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Distinct right frontal lobe activation in language processing following left hemisphere injury

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Right hemisphere activation during functional imaging studies of language has frequently been reported following left hemisphere injury. Few studies have anatomically characterized the specific right hemisphere structures engaged. We used functional MRI (fMRI) with verbal fluency tasks in 12 right-handed patients with left temporal lobe epilepsy (LTLE) and 12 right-handed healthy controls to localize language-related activity in the right inferior frontal gyrus (RIFG). During the phonemic task, LTLE patients activated a significantly more posterior region of the right anterior insula/frontal operculum than healthy controls ($P = 0.02$). Activation of the left inferior frontal gyrus (LIFG) did not differ significantly between the two groups. This suggests that, following left hemisphere injury, language-related processing in the right hemisphere differs from that with a functionally normal left hemisphere. The localization of activation in the left and right inferior frontal gyri was determined with respect to the anatomical sub-regions pars opercularis (Pop), pars triangularis (Ptr) and pars orbitalis (Por). In the LIFG, both healthy controls (8 out of 12) and LTLE patients (9 out of 12) engaged primarily Pop during phonemic fluency. Activations in the RIFG, however, were located mostly in the anterior insula/frontal operculum in both healthy controls (8 out of 12) and LTLE patients (8 out of 12), albeit in distinct regions. Mapping the locations of peak voxels in relation to previously obtained cytoarchitectonic maps of Broca's area confirmed lack of homology between activation regions in the left and right IFG. Verbal fluency-related activation in the RIFG was not anatomically homologous to LIFG activation in either patients or controls. To test more directly whether RIFG activation shifts in a potentially adaptive manner after left hemisphere injury, fMRI studies were performed in a patient prior to and following anatomical left hemispherectomy for the treatment of Rasmussen's encephalitis. An increase in activation magnitude and posterior shift in location were found in the RIFG after hemispherectomy for both phonemic and semantic tasks. Together, these results suggest that left temporal lobe injury is associated with potentially adaptive changes in right inferior frontal lobe functions in processing related to expressive language.

Keywords: right prefrontal cortex; language; functional MRI; epilepsy

Abbreviations: BOLD = blood oxygen level dependent; fMRI = functional MRI; LI = laterality index; LIFG = left inferior frontal gyrus; LTLE = left temporal lobe epilepsy; MNI = Montreal Neurological Institute; Pop = pars opercularis; Por = pars orbitalis; Ptr = pars triangularis; RIFG = right inferior frontal region; ROI = region of interest

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Introduction

With the advent of neuroimaging tools in the 1980s, increasing evidence has emerged for plasticity in the brain related to language functions (reviewed, Demonet *et al.*, 2005). Right hemisphere activation during language tasks following damage to the normal left hemisphere language network has frequently been reported (*see* below). The ways in which right hemisphere language processes following left hemisphere damage differ from normal right hemisphere language functions, however, have yet to be determined.

The right hemisphere forms an established part of the normal language network and is engaged by a number of functions primarily related to processing of general

concepts/context (Federmeier and Kutas, 1999) or establishing 'global coherence' (St George *et al.*, 1999). This normal right hemisphere language processing is thought to occur in 'homologues' of the left hemisphere language network (Bookheimer, 2002; Knecht *et al.*, 2003). However, detailed functional–anatomical information is limited. Adaptive reorganization of language functions following left hemisphere damage has also often been attributed to homologue regions in the right hemisphere (Weiller *et al.*, 1995; Mimura *et al.*, 1998; Gold and Kertesz, 2000; Staudt *et al.*, 2002; Taylor and Regard, 2003; Thivard *et al.*, 2005), particularly the right inferior frontal gyrus (RIFG) (Thulborn *et al.*, 1999; Warburton *et al.*, 1999; Perani *et al.*, 2003). (Thiel *et al.*, 2001). Studies of language functions in 'split-brain' patients, however, have found differences in the language processing abilities of the left and right hemispheres (Vargha-Khadem *et al.*, 1991; Stark and McGregor, 1997; Menard *et al.*, 2000; Pulsifer *et al.*, 2004) reflected in subtle deficits in aspects of language processing following left—but not right—hemispherectomy. These findings suggest that, despite a potential for the right hemisphere to compensate for left hemisphere damage, there are differences in the ability of the two sides to process aspects of language. In this study we aimed to characterize functional–anatomical differences in the nature of normal compared to potentially adaptively reorganized right hemisphere language-related activation.

Verbal fluency tasks are frequently used in functional imaging for language lateralization and have an established role in the investigation of patients following stroke (Warburton *et al.*, 1999), with tumours (Rutten *et al.*, 1999; Tucha *et al.*, 1999) and suffering from temporal lobe epilepsy (Lehericy *et al.*, 2000; N'Kaoua *et al.*, 2001; Adcock *et al.*, 2003; Woermann *et al.*, 2003). Such tasks are sensitive to relative shifts in activation to the right hemisphere after left-sided injury. Patients with seizures originating in the left temporal lobe, for instance, have been shown to have a greater degree of right hemisphere involvement in language (Rasmussen and Milner, 1977; Risse *et al.*, 1997; Knecht *et al.*, 1998, 2003; Springer *et al.*, 1999; Adcock *et al.*, 2003; Brazdil *et al.*, 2003; Liegeois *et al.*, 2004). This is thought to result from long-term chronic epileptic activity affecting normal language organization within the left hemisphere (Piccirilli *et al.*, 1988; Brazdil *et al.*, 2003; Janszky *et al.*, 2003).

In order to better define the role of the RIFG in functional reorganization of language following injury to the left language network, we investigated verbal fluency performance in patients with left temporal lobe epilepsy (LTLE) and in healthy controls using functional MRI (fMRI). Our aims were to determine first whether patients and controls activate the same anatomical regions of RIFG during verbal fluency performance and second whether regions engaged in the RIFG during the tasks constitute anatomical homologues of those recruited in the left inferior frontal gyrus (LIFG). A continued contribution of the left temporal lobe may confound interpretation of shifts in fMRI activation patterns. We therefore also explored the language localization of language-related activations following surgical removal of the left hemisphere in a young patient with Rasmussen's encephalitis. We aimed to determine not only whether fluency-related activation in this patient would engage the RIFG, but also to relate the functional anatomy of any RIFG activation in this patient to that in LTLE patients and in healthy controls.

Methods

Participants

Twelve preoperative right-handed patients with intractable LTLE (seven males, mean age 33.4, range 15–53) who were being evaluated by the Epilepsy Surgery Service at the Radcliffe Infirmary in Oxford were studied using fMRI. Patient demographics are presented in Table 1. All patients had EEG changes consistent with left temporal lobe onset of seizures. In a patient with an inferior

Table 1 LTLE patient demographics

Patient	Sex	Age	Age at onset (years)	Early complicated prolonged convulsion	Duration (years)	MRI diagnosis	Verbal/ non-verbal IQ	Amytal language laterality	fMRI phonemic fluency LI
1	M	53	30	No	23	Left HS	98/110	Left	0.38
2	M	52	7	No	44	Left HS	84/89	Left	0.69
3	F	31	4	Yes	26	Left HS	86/91	Left	0.61
4	M	27	12	No	15	Left HS	75/82	Left	0.59
5	M	32	18	No	14	Left amygdala DNET	105/103	Left	0.20
6	M	15	0.1	No	15	Left amygdala dysplasia	94/76	Left	0.78
7	F	39	3	Yes	36	Left HS	110/109	Bilateral	0.54
8	M	35	2	Yes	33	HS	66/84	Left	0.72
9	M	38	11	No	27	HS	107/99	Left	0.60
10	F	33	28	No	5	Normal MRI	105/119	Left	0.83
11	F	29	27	No	3	Grade II glioma	105	Left	0.77
12	F	28	11	Yes	17	MTS	103/100	Not done	0.01
Mean		34.3	12.8		23.08		94.8/96.5		0.56

HS = hippocampal sclerosis; MTS = mesial temporal sclerosis; DNET = dysembryoplastic neuroepithelial tumour.

temporal glioma (Patient 11) EEG changes were localized to the tumour region. Twelve healthy, right-handed, neurologically normal controls (five males, mean age 31.17, range 24–37) also took part in the study. Informed consent was obtained from all participants prior to scanning according to the Declaration of Helsinki. The study was approved by the Oxfordshire Research Ethics Committee.

Sodium amytal testing

Eleven of the twelve LTLE patients underwent amytal testing (Wada, 1949), a cerebral angiographic procedure during which the two brain hemispheres are sequentially anaesthetized with sodium amytal so that the contralateral hemisphere can be tested for language and memory functions independently. Amytal testing was performed in accordance with the Oxford protocol, previously described (Adcock *et al.*, 2003). Ten of the eleven LTLE patients were left hemisphere dominant for language on amytal testing, and one had bilateral language functions.

fMRI paradigm

LTLE patients and controls were scanned during standard 5 min verbal fluency tasks (Adcock *et al.*, 2003). During phonemic fluency testing, subjects viewed 10 alternating 30 s blocks of a flashing fixation cross (rest condition) and a letter of the alphabet (active condition). Subjects were asked to silently generate words beginning with the given letter for the duration of its presentation. For the semantic fluency task, a category name (e.g. ANIMALS) was presented for 30 s during which subjects were asked to think of members of that category (e.g. cats, birds, . . .). This was again alternated with 30 s rest blocks. Subjects completed a full run of the experiments out loud using different sets of stimuli prior to scanning at which time the number of words generated during each letter block was recorded for behavioural analyses.

Imaging parameters

Blood oxygen level dependent (BOLD)-fMRI scans were acquired on a 3 tesla Siemens-Varian whole-body MRI scanner using a birdcage radio-frequency head volume coil. Subjects wore earplugs and MR-compatible electrostatic headphones (MRC Institute for Hearing Research, UK) to attenuate scanner noise and facilitate communication with the experimenter. Foam padding was placed around the subject's head to minimize movement. A sagittal localizer scan was obtained to verify subject positioning and plan axial slice acquisition. Single-shot echo-planar T_{2^*}-weighted imaging was acquired continuously throughout the paradigm using the following acquisition parameters: TR = 3 s, TE = 30 ms, voxel dimensions $3 \times 4 \times 5$ mm, 5 mm slice thickness. Three-dimensional turbo flash T_1-weighted axial anatomical scans were also acquired for every subject using the same slice prescription as used for functional imaging data after completion of the fMRI tasks (TR = 12 ms, TE = 5 ms, slice thickness = 3 mm, 1.5 mm).

Image analysis

Data were analysed using the general linear model incorporated in the FMRIB Expert Analysis Tool (FEAT) (www.fmrib.ox.ac.uk/fsl/feat5/) (Worsley and Friston, 1995; Woolrich *et al.*, 2001). The following pre-processing steps from within the FEAT tool were applied: motion correction using MCFLIRT (Jenkinson and Smith, 2001; Jenkinson *et al.*, 2002); spatial smoothing using a Gaussian kernel of full-width half-maximum 5 mm; mean-based intensity normalization of all volumes by a constant factor and high-pass temporal filtering. Functional activation maps were generated using cluster statistics performed on all voxels above a threshold of $z = 2.3$ ($P < 0.01$).

Region of interest analysis

In addition to whole-brain cluster-based analysis for the calculation of language lateralization a region of interest (ROI) analysis was carried out for every subject using manually drawn masks of the left and right IFG on a standard Montreal Neurological Institute (MNI) 152 template. This mask was then used in FEAT to limit voxel-wise statistical analyses to the area within the mask ($P < 0.05$). Spatial smoothing within RIFG and LIFG masks was set to 7 mm. This method is more sensitive to activation within small ROIs as it reduces the stringency of multiple comparison corrections to include only the number of voxels within the specified mask. The resulting localized activation maps for every individual were registered to their T_1 structural image and the canonical standard space brain. The BOLD signal change within the RIFG and LIFG masks was calculated as a measure of activation changes and the coordinates of the voxel with the highest z-score (the 'peak voxel of activation') were recorded for all subjects within the RIFG and LIFG masks.

fMRI laterality index calculations

Left and right hemisphere masks were manually drawn on the standard MNI 152 brain incorporating the temporal, parietal and frontal lobes. A laterality index (LI) was calculated by determining the number of active voxels in the left compared to the right mask at a range of statistical levels [$LI = (L - R)/(L + R)$] as previously described (Adcock *et al.*, 2003). This resulted in values ranging from −1 to +1, with −1 indicating complete right hemisphere language dominance, +1 representing complete left hemisphere dominance and intermediate values reflecting varying degrees of laterality. Nine of the twelve patients were left-lateralized on fMRI, consistent with amytal, one patient was bilateral on fMRI but left hemisphere dominant on amytal and one patient was left-dominant on fMRI but bilateral on amytal. The patient with no available amytal results was classified as bilateral on the basis of their fMRI LI.

Voxel-count based laterality indices, although well suited to calculations across large regions, are also highly dependent on statistical thresholding (e.g. Adcock *et al.*, 2003). Measures of maximum signal change within an ROI have been suggested as a more reliable alternative. It is important to ensure with signal-based measures that laterality calculations are not biased by high peaks of activation within task-related but functionally non-essential regions (such as occipital activation during fluency tasks). As our group activation maps suggested dominant frontal lobe activation, we restricted our signal change laterality calculation to the frontal lobes. Maximum signal change was extracted from homologous left and right frontal lobe masks created on the MNI standard brain template and an LI was calculated using the above formula. All but one patient (Patient 11) had bilateral frontal activation for both tasks using this measure (mean 0.05, SD 0.21 during phonemic fluency; mean 0.13, SD 0.21 during semantic fluency). In the healthy control group, on the other hand, 4 out of 12 had left-dominant frontal activation during phonemic fluency (mean 0.21, SD 0.18), while 2 out of 12 had left-dominant frontal activation during semantic fluency (mean 0.15, SD 0.17). All other controls had bilateral frontal LI values.

No significant difference was observed between LTLE patients and healthy controls in frontal lobe laterality during semantic fluency ($t = -0.162$, $P = 0.873$) although a trend for less left-lateralized activation in LTLE patients relative to controls was observed for phonemic fluency ($t = -1.946$, $P = 0.065$).

Anatomical localization

We next located anatomical regions pars opercularis (Pop), pars triangularis (Ptr) and pars orbitalis (Por) on each subject's structural image in the LIFG and RIFG to determine whether RIFG activation was located in an anatomically homologous region to LIFG activation. This was done according to methods described by Foundas *et al.* (1998, 2001). The anterior horizontal ramus and anterior ascending ramus were located, forming the anterior and posterior borders of Ptr. The area between the anterior ascending ramus and the anterior subcentral sulcus was designated Pop. Both masks were bound superiorly by the inferior frontal sulcus. In addition, the functional location of peak activated voxels was related to Amunts *et al.*'s (1999) cytoarchitectonic maps of BA 44 (Pop) and BA 45 (Ptr) available from http://www.bic.mni.mcgill.ca/cytoarchitectonics/. Due to heavy overlap between the two cytoarchitectonic regions, we used a low amount of thresholding (3 out of 10) to aid classification.

Statistical analysis

Statistical analyses were performed using SPSS (v9.0). Multivariate analyses of variance (MANOVA) were used to detect differences between patient and control peak activation voxels in the ROIs. A repeated-measures ANOVA was used to determine whether peak voxels for semantic fluency differed from those obtained during phonemic fluency. The mean location of the peak voxels of activation in the RIFG, as well as 2 SDs from the mean, was determined in LTLE patients and healthy controls to obtain a distribution of these values in the two groups. Bayesian probability theorem testing was then used to determine the likelihood of the peak voxel of activation obtained in a patient following left hemispherectomy belonging either to the distribution of the healthy control group or that of the LTLE patient group.

Results

Behavioural data

LTLE patients generated significantly fewer words on average than controls in both phonemic ($t = 4.835$, $P < 0.001$, mean words) and semantic fluency ($t = 7.387$, $P < 0.001$) tasks (Table 3).

Whole-brain activation patterns for LTLE patients and healthy controls

Phonemic fluency task

In healthy controls, the phonemic fluency task significantly activated the inferior frontal gyrus, insular cortex, premotor regions and anterior cingulate gyrus on the left. Right hemisphere activation involved the insula, inferior occipital gyrus and anterior cingulate gyrus. Bilateral thalamic, putamen and cerebellar activation was also observed (Fig. 1A and Table 2). Increased activation in controls relative to patients was found in the left thalamus and insular cortex (Fig. 1B).

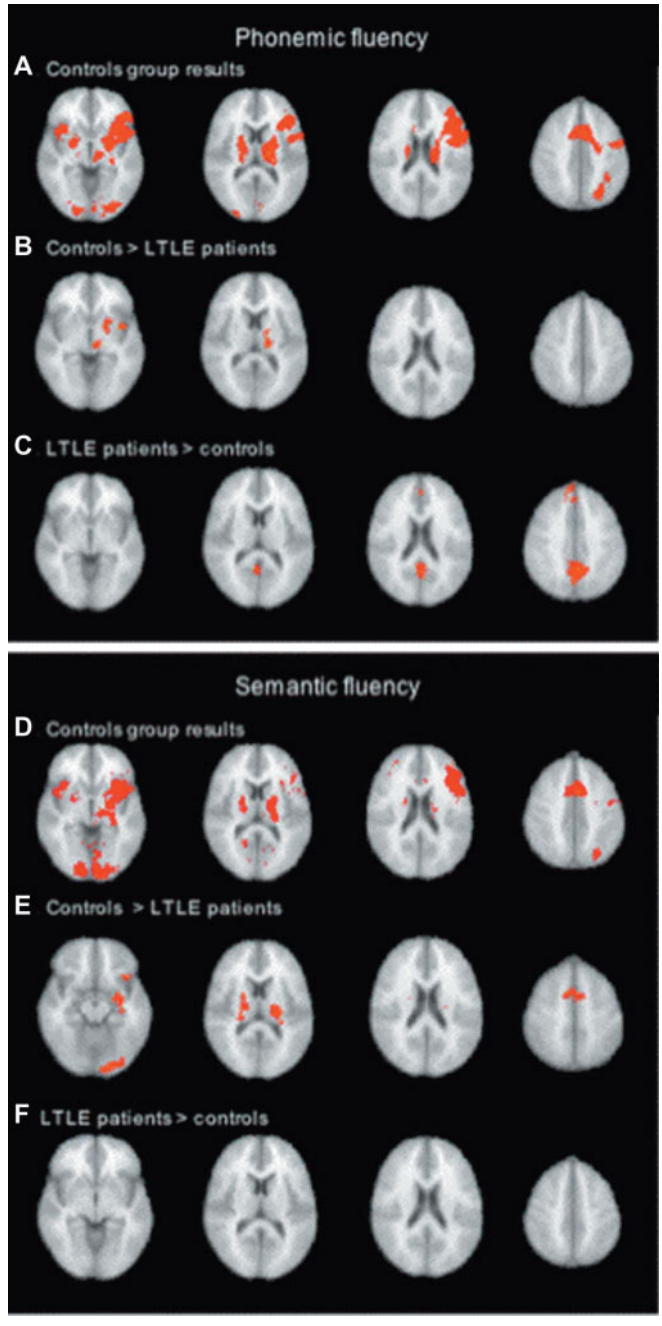

Fig. 1 Group-level mixed-effects activation maps in healthy controls and LTLE patients for phonemic (**A**–**C**) and semantic (**D**–**F**) fluency tasks. Healthy controls engaged a left-lateralized network involving left inferior frontal and insular cortex for phonemic fluency (**A**) and left inferior parietal lobe, bilateral lingual gyrus, putamen and anterior cingulate gyrus during semantic fluency (**D**). Controls had significantly increased activity relative to LTLE patients in the left thalamus and insula (**B**) for the phonemic task and increased activity in left inferior frontal cortex, left hippocampus, left inferior occipital, bilateral thalamus, putamen and anterior cingulate regions for the semantic task (**E**). Increased activity was observed during phonemic fluency in LTLE patients relative to controls in right medial frontal gyrus as well as bilateral posterior cingulate gyri and precuneus (**C**). No regions of increased activity in LTLE patients compared with controls during semantic fluency were found (**F**).

Table 2 Coordinates of peak clusters of activation for phonemic and semantic fluency tasks from group mixed-effects analysis

Phonemic fluency		Semantic fluency	
Coordinates (*x*, *y*, *z*)	Region	Coordinates (*x*, *y*, *z*)	Region
Healthy controls			
−40, 0, 26	L inferior frontal gyrus	20, −94, 2	R lingual gyrus
−40, 4, −12	L insular cortex	−26, −64, 42	L inferior parietal gyrus
−56, −4, 36	L premotor cortex	−28, −10, 4	L putamen
−4, 16, 40	L anterior cingulate	30, −4, 0	R putamen
34, 16, −2	R insular cortex	−10, 6, 42	L anterior cingulate
14, −100, −8	L inferior occipital gyrus	−10, −96, −8	L lingual gyrus
−30, −84, −12	R inferior occipital gyrus	44, 24, −12	R inferior frontal gyrus
8, 16, 36	R anterior cingulate	−44, 20, −12	L inferior frontal gyrus
		16, −16, 2	R thalamus
		−14, −26, 14	L thalamus
		−38, 48, 14	L middle frontal gyrus
		−34, 16, −8	L insula
		34, 16, −2	R insula
		0, 18, 36	Bil anterior cingulate
LTLE patients			
4, −56, 52	R precuneus	−10, −80, 4	L lingual gyrus
−64, −36, 22	L superior temporal gyrus	2, −86, −6	R lingual gyrus
62, −22, 14	R superior temporal gyrus	−34, 18, −6	L insular cortex
24, 30, 44	R middle frontal gyrus	0, 18, 36	Bil anterior cingulate
−8, 58, 32	L precuneus	−44, 36, 8	L inferior frontal gyrus
2, 58, 32	R medial frontal lobe		
12, −32, 4	R parahippocampal gyrus		

Millimetre coordinates of activated brain regions reported in the Montreal Neurological Institute system for verbal fluency tasks performed by LTLE patients and healthy controls.

In LTLE patients, the pattern of significant activation was less left-lateralized (independent-samples: $t = -2.49$, $P = 0.021$) than in controls, with activation in the right middle frontal, bilateral superior temporal gyrus, bilateral precuneus and right parahippocampal gyrus (Table 2). Significantly increased activation in LTLE patients compared to controls was observed in the right medial frontal gyrus as well as bilateral posterior cingulate gyri and precuneus (Fig. 1C).

Semantic fluency performance

During semantic fluency performance, controls activated a similar network to that engaged during phonemic fluency with activation predominantly in bilateral cerebellar, bilateral inferior frontal, insular, thalamic and anterior cingulate regions, with additional recruitment of left middle frontal gyrus, bilateral lingual gyrus and left inferior parietal lobe (Fig. 1D and Table 2). Healthy controls had significantly increased activation in the left inferior frontal, left hippocampal, left inferior occipital, bilateral thalamus, putamen and anterior cingulate regions relative to patients (Fig. 1E).

Data for two of the LTLE patients was affected by motion artefact during the semantic fluency task and had to be rejected. Group activation maps for the remaining 10 LTLE patients revealed primarily left inferior frontal and insular cortex, bilateral cerebellar, anterior cingulate and lingual gyrus activation (Table 2). There were no regions of increased activation in patients relative to controls (Fig. 1F).

We tested the extent to which relative shifts in functional organization occur in the brain may depend on the nature and timing of injury in this group. Differences in the localization of RIFG activation might exist between patients with early and late onset TLE. We compared hemispheric and frontal lobe laterality indices for both fluency tasks in early (<9 years) compared with late onset (>9 years) patients. The average hemispheric LI in the early onset group was 0.67 (SD 0.09), while the frontal lobe LI was −0.07 (SD 0.14) for phonemic fluency. In the late onset group, these LIs were 0.48 (SD 0.3) and 0.14 (SD 0.21), respectively. For semantic fluency, mean hemispheric LI in the early onset group was 0.47 (SD 0.46) and frontal lobe LI was 0.02 (SD 0.12), while in the late onset group these respective LIs were 0.54 (SD 0.25) and 0.2 (SD 0.24). No differences were seen between these groups in hemispheric LI during phonemic fluency ($t = 1.315$, $P = 0.218$) or semantic fluency ($t = 0.293$, $P = 0.208$). A trend was seen for differential frontal lobe laterality between the groups during phonemic ($t = -1.97$, $P = 0.077$) but not semantic fluency ($t = -1.37$, $P = 0.208$). The tumour patient (Patient 11) in particular may differ from the TLE group as a whole. This patient had experienced intractable temporal lobe seizures for only 3 years due to a grade II glioma. However, the tumour itself is likely to have been developing

for several years before the onset of seizures. We examined whether the mean signal change and LI measures in this patient diverged from the mean values of the group as a whole. All values lay within 2 SDs of the group means.

ROI activation analyses

Relative activation within RIFG

ROI analyses were used to better characterize the RIFG activation observed in both patients and controls. No significant difference was found in BOLD signal change in the RIFG between patients and controls either for phonemic fluency (t = 0.680, P = 0.503) or semantic fluency (t = −0.131, P = 0.897) (Table 3).

Localization of peak RIFG activation in LTLE patients and healthy controls

To test whether LTLE patients and healthy controls activated the same region of RIFG, the coordinates of the peak voxels of activation during phonemic fluency performance were compared (Table 4). LTLE patients activated a significantly more posterior (y-axis) region of RIFG than healthy controls (F = 6.304, P = 0.02). There was no significant difference along the x- or z-axis (P = 0.463 and 0.399, respectively). The distribution of peak locations for both groups is illustrated in Fig. 2. There was no significant difference in the location of peak voxels of activation between LTLE patients and healthy controls in the LIFG (P = 0.106, 0.782 and 0.858 for x, y and z directions, respectively).

Within the LTLE patient group, no significant difference was found in the locations of peak RIFG voxels between the phonemic and semantic fluency tasks (P = 0.402). In the healthy control group, however, a significant difference was found between the two tasks (F = 7.277, P = 0.021). *Post hoc* t-tests revealed this difference to result from a shift in the z direction (t = −2.515, P = 0.029) in the semantic compared with the phonemic condition.

The anatomical locations of peak voxel coordinates in the RIFG were also compared between early and late onset patients. No difference was seen in any direction between the two groups during phonemic fluency (x: F = 0.068, P = 0.799; y: F = 0.357, P = 0.563; z: F = 0.047, P = 0.833) or semantic fluency (x: F = 3.571, P = 0.101; y: F = 0.184, P = 0.681; z: F = 0.343, P = 0.576).

Table 3 Mean signal changes within the inferior frontal gyrus using ROI analysis

	Phonemic fluency			Semantic fluency		
	RIFG signal change (%)	LIFG signal change (%)	Fluency score	RIFG signal change (%)	LIFG signal change (%)	Fluency score
LTLE patient						
1	0.30	0.44	5	0.23	0.23	8
2	0.31	0.72	6	−0.21	−0.21	5
3	0.13	0.47	6	0.42	0.42	5
4	−0.02	1.04	7	−0.06	−0.06	7
5	0.06	0.67	6	Not available*	Not available*	9
6	−0.06	0.86	8	None	−0.13	10
7	0.05	0.42	9	Not available*	Not available*	9
8	0.01	0.98	7	−0.17	−0.17	7
9	0.12	0.44	8	0.17	0.17	5
10	−0.12	0.44	7	0.05	0.05	7
11	0.28	0.77	8	0.42	0.42	8
12	−0.13	0.08	11	−0.75	−1.02	7
Mean (SD)	0.08 (0.16)	0.61 (0.28)	7.38 (1.61)	0.01 (0.37)	−0.08 (0.41)	7.42 (1.93)
Healthy control						
1	−0.10	0.92	9	−0.15	0.7	12
2	0.10	0.98	12	0.26	0.93	12
3	0.10	0.47	11	0.27	0.26	12
4	0.14	0.86	9	−0.01	0.56	12
5	0.03	0.77	18	−0.06	0.5	13
6	0.24	0.77	13	−0.33	0.42	11
7	−0.07	0.82	15	0.26	0.93	11
8	−0.37	0.82	10	0.33	0.73	11
9	0.15	0.52	8	−0.76	0.49	13
10	−0.16	0.30	13	0.11	0.48	11
11	0.01	0.30	12	0.12	0.37	14
12	0.29	1.60	12	−0.14	0.29	14
Mean (SD)	0.03 (0.18)	0.76 (0.35)	11.83 (2.79)	−0.01 (0.31)	0.56 (0.22)	12.17 (1.1)

RIFG = right inferior frontal gyrus; LIFG = left inferior frontal gyrus; SD = standard deviation. *Due to motion artefact, data for two patients could not be interpreted and were excluded. Patient 7 did not show any activation in the RIFG during the semantic fluency task. The results for this patient were excluded from signal change analyses.

Table 4 Coordinates of peak voxels of activation in LTLE patients and healthy controls in canonical (standard) space

	Phonemic fluency		Semantic fluency	
	RIFG peak (*x*, *y*, *z*)	LIFG peak (*x*, *y*, *z*)	RIFG peak (*x*, *y*, *z*)	LIFG peak (*x*, *y*, *z*)
Patient				
1	28, 73, 38	71, 68, 48	25, 72, 41	73, 69, 44
2	29, 75, 36	73, 69, 51	19, 73, 46	70, 68, 51
3	28, 75, 35	69, 79, 44	18, 70, 37	69, 75, 47
4	26, 71, 38	70, 67, 45	25 70 38	70, 78, 44
5	22, 69, 37	67, 68, 44	Not available*	Not available*
6	14, 73, 38	70, 67, 41	None	66, 69, 51
7	23, 71, 36	65, 66, 50	Not available*	Not available*
8	24, 65, 49	67, 67, 47	24, 79, 44	66, 65, 49
9	28, 74, 35	69, 67, 48	29, 75, 35	68, 66, 49
10	22, 70, 33	63, 66, 53	27, 71, 36	63, 66, 51
11	24, 70, 38	71, 66, 42	18, 77, 50	63, 65, 50
12	20, 68, 48	74, 79, 45	28, 73, 41	64, 68, 43
Mean (SD)	24, 71.2, 38.4 (4.3, 3, 5)	69.1, 69.1, 46.5 (3.2, 4.7, 6.7)	23.7, 73.3, 40.9 (4.3, 3.1, 5)	67.3, 69.2, 47.6 (3.5, 4.4, 3.2)
Control				
1	15, 70, 45	72, 69, 52	15, 70, 46	71, 70, 52
2	18, 83, 38	68, 68, 52	22, 72, 52	65, 68, 53
3	19, 79, 45	69, 66, 47	28, 77, 38	61, 78, 36
4	27, 73, 36	68, 70, 53	17, 74, 35	64, 74, 45
5	28, 74, 34	68, 88, 49	23, 75, 47	65, 70, 48
6	28, 77, 38	61, 78, 36	29, 76, 41	69, 75, 46
7	17, 74, 34	68, 65, 48	21, 74, 47	67, 66, 49
8	27, 72, 37	64, 67, 50	25, 74, 37	69, 82, 45
9	28, 74, 37	68, 66, 50	28, 72, 41	70, 66, 48
10	28, 72, 36	62, 75, 35	21, 77, 46	67, 67, 51
11	17, 70, 37	65, 69, 51	26, 73, 37	72, 70, 52
12	18, 82, 42	66, 64, 49	22, 78, 36	66, 67, 49
Mean (SD)	22.5, 75, 38.3 (5.5, 4.3, 3.8)	66.6, 70.4, 47.7 (3.1, 6.9, 5.9)	23.1, 74.3, 41.9 (4.4, 2.4, 5.5)	67.2, 71.1, 47.8 (3.2, 5.1, 4.6)

RIFG = right inferior frontal gyrus; LIFG = left inferior frontal gyrus; SD = standard deviation; *Due to motion artefact, data for two patients could not be interpreted and were excluded. Patient 7 did not show any activation in the RIFG during the semantic fluency task. The results for this patient were excluded from voxel location analyses. Coordinates are reported in millimetres using the Montreal Neurological Institute system.

Relative localizations of RIFG and LIFG activations in LTLE patients and healthy controls

We segmented the left and right inferior frontal gyri into anatomical regions Pop, Ptr and Por on each subject's structural image to test whether RIFG activation during verbal fluency tasks was located in a region with precise anatomical homology to the LIFG. During phonemic fluency, the peak voxel of activation in the LIFG was located in Pop in 8 out of 12 healthy controls. In the RIFG, however, the peak voxels were located primarily in the anterior insula/frontal operculum (8 out of 12). The peak voxels of activation in LTLE patients were, likewise, located primarily in Pop in the LIFG (9 out of 12). In the RIFG they were located in the anterior insula/frontal operculum (8 out of 12) but more posteriorly to healthy controls.

During semantic fluency performance, a similar pattern was observed. In the healthy control group, the peak voxels of activation were located in Pop in the LIFG in 6 out of 12, with 2 out of 12 in Ptr. In the RIFG, 5 out of 12 clustered in the anterior insula/frontal operculum and 3 out of 12 were found in Pop. In the LTLE patient group, 4 out of 9 voxels in the LIFG were located medial or lateral to the masks and could not be confidently localized to an anatomical region, 2 out of 9 were located in Pop, 2 out of 9 in Ptr and only 1 out of 9 in anterior insula/frontal operculum. In the RIFG, however, the peak voxels for 5 out of 9 LTLE patients were localized to the anterior insula/frontal operculum. RIFG activation did not, therefore, precisely mirror LIFG anatomically either in patients or controls during either phonemic or semantic fluency performance (Fig. 3).

Amunts *et al.* (1999) have highlighted discrepancies between gross anatomy and underlying cytoarchitecture. It is possible, therefore, that despite surface anatomical differences left and right IFG activations could still be functionally homologous. To test this question, we related peak voxel locations in all subjects in the left and right IFG to previously derived cytoarchitectonic maps of BAs 44 (pars opercularis) and BA 45 (pars triangularis) (Amunts *et al.*, 1999). The results of this comparison differed only slightly from the surface anatomical observations: this analysis also suggested that left and right activations do not localize to the same regions of IFG. Classifying the location

of voxels during phonemic fluency on the basis of the cytoarchitectonic maps, the peak voxels of 9 out of 12 controls activated and 10 out of 12 patients activated pars opercularis (BA 44). In the RIFG, cytoarchitectonic classification suggested that at least half of subjects (7 out of 12 controls and 6 out of 12 patients) engaged a region of insula/frontal operculum outside of classical BA regions engaged in the left hemisphere. Semantic fluency findings were similar; in the LIFG, 9 out of 12 controls and 8 out of 9 patients had peak voxels located in BA 44 on the cytoarchitectonic maps. In the RIFG, again, cytoarchitectonic mapping revealed RIFG peaks to lie in anterior insula/frontal operculum in 5 out of 12 controls and 4 out of 9 patients, with a further 3 out of 9 patients and 6 out of 12 controls engaging BA 45.

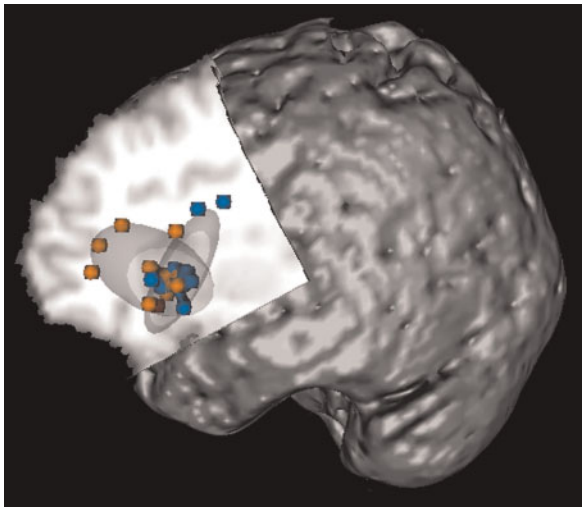

Fig. 2 The peak voxels of activation within the RIFG during phonemic fluency were plotted on a 3D MNI standard space brain for LTLE patients (blue) and healthy controls (yellow). The area covered by two standard deviations from the mean activation for both groups is represented in grey. The distribution of the peak voxels of activation in the RIFG differed significantly between the LTLE patient and control groups ($P = 0.02$) in the anterior–posterior direction (*y*-axis), with patients activating a more posterior region of the anterior insula/frontal operculum to controls.

Evidence for a shift in language-related activation after left hemispherectomy

To test further whether, following left hemisphere injury, the relative magnitude of RIFG activation increases, and the location shifts posteriorly in a potentially adaptive fashion, we performed fMRI studies on a patient with Rasmussen's encephalitis before and after surgical removal of the left hemisphere.

Clinical history

Patient RC was diagnosed with Rasmussen's encephalitis in 1993 at the age of 6, when he presented with intractable epilepsy affecting the right limbs and face in addition to cognitive decline. Within one year, he developed epilepsia partialis continua (EPC) and a progressive right hemiparesis, as a result of which he adopted a left-handed preference. EEG showed continuous high voltage slow waves with continuous spikes originating from the left frontoparietal electrodes. MRI revealed high T_2 signal in the left frontal lobe consistent with a focal encephalitis, and progressive left hemisphere atrophy. The patient tested negatively for anti-GluR3 antibodies. In 2000, following improvement in the patient's

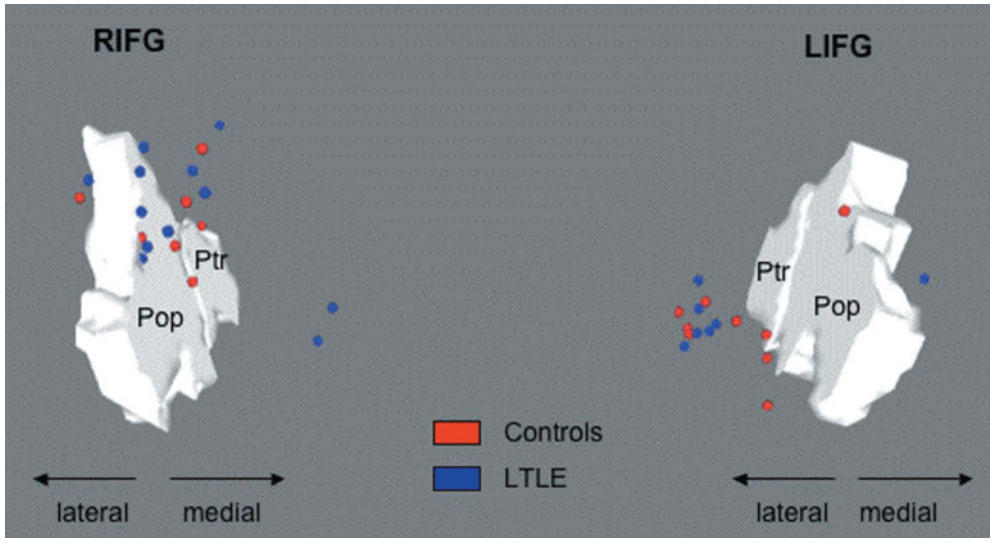

Fig. 3 The locations of peak voxels of activation during phonemic fluency for LTLE patients (blue) and healthy controls (red) with respect to masks of anatomical regions pars opercularis (Pop) and pars triangularis (Ptr) in the left and right inferior frontal gyri. The left and right hemisphere masks are shown from a similar angle to demonstrate the lack of correspondence between the anatomical locations of the peaks in the two hemispheres.

neuropsychological profile after plasmapheresis, fMRI studies were performed to localize language functions using phonemic and semantic fluency tasks. Due to RC's young age at the time of initial fMRI examination, the tasks were shortened to 3 min (6 alternating blocks of rest and active conditions) for the preoperative session. In 2002, at the age of 14, EPC recurred and RC's cognitive abilities declined once more. He subsequently underwent unilateral left carotid amytal testing to determine if the right hemisphere would support language and memory. There was no significant speech arrest, minimal dysphasic errors and no important memory impairment. He subsequently underwent a successful left anatomical hemispherectomy. RC has been seizure-free since the operation. Postoperative fMRI was performed in 2004. As he was 16 at this time he completed the full 5 min adult versions of the tasks.

Whole-brain activation results for the phonemic fluency task

Preoperative fMRI activation maps for RC revealed a bilaterally distributed network of language-related activation involving primarily bilateral inferior frontal and superior temporal regions with phonemic and semantic fluency tasks (Fig. 4). Postoperatively, activation was limited almost exclusively to the RIFG (Fig. 4). Mean word generation scores pre- and postoperatively were similar (on average four words in 30 s).

ROI results

Examination of mean BOLD signal change in the RIFG for both tasks revealed an increase postoperatively of 0.24% in the phonemic task (from preoperative 0.30% to postoperative 0.54%) and 0.21% in the semantic task (from preoperative 0.13% to postoperative 0.34%).

ROI activations related to semantic fluency and picture naming performance

The locations of peak voxels of activation for both language tasks performed by RC on preoperative and postoperative scans were compared. Preoperatively, the peak voxels for letter fluency and category fluency were located in Ptr and a location just superior to Pop, respectively. Postoperatively, the peak for phonemic fluency was located more medially and posteriorly in the frontal operculum/anterior insula. The peak voxel of activation for semantic fluency likewise was shifted posteriorly and medially to a region of frontal operculum/anterior insula.

Localization of RC's activation with respect to LTLE patients and healthy controls

Patient RC's peak voxel for phonemic fluency was plotted with respect to the LTLE patient and healthy control group peaks (Fig. 5). We tested the relative likelihood that this peak voxel of activation in the RIFG for RC clustered with either

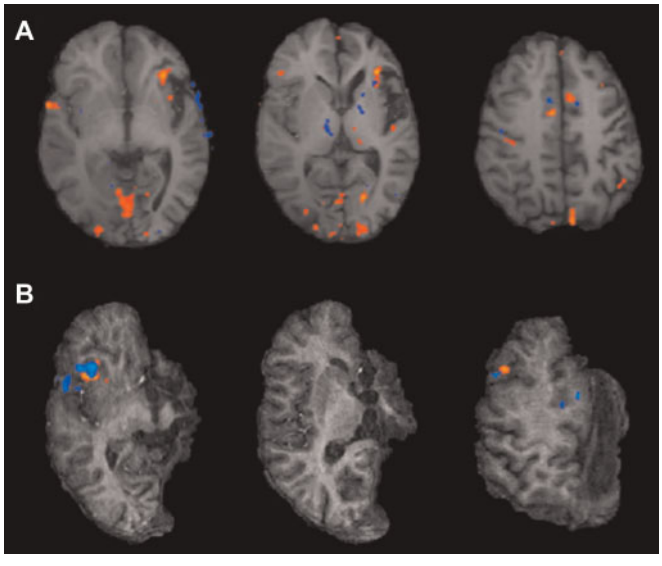

Fig. 4 Whole-brain fMRI activation maps for patient RC during phonemic (red) and semantic (blue) fluency tasks. Despite engagement of a bilateral temporo-frontal network for verbal fluency tasks preoperatively (**A**), postoperative activations for both tasks involved primarily the right inferior frontal lobe (**B**).

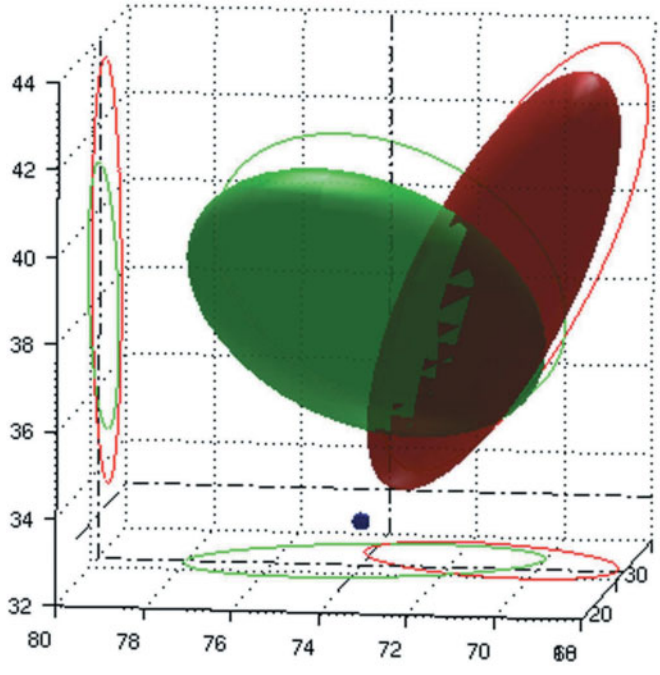

Fig. 5 The two ellipses depict two standard deviations from the mean locations of activation determined on the basis of the peak voxels of activation for healthy controls (green) and LTLE patients (red). The blue sphere located below the LTLE patient ellipse represents the location of the peak voxel of activation observed in Patient RC following hemispherectomy during phonemic fluency performance.

the mean LTLE patient activation or that of the healthy control group using Bayesian probability theorem testing. The likelihood of RC's peak voxel in the RIFG belonging to the patient group (71%) was over 2-fold greater than for belonging to the healthy control group (29%).

Discussion

Using fMRI with verbal fluency tasks, we found differential engagement of the RIFG between LTLE patients and healthy controls. This suggests firstly that verbal fluency following left hemisphere damage does not rely on right hemisphere regions normally engaged by the task but involves recruitment of a more posterior RIFG site. Secondly, activation in the RIFG in LTLE patients involved anatomical regions distinct from those recruited in the LIFG. This shows that RIFG regions involved in language processing following left temporal lobe damage are not simple anatomical homologues of LIFG language regions. RIFG activation in healthy controls, likewise, was not anatomically homologous to LIFG activation. Strengthening the interpretation of our cross-sectional study, longitudinal observations in a patient with Rasmussen's encephalitis showed similar relative changes in localization of activation in the RIFG after left hemispherectomy.

Reorganization of language functions to the RIFG following left temporal lobe damage

Our results suggest that the RIFG plays a central role in the reorganization of language functions following left hemisphere injury. Although imperfect correlations between fMRI and the 'gold standard' functional mapping technique—intraoperative electrocortical stimulation mapping—were recently reported (Roux *et al.*, 2003), the right inferior frontal sulcus was recently identified as forming part of a functionally relevant right hemisphere compensatory network following left temporal lobe resection (Noppeney *et al.*, 2005). These authors also determined that increased reading ability following surgery was predicted by increased activity in this region. Similarly, Thivard *et al.* (2005) found that LTLE patients with atypical language LIs had higher scores on neuropsychological measures (particularly phonemic fluency, semantic fluency and delayed verbal memory) than patients with normal LIs, suggesting that the right hemisphere in these patients makes a positive contribution to language maintenance/recovery following chronic left temporal lobe seizures. Thiel *et al.* (2001) observed language-related activation in right frontolateral regions in over half of their tumour patients, but found no difference in performance measures on the task between patients with dominant and patients with non-dominant hemispheric activations, which they interpreted to suggest that right frontal activation performs a compensatory role. Interestingly, although right frontal activations engaged primarily BAs 44 and 45 in these tumour cases, almost half of the patients with right frontal activations recruited ulterior sites, including the anterior insula. Most recently, an elegant recent study by the same group (Thiel *et al.*, 2005) using both repetitive transcranial magnetic stimulation (rTMS) and PET during verb generation found that left-sided tumour patients with greater right-hemisphere activation on PET were slowed by stimulation delivered over the RIFG but not over the LIFG, while healthy controls and left-lateralized patients were slowed by rTMS over LIFG, but not RIFG. Our results, therefore, are consistent with the emerging notion that the RIFG contributes to language processing following left hemisphere injury (although using distinct cytoarchitectonic regions), and extend Noppeney *et al.*'s (2005) findings by demonstrating that these effects occur preoperatively in the context of chronic mesial temporal lobe seizures.

Functional reorganization in the language network is highly dependent on the nature of the lesion and its chronicity, as well as individual factors (Liegeois *et al.*, 2004). Thiel *et al.* (2001) demonstrated right frontolateral activation during a verb generation task in more than half of their sample of tumour patients. However, this pattern was seen only in patients with extensive tumours affecting the left prefrontal or superior temporal regions suggesting that compensatory functional shifts of language to the right hemisphere might occur only in chronic disease states in which restoration of the normal left hemisphere language network is not possible. Despite absence of evidence in our study, language-related activation changes seen in the adult brain also may differ from those arising from injury early in development (Staudt *et al.*, 2001; Krageloh-Mann, 2004; Liegeois *et al.*, 2004).

'Reorganized' functions do not co-localize with 'normal' right hemisphere language processes

The relationship between reorganized right hemisphere language functions and normal right hemisphere processes, however, remains unclear. In recent years a number of studies have focused on uncovering the nature of right hemisphere language processing following left hemisphere injury. Angrilli *et al.* (2003) found differences not only in the functional anatomy but also the temporal dynamics of impaired language processing in post-stroke aphasics using electroencephalographic recordings during rhyming and semantic tasks. Furthermore, there is typically a decline in right hemisphere mediated visuo-spatial functions following relative shifts in language from the left to the right hemisphere (Helmstaedter *et al.*, 1994; Loring *et al.*, 1999). As the localization of the mean RIFG activation in our LTLE patients was distinct from that in healthy controls our results are consistent with a functional difference in normal compared with the potentially adaptive right hemisphere language functions.

Lack of anatomical homology between left and right inferior frontal activations

Our second observation that RIFG activation did not appear to anatomically, or cytoarchitectonically, mirror that seen in the LIFG in either patients or controls challenges the notion that right hemisphere language processing engages homologues of the dominant left hemisphere both normally (Bookheimer, 2002; Knecht *et al.*, 2003) and following left hemisphere injury (Thulborn *et al.*, 1999; Warburton *et al.*, 1999; Perani *et al.*, 2003). However, the exact functional anatomy underlying normal right hemisphere language processing has not been described in detail. Differences have been found in specialized language processing performed by the two hemispheres (Bottini *et al.*, 1994; Richards and Chiarello, 1997; Federmeier and Kutas, 1999; Taylor and Regard, 2003; Deacon *et al.*, 2004). For example, the RIFG is thought to be primarily concerned with general semantic processes such as constructing context (reviewed, Bookheimer, 2002; Taylor and Regard, 2003). The LIFG, although also important for semantic tasks, is additionally concerned with individual word processing not found in the RIFG (Fiebach and Friederici, 2004). A functional dissociation between phonological and semantic processes has also been demonstrated within the LIFG (Devlin *et al.*, 2003), for which there is no evidence in the RIFG. Differences in the nature of LIFG and RIFG language processes may account for the lack of homologous activations in our study.

Methodological considerations

Potential limitations of our study concern the resolution of structural images, repeatability of peak voxel measures and registration of peak voxels to a standard template. Although anatomical boundaries may be easily defined on 3 and 1.5 mm T_1 structural scans, increased variance is introduced using such slice prescriptions compared with acquiring 1 mm isotropic scans. As we acquired slices in the axial plane this may have affected our ability to identify significant peak voxel shifts in the *z*, or inferior–superior, direction. However, the *y* plane (anterior–posterior), in which we observed significant differences in fMRI activation between our patient and healthy control groups, should not have been affected substantially.

Interpretation of our longitudinal results in patient RC depends on the repeatability of the peak voxel activations. There is no fully generalizable information concerning the variation in localization of peak voxels in fMRI data across scanning sessions. However, the inter-session variability in a single set of fMRI data was recently shown to be comparable to within-session variability (Smith *et al.*, 2005). Examining directly the question of repeatability of voxel localization, repeat scanning of 10 healthy controls in this study revealed no significant difference in the location of the peak voxels of activation between the first and second scans during phonemic fluency (repeated-measures ANOVA: $F = 0.136$ $P = 0.721$).

A potential third limitation concerns registration of individual structural and EPI data to a standard template. Chau and McIntosh (2005) recently highlighted limitations associated with such spatial transformations. As these authors point out, an identical point in standard space may correspond to a different anatomical region on individual structural images. This is most obvious using the conventional linear (as opposed to non-linear) registration methods. It is not, however, possible to directly test differences in localization between groups of subjects without transforming the individual subject points into the same space. By performing all our analyses and reporting coordinates in MNI space we have avoided additional variance being introduced by secondary registrations to Talairach space. In addition, we compared the locations of peak voxels for phonemic fluency in the LIFG in our healthy control subjects on individual structural images and following transformation to the normalized brain. Good correspondence was observed between the anatomical locations of the peaks in the two spaces. None of the peak voxels was located in a different anatomical region of LIFG on the standard compared to the individual structural brain in any subject.

Registration of peak voxels to the standard MNI template was particularly difficult in patient RC following hemispherectomy. For this reason, the anatomical locations of peak voxels were described on his T_1 structural image in native rather than in standard space.

Additional registration issues may result from structural differences between the LTLE patient and healthy control groups. Recent voxel-based morphometry (VBM) studies have identified extra-temporal atrophy in patients with unilateral TLE (Keller *et al.*, 2002*a*, *b*, 2004; Bernasconi *et al.*, 2004). Cortical atrophy in the LTLE patients could result in biased registration of functional data between the patient and control groups. Although such registration issues may result in changes in localization of activation in the left IFG as well as in the right IFG, an independent-samples *t*-test failed to reveal a difference between the average scaling applied in patients (mean = 1.11) compared to controls (mean = 1.08) ($t = -0.957$, $P = 0.349$). This suggests that there are no gross registration differences between the two groups. As a result, any structural differences are unlikely to have driven the functional–anatomical difference we observed in RIFG language-related activation.

Conclusions

The extent to which our findings extend to language processing following left hemisphere injury more generally will need to be investigated further. It is likely that activation within key regions will depend on the specific left hemisphere regions affected by pathology, the nature of pathology, the extent of language impairment/recovery and the specific language functions tested. The similarity between the results obtained in preoperative LTLE patients and in our hemispherectomy patient for both fluency tasks suggests, however, that these

findings may have more widespread implications. These results, for example, suggest the possibility of predicting language outcome following left temporal lobectomy for epilepsy on the basis of measuring not only the extent of preoperative right hemisphere activation, but also its location.

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