Language reorganization in children with early-onset lesions of the left hemisphere: an fMRI study

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Summary
It is widely assumed that following extensive damage to the left hemisphere sustained in early childhood, language functions are likely to reorganize and develop in the right hemisphere, especially if the lesion affects the classical Broca’s or Wernicke’s language areas. In the present study, functional MRI (fMRI) was used to examine language lateralization in 10 children and adolescents with intractable epilepsy who sustained an early lesion in the left hemisphere. Lesions were adjacent to or within anterior language cortex in five patients, while they were remote from both Broca’s and Wernicke’s areas in the remainder. A lateralization index was calculated on the basis of the number of voxels activated in the left and right inferior frontal gyri when performing a covert verb generation task. Only two patients were right-handed, suggesting a high incidence of functional reorganization for motor control in the remaining patients. Five out of 10 showed bilateral or right language lateralization, but lateralization could not be inferred from the proximity of lesions to classical language areas on an individual basis. Lesions in or near Broca’s area were not associated with inter-hemispheric language reorganization in four out of five cases, but with perilesional activation within the damaged left hemisphere. Paradoxically, lesions remote from the classical language areas were associated with non-left language lateralization in four out of five cases. Finally, handedness, age at onset of chronic seizures, and site of EEG abnormality also showed no obvious association with language lateralization. In conclusion, it is difficult to infer intra- versus inter-hemispheric language reorganization on the basis of clinical observations in the presence of early pathology to the left hemisphere.

Keywords: cerebral dominance; language; early pathology

Abbreviations: fMRI = functional MRI; ICA = intracarotid amobarbital; LI = lateralization index


Introduction
It is now well established that extensive damage to the left cerebral hemisphere in adults can result in profound and chronic aphasia. In contrast, comparable lesions of the left hemisphere suffered during childhood rarely result in pronounced speech and language disorders (Woods and Teuber, 1978; Woods and Carey, 1979; Vargha-Khadem et al., 1985, 2000; Thal et al., 1991). The gross sparing of speech and language functions after early lesions of the left hemisphere has been attributed to the impressive plasticity and reorganizational capacity of the immature brain, which may enable speech and language functions to develop in the right hemisphere.

In cases of left hemisphere injury, it is widely assumed (Rasmussen and Milner, 1977; Devinsky et al., 1993; Isaacs et al., 1996; Lazar et al., 2000) that such inter-hemispheric language reorganization occurs when lesions either encroach on language areas (i.e. Broca’s and Wernicke’s) or are very extensive, while lesions remote from language cortex do not result in inter-hemispheric language reorganization (Devinsky et al., 1993; Isaacs et al., 1996; Lazar et al., 2000). However, recent findings have called this assumption into question. Using cortical stimulation to map eloquent cortex, Duchowny et al. (1996) have shown that developmental lesions accompanied by
patients with early-onset seizures originating in the left hemisphere can be associated with language functions within that hemisphere. Similarly, developmental tumours near language areas do not necessarily lead to speech and language reorganization to the right hemisphere, as assessed by the intracarotid amobarbital (ICA) procedure (DeVos et al., 1995). The effect of lesion site on speech and language lateralization following early pathology of the left hemisphere therefore remains unclear. Unfortunately, the ICA procedure does not address the issue of intra-hemispheric reorganization, and electrocortical stimulation does not provide information about the functions subserved by the non-stimulated hemisphere. Functional MRI (fMRI) is a useful non-invasive tool to address these issues.

Neuroimaging studies of both adults (Muller et al., 1999b) and children (Duncan et al., 1997; Muller et al., 1998a, b, 1999a) have indicated that right hemisphere language lateralization is more likely to be observed after early (i.e. sustained before age 5 years) rather than late (i.e. after age 5 years) left hemisphere injury. This finding is consistent with results of studies using ICA (Rasmussen and Milner, 1977; Satz et al., 1988; Helmstaedter et al., 1997) and the dichotic listening task (Isaacs et al., 1996) to assess language lateralization. In the latter study, right hemisphere language representation deduced from left-ear advantage was associated with pronounced motor deficits in the right hand, suggesting that right hemisphere language representation was more likely to result after extensive lesions of the left hemisphere. Unfortunately, in patients with early injury, the effect of the proximity of the lesion to language areas on reorganization of this function has never been examined using fMRI. Clarifying this issue could improve outcome prognosis in children who are candidates for the surgical resection of the lesion.

In the present study, an fMRI task was used to determine lateralization of activation within the anterior language area (Broca’s area) in 10 children and adolescents who suffered an early lesion of the left hemisphere. In half the patients, lesions were adjacent to or within anterior language cortex, while in the other half lesions were remote from both Broca’s and Wernicke’s areas. fMRI results obtained from the patient group were compared with those obtained from a group of children (Duncan et al., 1988; Helmstaedter et al., 1997) and the dichotic listening task (Isaacs et al., 1996) to assess language lateralization. In the latter study, right hemisphere language representation deduced from left-ear advantage was associated with pronounced motor deficits in the right hand, suggesting that right hemisphere language representation was more likely to result after extensive lesions of the left hemisphere. Unfortunately, in patients with early injury, the effect of the proximity of the lesion to language areas on reorganization of this function has never been examined using fMRI. Clarifying this issue could improve outcome prognosis in children who are candidates for the surgical resection of the lesion.

The study was approved by the local Ethics Research Committee. Informed consent was obtained from the parents of all participants as outlined by the Great Ormond Street Hospital for Children/Institute of Child Health Research Ethics Committee.

Material and methods
Control group
This group consisted of 10 participants, five children aged 8–12.4 years (mean age 10.1 years), and five adolescents aged between 14:4 and 16:10 years (mean age 15.8 years). Informed consent was obtained from the parents of all participants as outlined by the Great Ormond Street Hospital for Children/Institute of Child Health Research Ethics Committee.

Patients
Ten patients (Table 1), aged 7–18 years, with early pathology of the left hemisphere on MRI (Fig. 1) participated in this study. Their right hemispheres showed no structural abnormality on MRI. Verbal IQs ranged from 65 (exceptionally low range) to 126 (high range), but no patient presented with clinical dysphasic symptoms at the time of scanning. In five patients, the lesions were remote from classical language areas, located in the hippocampal, parahippocampal, or temporal pole regions. In the remaining five patients, the lesions were adjacent to or within anterior language cortex, located within or close to Broca’s area in the frontal or centro-frontal regions in four cases, and in the anterior superior temporal gyrus (Devinsky et al., 1993) in one case. Two patients presented with a right-sided motor weakness.

All patients suffered from drug-resistant seizures arising from the left hemisphere and were investigated as potential candidates for epilepsy surgery. During clinical investigation, the patients underwent standard video-EEG telemetry and structural MRI. An extensive neuropsychological assessment was also performed to assess language and memory functions, as well as handedness (Crovitz and Zener, 1962). As part of the handedness inventory, participants were asked which hand they favoured to perform 18 everyday activities, some of which used both hands (e.g. hammering a nail, opening a tin). Rankings between 18 and 34 represent right-hand preference, those between 35 and 54 indicate mixed handedness, whilst those between 55 and 90 suggest left-hand preference.

Evaluation of EEG abnormalities
Children underwent EEG video-telemetry as part of the pre-surgical investigation, using standard techniques of electrode placement and recording. Interictal and ictal EEG changes including abnormal rhythmic activity, spikes and sharp waves were evaluated by a paediatric clinical neurophysiologist, who was blind to the results of the fMRI and MRI findings. EEG abnormalities were categorized as unilateral or bilateral, and, if the latter, any lateralized predominance was noted. Ictal and interictal changes were assessed separately. Localization was assessed using normal criteria for clinical interpretation. Changes seen at F7 or F9 were interpreted as temporal unless maximal involvement was seen at F3 or Fp1, when they were interpreted as being of frontal origin.

fMRI data acquisition
MRI was performed on a 1.5 T Siemens Vision System (Erlangen, Germany). Anatomical images were obtained from multi-slice T1-weighted FLASH (fast low angle shot) images [TR (repetition time) = 31 ms, TE (echo time) = 11 ms, flip angle 40°, matrix size 256 × 256 × 64, voxel size 0.75 × 0.75 × 3 mm]. Functional MRI data were acquired using a whole brain 3D EPI (echo-planar imaging) sequence (TR = 87 ms, TE = 40 ms, flip angle = 30°, matrix 64 × 64 × 64, 3 mm isotropic voxels). The total acquisition time for each 3D data set was 5.6 s. For each participant, two consecutive runs of 120 3D data sets were collected. Each run consisted of 10 task/rest cycles with six data sets in each cycle. The presentation of the first stimulus of each cycle was triggered automatically by the first image in that cycle.

Since good correlations have been reported (Hertz-Pannier et al., 1997; Benson et al., 1999; Lehericy et al., 2000) between lateralization of fMRI activation during covert generation tasks
and language lateralization determined with invasive techniques such as ICA, a verb generation task was used here. During the task period, participants were asked to generate covertly single verbs to concrete nouns (~1.5 syllables in length) presented via earphones every 2.8 s (~12 nouns per task period). The word lists were generated from a PC using in-house software. Before entering the scanner, all participants were asked to generate verbs to nouns overtly to ensure that they could perform the task successfully. The inter-stimulus interval was increased to 4 s for those patients who did not manage to produce a response within 3 s. During the rest period, bursts of amplitude-modulated noise were presented at the same rate as the nouns (every 2.8 or 4 s). Scanning time was 12 min per run, which made the total experiment (anatomical and functional images) ~40 min long.

**fMRI data analysis**

The images were analysed using the Statistical Parametric Mapping software (SPM99, Wellcome Department of Imaging Neuroscience, London, UK. http://www.fil.ion.ucl.ac.uk/spm). Images were realigned, co-registered and then smoothed to three times the original voxel size. The statistical analysis involved the comparison of task versus rest states in a block design.

**Lateralization index**

For each participant, a lateralization index (LI) was computed. First, the highest activation voxel in the inferior frontal gyrus was identified [note: LI was calculated at \( P < 0.05 \) for patient 10 as no voxel was significantly activated at \( P < 0.01 \)]. The number of significantly activated voxels within a 20 mm radius spherical volume of interest centred on this voxel was then computed. A homologous voxel relative to the midline was chosen in the contralateral hemisphere, and an equivalent spherical volume centred on this voxel was again used to calculate the number of significantly activated voxels. The LI was obtained by computing \( \frac{n_R - n_L}{n_R + n_L} \), where \( n_L \) and \( n_R \) are the number of activated voxels in the left and in the right hemisphere, respectively. Participants with a negative LI were considered left lateralized for language, while those with a positive LI were considered right lateralized. Participants whose LI ranged from -0.1 to 0.1 were considered to have bilateral language representation. This choice of criteria for lateralization (which particularly influences the classification of patients 7, 8 and 9) was made on the basis of lateralization results obtained from both invasive investigations (ICA and electrocortical stimulation) and a non-invasive method which involves the direct statistical comparison of left and right hemisphere fMRI activation (Statistical Lateralization Maps). Lateralization maps could not be used in the present study because normalization of MRIs to a template, which is required for analysis, would have been considerably affected by the presence of large lesions and vascular abnormalities in some patients described here (for details on the method see Liégeois et al., 2002).

**Results**

**fMRI lateralization index**

In the control group, the fMRI pattern of activation (Table 2) was very similar to that found in other studies using covert generation paradigms (e.g. Holland et al., 2001) Activation
involved the left inferior frontal gyrus (i.e. Broca’s area), as well as the posterior middle temporal region (Wernicke’s area). LIs were calculated on the basis of fMRI activation in the inferior frontal gyrus, as this locus has been shown to be most reliable for assessment of language lateralization (Lehericy et al., 2000).

The LIs of all participants are presented in Fig. 2. All control children and adolescents showed left hemisphere lateralization. Five patients also showed left hemisphere lateralization, while five others showed non-left lateralization, either bilateral (one case) or right dominant (four cases). Overall, the LI of patients (mean = 0.002, SD = 0.74) and that of control participants (mean = ±0.71, SD = 0.23) differed significantly (Mann-Whitney test, P = 0.026), control participants being more strongly left lateralized.

**fMRI language lateralization and lesion location**

Out of the five cases whose lesions were located near or in Broca’s area, four showed left hemisphere lateralization for language (Fig. 3A). In these four cases, fMRI activation was detected at the edge of the lesion, either more anteriorly (patients 6 and 3) or more dorsally (patients 7 and 9).

Patient 7 is remarkable, as she is the only patient with a congenital lesion restricted to Broca’s area. fMRI activation was detected above the lesion in the middle frontal gyrus. This atypical language locus was confirmed with electrocortical stimulation of this region, which induced speech disturbance. Moreover, this patient did not present any speech or language disorder following focal resection of the lesion.

Patient 10, who had polymicrogyria surrounding the left sylvian fissure, showed activation not only in the right inferior frontal gyrus, but also within the polymicrogyric cortex in the left hemisphere (not shown), slightly more posteriorly to Broca’s area. The LI was calculated on the basis of activation in the right inferior frontal region and, since no activation was detected in the left hemisphere homotopic region, it was concluded that there was right lateralization. It may be more accurate to classify this patient as having bilateral language representation, but this is impossible to ascertain as invasive monitoring and surgery were not performed. What is clear in this case, however, is that language activation was not left lateralized. This patient also illustrates the limits of the LI method when bilateral activation is not symmetrical (Liégeois et al., 2002).

It may have been predicted that an early extensive lesion affecting the perisylvian region would be associated with right hemisphere language lateralization. The results from patients 3 and 6 revealed that, in those two cases, frontal activation was detected anterior to the lesion, with no detectable activation in the homologous region of the right hemisphere.

Out of the five patients with lesions remote from the classical language areas, four did not show left hemisphere language lateralization (three right, one bilateral, see Fig. 3B). In three patients, anterior fMRI activation was detected in the inferior frontal gyrus, i.e. the Broca’s area homologue in the right hemisphere. The only exception was patient 8 who showed bilateral activation in the frontal operculum.

**fMRI language lateralization and clinical observations (Table 1)**

Only two patients were right-handed, while four were left-handed and four showed mixed handedness. Non-right handedness was equally often associated with right/bilateral...
(four patients) as with left (four patients) fMRI language lateralization (Fisher’s exact test, $P = 0.78$).

EEG abnormality in the left frontal lobe was equally often associated with left (four patients) as with non-left (four patients) fMRI language lateralization (Fisher’s exact test, $P = 0.10$). Similarly, the presence of EEG abnormality in the right hemisphere was associated with left hemisphere language lateralization in four cases and with non-left lateralization in three cases (Fisher’s exact test, $P = 0.50$).

Finally, early onset of chronic epilepsy (i.e. before age 5 years) emanating from the left hemisphere was equally often associated with left (three patients) as with non-left (three patients) language lateralization (Fisher’s exact test, $P = 0.74$). The same finding applied if the ages at first seizure were taken into account.

### Post-surgical outcome

Seven patients underwent surgery, including one who had resective surgery following invasive subdural electrode monitoring (patient 7) and one with functional stimulation during awake craniotomy (patient 6). Patients 2, 5 and 8 underwent a temporal lobectomy. Lesionectomies were performed on patients 9, 4 and 7, and an anterior lesion resection was performed on patient 6. None of these patients presented with any reported postoperative speech or language disorders.

Formal postoperative neuropsychology assessment is available in two of the seven patients. One year after surgery, verbal intelligence had remained stable in patient 5 and had increased by 16 points in patient 7. Formal postoperative neuropsychological assessment is yet to be performed in the five remaining patients, but no deterioration in language abilities has been observed clinically.

### Discussion

The present study provides further evidence that fMRI is feasible in young epileptic patients, even in the presence of restricted intellectual abilities (Hertz-Pannier et al., 1997; Booth et al., 1999). In this group of children and teenagers with epilepsy associated with cortical lesions, while the majority (eight out of 10) were of left or mixed handedness, atypical language lateralization was found in only half. Moreover, contrary to the findings reported by Rasmussen and Milner (1977), lesions encroaching on one or both classical language areas rarely resulted in the reorganization of speech and language functions to the right hemisphere. In contrast, remote lesions were often associated with atypical language lateralization. Most patients showed lateralization patterns that could not have been inferred from clinical observations.

### Language lateralization in children with early lesions in the left hemisphere

Whilst all control participants showed a left hemisphere lateralization for language, half of the patient group showed...
right or bilateral language representation. Although our sample is small, this high proportion of non-left lateralization (50%) is consistent with findings from previous studies using ICA (55% in Rasmussen and Milner, 1977), dichotic listening (60% in Isaacs et al., 1996) and fMRI (Springer et al., 1999) to assess language lateralization. Furthermore, the cases of right hemisphere representation showed fMRI activation in the region homologous to Broca’s area in the right hemisphere, consistent with other reports (Booth et al., 1999; Staudt et al., 2002). Despite our small sample, a 50% proportion of non-left language lateralization is particularly high compared with the 4% found in right-handed adults, and the 27% (10% in Pujol et al., 1999) found in the strongly left-handed adult population (Knecht et al., 2000). These results corroborate suggestions that the developing brain has far greater reorganizational capacity than the adult brain with respect to language (Woods and Teuber, 1978; Woods and Carey, 1979; Vargha-Khadem et al., 1985, 2000; Thal et al., 1991), since the majority of adults remain left lateralized for language following left hemisphere injury (Benson et al., 1999).

**Language lateralization and lesion location**

Based on earlier studies of large groups of patients (Rasmussen and Milner, 1977; Isaacs et al., 1996), it was hypothesized that early lesions near or within Broca’s area would be associated with language reorganization to the right hemisphere. In our group, the data from only one patient (case 10) out of five with lesions encroaching on, or very close to, language cortex agreed with this prediction. In the remaining four patients, fMRI activation was located very close to abnormal cortex, and no significant activation in the right inferior frontal region was detected in patients 3, 6 and 7. These results are consistent with findings from invasive techniques indicating that developmental lesions in language areas do not always lead to inter-hemispheric language reorganization (Duchowny et al., 1996), and that language functions can develop within the left hemisphere around childhood onset tumours (DeVos et al., 1995). Similarly, in our sample, when lesions were located near or encroaching on Broca’s area, there seemed to be a strong predisposition for intra-hemispheric language reorganization. Perilesional reorganization has also been observed in adults who suffered a

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**Fig. 3** Horizontal and sagittal views of fMRI maximal activation in the frontal cortex (crosshair) during covert verb generation, displayed at a threshold of $P < 0.01$, uncorrected for multiple comparisons, except for patient 7 where $P < 0.05$. (A) Left lateralized language representation; (B) right lateralized or bilateral language representation. Activation maps are superimposed on each patient’s T1-weighted image. The patient number is indicated in the left-hand corner in each case. L = left hemisphere; R = right hemisphere. Slice position is indicated in the $z$ dorsal–ventral axis (negative, ventral). Sagittal images show the left hemisphere in A and the right hemisphere in B.
left inferior frontal stroke and showed good language outcome (Karbe et al., 1995; Rosen et al., 2000).

Another unexpected finding was that the majority of our patients with lesions in the hippocampal, parahippocampal or temporal pole regions showed right lateralized or bilateral language representation. These lesions were much less extensive than those previously described (Rasmussen and Milner, 1977), and were remote from Wernicke’s area. Right hemisphere language lateralization has been observed previously in adults who suffered from early temporal epilepsy, using PET (Muller et al., 1999b) and ICA (Rausch and Walsh, 1984), and in a small proportion of children and adults with temporal lobe epilepsy using fMRI (Springer et al., 1999; Gaillard et al., 2002). Atypical speech representation assessed by ICA has also been reported in 20 out of 64 adults with medial temporal lobe epilepsy due to left hippocampal sclerosis (Janszky et al., 2003). The reason why early abnormality in temporal regions would cause language to be predominantly subserved by the right hemisphere remains unclear. It is possible that the spreading of epileptic discharges to language regions located in the left temporal cortex, such as the inferior temporal cortex (Luders et al., 1991) and the anterior temporal pole (Devinsky et al., 1993), may cause the frontal language network to represent this function within the right hemisphere. The overall results from the present study indicate that lateralization of language functions cannot be inferred from the proximity of lesions to classical language areas in children who suffer from developmental or early brain pathology.

Language lateralization and clinical observations

It was expected that patients with right-hand preference were likely to show left hemisphere language representation, whereas those with mixed or left-hand preference were likely to show right or bilateral language representation. Results from the literature (Rasmussen and Milner, 1977; Hinz et al., 1994; DeVos et al., 1995; Janszky et al., 2003) and those from the present study suggest that although right-handedness is often associated with left hemisphere lateralization, non-right-handedness is not a good predictor of inter-hemispheric reorganization of language functions. Indeed, in our group, only two patients were right-handed, indicating a high proportion of functional reorganization for hand motor control. One example of the lack of a systematic relationship between handedness and language lateralization is patient 3, who suffered from right congenital motor weakness and whose lesion involved the sensorimotor cortex, but showed fMRI activation in the left inferior frontal gyrus. This finding is in disagreement with the claim of a causal link between pathological left-handedness and right lateralization for language (Devinsky et al., 1993). It similarly has been shown that a small proportion of patients who suffer from early-onset left-sided temporal epilepsy can develop right language lateralization and remain right-handed (Rausch and Walsh, 1984). It is therefore important to distinguish between results obtained at the group level (i.e. Woods et al., 1988; Springer et al., 1999) and their predictive value at an individual level. Because of evidence of a certain degree of dissociation between hand motor control and language lateralization, it is not possible to predict language reorganization based on a shift in handedness, especially in patients with either neurodevelopmental or early pathology of the left hemisphere.

Our results also suggest that the age at onset of chronic epilepsy does not predict language lateralization, consistent with conclusions drawn from a recent study on patients with focal medial temporal lobe epilepsy of early onset (Janszky et al., 2003). Additionally, although it was hypothesized that EEG abnormality in the left frontal lobe or in the right hemisphere would prevent language organization in those regions, no such evidence was observed. This may not be surprising if one considers that one of our patients, case 10, even showed fMRI activation within polymicrogyric cortex, consistent with the idea that abnormal cortex can be functionally active (Marusic et al., 2002). It seems possible, therefore, for cognitive functions to develop in structurally abnormal regions, particularly in the presence of developmental pathology.

In conclusion, results from the present study confirmed that non-left language lateralization is more common in patients who suffer from early or developmental left hemisphere lesions than in control children. Nevertheless, in these same patients, the factors that have been thought to impact on language reorganization, such as handedness and lesion proximity to language regions, do not seem to have a predictive value at an individual level.

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