naming test scores (McKenna *et al.*, 1983), showed only a statistical trend towards a difference between the groups ($H(2) = 5.89$; $p = 0.05$; Table 2). Exploratory subsequent pairwise comparisons indicated lower naming scores in L-TLE patients vs. controls ($p = 0.03$), whereas there was no difference between the two patient groups ($p = 0.07$) or between R-TLE patients and controls ($p = 0.95$).

Table 2. Estimated intellectual level (derived from performance on NART) and naming scores in patients and controls. Data are shown as mean (SD) and range.

	<i>L-TLE</i>	<i>R-TLE</i>	<i>Controls</i>
NART IQ range	95.1 (11.1)** 72–121	99.8 (11.3)* 80–120	107.9 (10.0) 89–126
Naming score range	14.9 (6.0) 4–26	17.8 (5.4) 7–26	18.0 (5.4) 6–28

Note: L-TLE = left temporal lobe epilepsy; NART IQ = Intellectual level derived from performance on National Adult Reading Test; R-TLE = right temporal lobe epilepsy; SD = standard deviation.

* = independent sample t-test R-TLE<CTR, $p=0.03$

** = independent sample t-test L-TLE<CTR, $p<0.001$

3.3. Main effects

3.3.1. Auditory naming

Main effects across all groups were observed in the left posterior inferior temporal gyrus, left posterior and anterior middle temporal gyrus, left superior frontal gyrus (including the supplementary motor region), left lingual gyrus, and left anterior cingulate. Further activations were seen in the right cerebellum as well as bilateral inferior frontal gyrus, bilateral thalamus and bilateral superior occipital gyrus (Supplementary Table 1, Figure 1). There were no significant differences among the three groups.

3.3.2. Picture naming

Main effects across all subjects were observed in the left fusiform gyrus, left inferior frontal gyrus, left superior frontal gyrus (supplementary motor region) as well as left middle occipital gyrus. Further activations were seen in the right inferior temporal gyrus, right cerebellum and bilateral inferior occipital gyrus (Supplementary Table 1, Figure 1). There were no significant differences among the three groups.

3.4. Correlation of fMRI activations with clinical naming scores

For auditory naming, a correlation of greater fMRI activations with higher clinical naming scores was observed in the left posterior inferior temporal gyrus, the left thalamus and left superior frontal gyrus (supplementary motor region) across groups. For picture naming, increased activation correlated with better naming scores in the left fusiform gyrus across groups. Inter-group comparisons did not indicate a significant difference of the correlations among groups (Supplementary Table 2, Figure 2). Of note, there were no areas in any of the groups for both fMRI tasks which showed reduced fMRI activation with better naming scores.

3.5. Functional Connectivity (Psychophysiological interaction; PPI)

3.5.1. PPI Auditory naming

Across groups, the left posterior inferior temporal seed region (derived from the individual peak response in the left posterior inferior temporal lobe, defined from group activation maps, Figure 1), showed task-related functional coupling with the left anterior superior, middle and inferior temporal gyrus, left transverse temporal gyrus (Heschl's gyrus) and left superior frontal gyrus (supplementary motor region). Further significant connectivity was observed to the right anterior (temporal pole) and posterior superior temporal gyrus as well as bilateral posterior middle temporal gyrus, bilateral precentral gyrus and bilateral cerebellum (Supplementary Table 3, Figure 3). There were no significant differences in functional connectivity among the three groups.

3.5.2. PPI Picture naming

Across groups, functional coupling was observed between the left posterior inferior temporal lobe and the left anterior superior temporal gyrus (including the temporal pole) and the left posterior fusiform gyrus as well as the right inferior occipital gyrus, right cerebellum and

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bilateral precentral gyrus (Supplementary Table 3, Figure 3). There were no significant differences in functional connectivity among the three groups.

3.6 Correlation of functional connectivity with naming scores

For auditory naming, connectivity values between the left posterior inferior temporal seed region and the left orbitofrontal gyrus correlated with better clinical naming scores across the three groups.

For picture naming, a positive association between clinical naming scores and functional connectivity between the left temporal lobe seed and the left precentral gyrus was noted across groups (Supplementary Table 4, Figure 4). Inter-group comparisons did not indicate a significant difference in the correlations among groups. Of note, there were no areas in the brain of greater functional connectivity with poorer naming scores for any group in both fMRI tasks.

3.7 Correlation of functional connectivity with age of onset of epilepsy and disease duration in L-TLE and R-TLE patients

For auditory naming, L-TLE patients showed greater functional connectivity between the left inferior temporal gyrus and the left anterior middle temporal gyrus and the left inferior frontal gyrus with later age of onset of epilepsy. In addition, the shorter the disease duration, the stronger the connectivity to the left precentral gyrus and posterior superior temporal gyrus (Supplementary Table 5, Figure 5).

For picture naming, L-TLE patients showed greater connectivity between the left fusiform gyrus and the left precentral gyrus with later age of onset of epilepsy and shorter disease duration. Additionally, shorter disease duration was associated with greater connectivity to the left temporal pole (Supplementary Table 5, Figure 5).

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R-TLE patients did not show any suprathreshold correlations of functional connectivity seeding from the left posterior temporal lobes with age of onset or disease duration for any of the fMRI tasks and group comparisons indicated stronger correlations for L-TLE than R-TLE patients (Supplementary Table 5, Figure 5).

4. Discussion

Across all subjects (L-TLE, R-TLE, controls), auditory and picture naming elicited robust activations in the left posterior inferior temporal lobe, which were functionally coupled to bilateral temporal and inferior frontal lobe regions. Left posterior temporal lobe activations and the strength of functional connectivity to other brain regions correlated with better clinical naming performance, without intergroup differences. For L-TLE patients, stronger functional connections between the left posterior inferior temporal lobe and other language-specific cortical regions was associated with later age of epilepsy onset as well as with shorter disease duration. Our findings highlight the importance of probing the integrity of temporal lobe language networks and could provide an explanation for impaired naming performance in TLE, especially in patients with an early onset of seizures and long disease duration.

4.1. fMRI activations in posterior inferior temporal regions and association with clinical naming performance

While most clinically applied language fMRI paradigms involve tasks that mainly activate frontal lobe language areas, such as the verbal/letter fluency task or verb generation task (Woermann *et al.*, 2003; Szaflarski *et al.*, 2008; Bonelli *et al.*, 2012), we aimed to highlight temporal lobe language networks in our cohort, since it has been suggested that reorganisation

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of language networks in TLE patients might predominate in temporal lobe as compared to frontal lobe networks (Thivard *et al.*, 2005).

We clinically validated our fMRI tasks showing that the temporal lobe fMRI activation maxima of both naming tasks as well as their functional connections were associated with better clinical naming performance in TLE patients and controls. By employing two overt language tasks, auditory naming and visual naming, we could demonstrate consistent activations in left posterior temporal lobe regions, specifically the posterior inferior temporal gyrus and fusiform gyrus, in healthy controls and patients with L-TLE or R-TLE. Auditory naming activated the left posterior inferior temporal gyrus and visual naming activated the left fusiform gyrus across groups, which was correlated with better clinical naming performance. Both inferior temporal gyrus and fusiform gyrus have been extensively described to be associated with semantic processing in fMRI studies (see Binder *et al.*, 2009 for a review) and lesion studies suggest that resection of the left inferior temporal gyrus, fusiform gyrus, middle temporal gyrus and parahippocampal gyrus are associated with a decline in clinical naming performance, with the most relevant association found for the fusiform gyrus (Wilson *et al.*, 2015).

Auditory naming activations were also observed in the left posterior and anterior middle temporal gyrus, for which a strong association with lexical-semantic processing has been described. The posterior middle temporal gyrus is particularly thought to represent a crucial link between the initial phonological processing and subsequent semantic processing (Middlebrooks *et al.*, 2017).

Picture naming also activated the right inferior temporal gyrus in all groups. Involvement of right temporal regions has been described previously and has usually been interpreted as an expression of high demands on semantic processing (Démonet *et al.*, 1992; Pugh *et al.*, 1996; Kircher *et al.*, 2001). Auditory naming also activated the left anterior cingulate and bilateral

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thalamus, which have been attributed to decision making during semantic attention tasks as part of cortico-thalamic networks (Hebb and Ojemann, 2013; Li *et al.*, 2017).

Both auditory and picture naming were further associated with activations in the left inferior frontal gyrus and the left supplementary motor region. While the role of the inferior frontal gyrus in the language system was initially attributed mostly to language production, its critical role in semantic processing is now widely accepted. Lesion as well as functional imaging studies suggest that both anterior regions of the inferior frontal gyrus such as pars orbitalis or pars triangularis as well as posterior regions including pars opercularis are involved in the semantic network and play a role in lexical retrieval, verbal working memory, and naming (Bookheimer, 2002; Binder *et al.*, 2009; Middlebrooks *et al.*, 2017). The dominant supplementary motor area (SMA) has been attributed a role in higher-order function in language production, and resection or damage to this region frequently results in the SMA syndrome, which involves difficulties with initiation of speech and generally reduced spontaneous speech output (Rostomily *et al.*, 1991).

4.2. Task-related functional connectivity of temporal lobe language networks

Seed-based whole-brain functional connectivity (PPI) analyses demonstrated functional coupling of the left inferior posterior temporal region to other brain regions related to the language network, most importantly bilateral temporal and frontal lobe areas.

In the auditory naming task, this included the left anterior superior, middle and inferior temporal gyrus and left Heschl's gyrus, the right temporal pole, and the bilateral posterior middle temporal gyrus as well as inferior part of the precentral gyrus.

For the visual naming task, connectivity from the left posterior inferior temporal seed region included the ipsilateral anterior superior temporal gyrus (including the left temporal pole), the bilateral inferior precentral gyrus and right occipital gyrus.

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The observed functional connectivity patterns elicited by auditory and visual naming tasks primarily involved ipsi- and contralateral temporal and occipital cortex and bilateral frontal lobe regions, which is supported by conceptual models of language networks as well as investigations using language fMRI activation and connectivity analyses. The role of a bilateral, left-lateralised temporal lobe language network has been extensively studied, especially in regard to semantic processing (see e.g. Binder *et al.*, 2009 for a review) and the involvement of the bilateral superior temporal gyri has been described for an auditory semantic decision task as well as auditory and visual naming tasks in both healthy volunteers and TLE patients (Friederici *et al.*, 2003; González *et al.*, 2016). The temporal pole has been suggested to represent a “semantic hub” linked to complex semantic processing and it is well-known that resection of the dominant temporal pole may result in naming deficits in a large proportion of patients (Sabsevitz *et al.*, 2003; Binder *et al.*, 2011; Goucha and Friederici, 2015; Middlebrooks *et al.*, 2017).

The observed connectivity patterns to frontal lobe regions in our study primarily involved the inferior part of the precentral gyrus. This involves the ventral premotor cortex, just posterior to the pars opercularis of the inferior frontal gyrus, which represents the primary component of the original Broca’s area (Dronkers *et al.*, 2007; Tate *et al.*, 2014; Yagmurlu *et al.*, 2016). Given its close vicinity to the orofacial primary motor cortex, the ventral premotor cortex has been attributed a critical role in phonologic processing bilaterally (Duffau *et al.*, 2003; Sanai *et al.*, 2008; Chang *et al.*, 2015; Yagmurlu *et al.*, 2016) and its activation has been described in healthy volunteers using an auditory semantic decision task (Friederici *et al.*, 2003). Our findings are further supported by previous functional connectivity analyses derived from resting-state and task-derived fMRI in healthy controls and TLE patients showing an interconnection of left anterior temporal lobe regions with ipsilateral temporal and frontal lobe regions (Bettus *et al.*, 2009; Pravata *et al.*, 2011), and also with homologous areas in the right hemisphere (Hurley *et al.*, 2015).

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Lastly, the right occipital cortex has been involved in object naming. Price and colleagues (Price *et al.*, 2005) conducted a meta-analysis of functional imaging studies on object naming and found bilateral involvement of the occipito-temporal cortex for visual naming. However, greater involvement of the right occipital cortex was noted when “high-level” baselines were employed, which controlled for visual processing and speech production (Price *et al.*, 2005).

4.3. Relation of functional connectivity to clinical naming performance

The strength of functional connectivity seeding from the left posterior inferior temporal gyrus to the left orbitofrontal gyrus during auditory naming, and from the left fusiform gyrus to the left precentral during visual naming was correlated with better clinical naming scores with no difference of correlations between groups.

There is a dearth of investigations on the relation of task-related functional connectivity of language regions with clinical naming performance in TLE. Pravata and colleagues (2011) investigated functional connectivity between 6 predefined regions in the left and right frontal and temporal lobes using a verb generation task and found a correlation with verbal IQ for connectivity values within the left hemisphere in L-TLE patients, however, naming was not assessed. The orbitofrontal cortex has been attributed to semantic processing and decision making (Middlebrooks *et al.*, 2017) and reduced connectivity between medial temporal regions and the left orbitofrontal cortex have previously been described in L-TLE patients (Voets *et al.*, 2009).

Vlooswijk *et al.* (2010) found a significant correlation of functional connectivity between left inferior and middle frontal regions for a word generation fMRI paradigm with clinical performance on a semantic fluency task and a text reading task. There was, however, no correlation of clinical language performance with connectivity between left temporal and left frontal regions. Crucially, our findings emphasise the clinical relevance of assessing

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functional connectivity of temporal lobe language networks in TLE using auditory and visual naming paradigms with active control conditions.

4.4. Correlation of functional connectivity with disease duration and age of onset of epilepsy

In L-TLE patients, functional seeding from the left inferior temporal gyrus to left anterior middle temporal gyrus and posterior superior temporal gyrus as well as to the left precentral gyrus was associated with shorter disease duration and a later disease onset. Group comparisons indicated stronger correlations for L-TLE than R-TLE patients, in which no suprathreshold correlations were observed (Supplementary Table 5, Figure 5).

Recently, functional connectivity in left hemisphere language networks was investigated in children with and without focal epilepsy using a principal component analysis (PCA) approach derived from an auditory semantic decision fMRI task (Croft *et al.*, 2014). Reduced activation of left hemisphere language networks and poorer language performance were observed in children with epilepsy compared to controls, but no correlation of intrahemispheric functional connectivity with age of onset or disease duration was demonstrated, which might have been attributable to an insufficient duration of epilepsy to cause changes in functional connectivity (Croft *et al.*, 2014). In adults, a study in patients with TLE did not show a correlation of task-derived functional connectivity with disease duration or age of onset of epilepsy (Vlooswijk *et al.*, 2010). Our study therefore provides evidence for disruption of left temporal lobe language networks in TLE patients by both an early onset of epilepsy as well as prolonged disease duration. This might represent an expression of impaired recruitment of language networks caused by an early onset of seizures and prolonged disease duration, which is in accordance with clinical findings of impaired clinical naming performance associated with longer duration of epilepsy (Thompson and Duncan, 2005; Thompson *et al.*, 2015). Stronger correlations in L-TLE compared to R-TLE patients

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argue for the reorganisation of temporal lobe language networks ipsilateral to the seizure onset zone in L-TLE, in accordance with previous findings (Thivard *et al.*, 2005).

4.5. Strengths and limitations

Our study has several methodological strengths. First, we applied a seed-based whole-brain connectivity approach instead of using predefined regions of interest, and we investigated task-related functional connectivity instead of resting-state fMRI, since it has been suggested that task-derived language networks allow stronger inferences regarding activation patterns and behaviour as compared to resting-state analyses (Calhoun *et al.*, 2008). Second, we used an active control condition in both our language fMRI tasks to create our fMRI contrasts and activation maps, i.e. reversed speech in the auditory naming task and scrambled pictures/faces in the visual naming task, followed by an irrelevant overt response (saying out loud “one, two”) by the participants. This diminishes activations caused by the type of stimulus presentation (auditory vs. visual input) as well as motor cortex activations and movement artifacts caused by overt language production (González *et al.*, 2016). If rest is used as a control condition, specific brain networks can be activated, but the DMN, a task-negative network which activates in the absence of a cognitive task, shows significant overlaps with brain areas related to semantic processing, which can lead to subtraction of task-related activation in those areas (Raichle *et al.*, 2001; Binder *et al.*, 2009). Third, we used overt language tasks, offering the benefit to control for task performance (Croft *et al.*, 2014; González *et al.*, 2016). As noted previously (Gartus *et al.*, 2009; Leuthardt *et al.*, 2012), overt speech production elicits substantial perisylvian cortical activation, which is negated by creating appropriate contrasts essentially subtracting motor activity (González *et al.*, 2016). Fourth, we used conservative statistical thresholds that allow inferences to be made about patients with TLE as a population.

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There are also several limitations to our work. Patients had a lower intelligence level than controls, which was mitigated by including IQ as a covariate of no interest for all analyses, including correlation analyses with clinical factors. There were no group differences in clinical naming scores, although there was a trend towards impaired naming in L-TLE patients. Lastly, we have not yet investigated structural connectivity correlations with our functional connectivity findings and their relation to clinical factors. Previous results from resting-state fMRI in healthy subjects suggest a reflection of functional connectivity by white matter tracts derived from diffusion tensor imaging (DTI; Greicius *et al.*, 2009). Structural reorganisation of white matter tracts has been suggested to reflect the altered functional language lateralisation in L-TLE patients (Powell *et al.*, 2007) and impaired integrity of both dorsal and ventral white matter language tracts as expressed by increased diffusivity or decreased fractional anisotropy measures have been reported to be associated with impaired clinical naming performance in TLE (McDonald *et al.*, 2008).

4.6. Clinical implications

Anterior temporal lobe resection is an effective treatment option for individuals with refractory TLE, leading to seizure remission in up to 80% of patients for over one year (de Tisi *et al.*, 2011). An important caveat, however, are the naming and word finding difficulties that might ensue. Previous verbal fluency fMRI tasks have been shown to be sensitive, but not specific predictors of word-finding difficulties following temporal lobe resections (Bonelli *et al.*, 2012). We show that the functional anatomy of naming is related to disease characteristics, particularly in patients with a left hemisphere seizure onset. Stronger connectivity to the “to-be-resected” left temporal pole in patients with shorter disease duration and later age of onset of seizures might implicate a higher risk of developing naming deficits following anterior temporal lobe resection. This might have implications for the prediction of

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naming deficits following surgery and for surgical planning. Ongoing prospective studies are addressing this issue.

4.7. Conclusions

Naming and word finding difficulties are frequently encountered in TLE, particularly when the seizure focus is located in the left hemisphere, and naming decline is a major concern following language-dominant anterior temporal lobe resections. Using auditory and visual naming fMRI paradigms, this study provides novel evidence of an association between task-related functional connectivity of left posterior temporal lobe language networks with clinical naming in TLE and controls. Earlier age of onset and longer duration of L-TLE are shown to be associated with more profound disruption of these networks.

This suggests a disturbance of temporal lobe networks ipsilateral to the hemisphere of seizure onset caused by an early and prolonged detrimental effect of epilepsy on the left temporal lobe. This clearly highlights the importance of early diagnosis and treatment of TLE, and longitudinal investigations are warranted to investigate the plasticity of these networks, especially in regard to epilepsy surgery.

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Figure Captions

Figure 1. fMRI activations across all three groups (L-TLE, R-TLE, controls) for auditory naming and picture rendered and superimposed on sagittal and coronal images. The crosshairs indicate the location of the orthogonal slices.

Auditory naming (upper row): Crosshair showing left inferior temporal gyrus activations (coordinates x y z: -48 -50 -18). Sagittal/coronal slices also show left middle temporal, left inferior frontal and bilateral occipital activations.

Picture naming (lower row): Crosshair showing left fusiform gyrus activations (coordinates x y z: -34 -46 -16). Sagittal/coronal slices also show left frontal and right cerebellar activations. All activations are shown at $p < 0.05$, voxel-wise corrected for multiple comparisons (FWE).

Note: A = anterior; FWE = family-wise error; L = left; P = posterior; R = right;
TLE = temporal lobe epilepsy.

Figure 2. Increased fMRI activations with higher clinical naming scores across all three groups (L-TLE, R-TLE, controls) superimposed on sagittal and coronal images shown masked for the group effects at $p < 0.001$, uncorrected, extent threshold 10 voxels.

Activations are significant corrected for multiple comparisons using a small volume correction within a sphere of 8 mm radius (FWE; $p < 0.05$) at the location of activation maximum in the temporal and frontal lobe regions of interest.

Top row: Correlations with activations in the left posterior inferior temporal gyrus for auditory naming. Lower row: Correlations with activations in the left fusiform gyrus for picture naming.

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Note: A = anterior; L = left; P = posterior; R = right; TLE = temporal lobe epilepsy.

Figure 3. Functional connectivity (psychophysiological interaction; PPI) from the left temporal lobe seed region across all three groups for auditory naming and picture naming tasks. Functional connectivity change shown rendered at $p < 0.05$, corrected for multiple comparisons (FWE).

Green ellipsoids represent the left temporal lobe seed region.

Note: FWE = family-wise error; L = left; PPI = psychophysiological interaction; R = right.

Figure 4. Correlations of functional connectivity of auditory naming (seed region: left inferior temporal gyrus) and picture naming (seed region: left fusiform gyrus) with clinical naming scores across the three groups. Areas of significant connectivity are shown superimposed on coronal images masked for the group effects at $p < 0.001$, uncorrected, extent threshold 10 voxels. Connectivity values are significant corrected for multiple comparisons using a small volume correction within a sphere of 8 mm radius (FWE; $p < 0.05$) at the location of activation maximum in the temporal and frontal lobe regions of interest.

Top row: Correlations with left orbitofrontal gyrus connectivity values during auditory naming. Lower row: Correlations with left precentral gyrus connectivity values during picture naming.

Green ellipsoids on sagittal images represent the left temporal lobe seed region.

Note: A = anterior; L = left; P = posterior; R = right.

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Figure 5. Correlations of functional connectivity with disease characteristics in L-TLE patients for auditory naming and picture naming tasks. Functional connectivity is shown superimposed on coronal images masked for the group effects at $p < 0.001$, uncorrected, extent threshold 10 voxels. Connectivity values are significant corrected for multiple comparisons using a small volume correction within a sphere of 8 mm radius (FWE; $p < 0.05$) at the location of activation maxima in the temporal and frontal lobe regions of interest. Positive correlations were observed for age of onset (upper row) and negative correlations were observed for disease duration (lower row). Green ellipsoids represent the left temporal lobe seed region.

Note: A = anterior; L = left; P = posterior; R = right; TLE = temporal lobe epilepsy;

(+) = positive correlation; (-) = negative correlation.