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CLINICAL ARTICLE

Atypical speech activations: PET results of 92 patients with left-hemispheric epilepsy

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Abstract
Purpose Language lateralization and factors that may influence language lateralization were investigated using positron emission tomography.
Methods Ninety-two right-handed patients who had left-sided lesions (tumors, focal cortical dysplasia, and vascular lesions) and 19 right-handed normal subjects were included and synonym generation task was used for evaluation of language lateralization.
Results As expected, the majority of individuals in both groups showed left hemisphere dominance. Lesions in the vicinity of language-related areas did not alter patterns of activation responses. However, atypical inferior frontal gyrus (IFG) activations (33.6%) were more commonly observed in the patient group than in the control group (21%). There were no clear right-sided IFG activations in the control group but almost 28% of the patients showed clear right-sided IFG activations. Atypical language lateralization was strongly correlated with duration of seizure (p=0.01) and early age at onset (p=0.03).
Conclusions Our data provide evidence for inter-hemispheric plasticity related to language function as a response to lesions involving the left hemisphere. A better understanding of the dynamic organization of the brain and about the interaction between the lesion and reactional plasticity will lead to changes in surgical strategy, which will enable us to perform a total removal of the lesion involving eloquent brain areas with improved functional outcome.

Keywords Brain · Cerebral dominance · Language · Lateralization · PET · Plasticity

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Introduction

Although it is an old concept, the notion of brain plasticity has gained popularity during the last two decades, especially with the advent of neuroimaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). These non-invasive neuroimaging techniques, which enable visualization prior to surgery of crucial brain areas important for language and sensorimotor function, and which can be integrated with neuronavigation systems, have largely eliminated the need for invasive techniques such as intraoperative electrical cortical stimulation mapping. More importantly, advanced functional brain imaging has led us to question the canonical view of "fixed functional organization" of the brain, suggesting the existence of greater plasticity within the central nervous system. Language networks have been one of the great target areas with respect to the question of

brain plasticity and there has long been a vast literature on the topic of language lateralization, dating back to the first description of the association between compromised language production and brain lesions of the left hemisphere by Paul Broca in 1861 [6].

It has widely been accepted that language production in right-handed subjects is the function of the left hemisphere [5]. In almost 90-95% of healthy subjects language functions are carried out by the left hemisphere but early damage to the left hemisphere can result in atypical representation (bilateral or right-lateralization) [26, 44]. In right-handed patients with left (dominant) hemispheric lesions, including stroke [46], brain tumors [41, 53, 54], and even left hippocampal sclerosis [1, 51], atypical language activations have frequently been reported in PET and fMRI studies and the incidence of atypical language lateralization has been found to be high in patient with early brain lesions [2, 38, 40–42, 50]. Atypical language lateralization has mostly been studied in patients with dominant hemispheric stroke and clinical studies including brain tumors have started to appear in the literature. To date, the largest activation PET study to be reported included 61 right-handed patients with tumors of the left hemisphere, and they showed atypical speech activations in 63% of their patients [53]. Other PET and fMRI studies have also shown similar incidence rates of atypical speech lateralization in smaller series of patients with dominant hemisphere tumors [27, 36, 40, 54]. The most important question raised following neuroimaging studies regarding the atypical language activations is how to interpret right or non-dominant PET or fMRI activations because neuroimaging studies can only show language-related areas but can never prove if these areas are essential for the language task. This question was addressed by Thiel et al. [52], who recently showed the essential language function of the right hemisphere by using functional neuroimaging-guided repetitive transcranial magnetic stimulation in 14 patients with known or suspected left hemisphere gliomas. Despite the limitations, functional neuroimaging studies regarding plasticity have provided valuable information and started to change the surgeons' surgical strategies in patients with the brain tumors invading crucial areas.

Our aims in this report include: (1) to provide results from the Montreal Neurological Institute (MNI), (2) to describe typical and atypical language activations on PET in healthy control subjects and in patients, (3) to compare the language lateralization indices between the patients and controls to test the hypothesis that atypical dominance is more common in patients with left-sided lesions, and (4) to identify the effect of some variables, such as early onset and duration of epilepsy, gender, duration, location and the histological type of lesions.

Materials and methods

Patients

In this study we included 92 right-handed patients who had been diagnosed with left hemispheric lesional epilepsy. All patients were operated on, due to either cortical dysplasia or tumors at the MNI. The patient group included 41 males and 51 females; mean age 32.4±11.4 years at the first surgery (Table 1). Twenty-four patients underwent more than one surgical procedures and histopathological diagnosis revealed tumors in 58, focal cortical dysplasia (FCD) in 18, and vascular lesions in 16 patients.

Controls

In this study, the control group consisted of 19 right-handed subjects (ten female and nine male; average age of 37.9± 3.3 years) without known history of neurological or psychiatric illness.

Task paradigm

In the PET scanner patients and control subjects were presented word-repetition and synonym generation tasks,

Table 1 Demographic information of the 92 patients included in this study

Factors	Frontal (n=45)	Temporal (n=28)	Parietal (n=15)	Insular (n=4)	Total (n=92)
Mean age at 1st surgery (years)	33.3±12.7	31.0±11.7	30.5±10.7	39.7±7.4	32.4±11.4
Sex (male/female)	20/25	14/14	5/10	2/2	41/51
Mean age at onset (years)	24.0±17.0	25.4±14.1	17.1±15.5	9.1±11.2	22.6±16.0
Onset[a] (early/late)	8/37	3/25	4/11	2/2	17/75
Mean duration (years)	10.8±13.4	5.4±7.5	13.3±11.6	30.5±18.4	10.4±12.7
Deficit[b] (yes/no)	11/34	3/25	2/13	0/4	16/76

[a] Early and late onset of epilepsy represent the onset≤5 and>5 years, respectively

[b] Deficits related to language such as expressive or receptive aphasia

which has been reported elsewhere in the literature [32]. Written informed consent from all patients and controls was obtained after a full explanation of the purpose of the study.

PET scanning

PET scans were obtained using a Siemens ECAT HR+, which produced 15 image slices at an intrinsic image resolution of 5.0×5.0×6.0 mm [22]. Relative cerebral blood flow (rCBF) after intravenous bolus injection of 5 mCi of $H_2{}^{15}0$ [43] was measured for each condition. Data were reconstructed using a 20 mm Hanning filter. MRI data were obtained on a 1.5-T Philips MR Scanner to provide localization of functional data (T1-FFE: TE 10 ms, TR 18 ms, flip angle 30 degrees). The MR volumes were co-registered with the PET data [22]. The matched MRI-PET data were linearly resampled into a stereotaxic standardized coordinate system [21] using a multi-scale, feature-matching algorithm that matches the native image of each brain to a template along the anterior and posterior commissure (AC-PC) lines [10]. The functional data were normalized for global CBF value and the mean CBF change was obtained [23]. We applied a spherical Gaussian filter with 18-mm full width at half maximum kernel size. This resulting volume was converted to *t*-statistical representation by dividing each voxel by the mean standard deviation in a normalized CBF for all intra-cerebral voxels [56].

Regions of interest

Regions of interest (ROIs) were restricted to the cerebral areas that are known to be essential for language processing. These regions comprise (1) the inferior frontal gyrus (IFG) or classic Broca area [including pars orbitalis (BA 47), triangularis (BA 45), and opercularis (BA 44)], (2) the supramarginal gyrus (SMG; BA 40), (3) the angular gyrus (AG; BA 39), (4) the posterior part of the superior temporal gyrus, including the auditory cortex (STG; BA 42), (5) the posterior part of the middle temporal gyrus (MTG; BA 20), and (6) the supplementary motor area (SMA). In addition to the above mentioned supratentorial ROIs, we also included the cerebellum in the analysis because activity contralateral to the dominant hemisphere is often observed in tasks of language generation and production. Anatomical ROIs (seven in this study) were delineated in standardized-space using an iterative non-linear registration model-based segmentation algorithm and a neuroanatomical atlas [9, 10].

Functional activation data

We obtained activation images through subtraction analysis on the normalized PET data, in which the average for the three synonym-generation scans was subtracted by the average of the three word-repetition scans. Activations in several anatomical ROIs were found to be significant based on a criterion of $t \geq 2.5$ [56].

Laterality index calculations

To assess the extent of inter-hemispheric differences in functional activation, we computed a lateralization index (LI) for each subject for each ROI. The measure was determined according to the formula: $LI = [(\sum L_i - \sum R_i)/(\sum L_i + \sum R_i)]$, where L_i represents a significantly acti-

Table 2 Mean and standard deviations of the laterality indices (LIs) related to each ROI of the patients and controls. A negative LI indicates atypical lateralization (right or bilateral) and a positive LI+ indicates typical lateralization (left) (*IFG* inferior frontal gyrus, *IPL* inferior parietal lobule, *MTG* middle temporal gyrus, *Suppl.* supplementary, *STG* superior temporal gyrus)

Factors	Frontal (n=45)	Temporal (n=28)	Parietal (n=15)	Insular (n=4)	Total (n=92)	Controls (n=19)
Frontal lobe (IFG)						
1. Broca	0.17±0.4	0.16±0.4	0.29±0.4	−0.18±0.3	0.17±0.4	0.33±0.3
Frontal lobe (Medial)						
2. Suppl. motor area	0.19±0.2	0.20±0.3	0.25±0.3	−0.13±0.2	0.19±0.3	0.24±0.3
Parietal lobe (IPL)						
3. Supramarginal gyrus	−0.29±0.4	−0.02±0.3	0.09±0.4	−0.31±0.5	−0.14±0.4	−0.26±0.2
4. Angular gyrus	−0.14±0.4	−0.07±0.3	−0.26±0.5	−0.05±0.5	−0.13±0.4	−0.13±0.3
Temporal lobe						
5. STG	0.31±0.3	0.37±0.3	0.36±0.3	−0.02±0.6	0.32±0.3	0.19±0.2
6. MTG	0.22±0.4	0.43±0.3	0.43±0.3	0.05±0.5	0.31±0.4	0.37±0.3
Cerebellum						
7. Cerebellum[a]	−0.37±0.3	−0.39±0.3	−0.27±0.2	−0.44±0.2	−0.36±0.3	−0.27±0.2

[a] The right side in the cerebellum is the typical lateralization

vated voxel within the ROI in the left hemisphere, R_i represents a significantly activated voxel within the homologous region in the right hemisphere. Language lateralization was considered "left-sided" if the LI was greater than +0.2 and "right-sided" if LI was less than −0.20. An LI between +0.2 and −0.20 was taken to reflect bilateral language representation. The minimum and maximum values from the above formula ranges from −1 to +1, with −1 indicating *complete right* hemisphere language dominance, +1 indicating *complete left* hemisphere dominance, and "0" indicating represents complete *bilateral* hemispheric dominance.

Table 3 Number of the atypical activations of each ROI in the patients and controls in the first (preoperative) PET scans. LI^- indicates atypical lateralization (right or bilateral) and LI^+ indicates typical lateralization (left) (*AG* angular gyrus, *Comp. Bil.* complete bilateral, *SMA* supplementary motor area, *SMG* supramarginal gyrus)

Factors	Frontal (n=45)	Temporal (n=28)	Parietal (n=15)	Insular (n=4)	Total (n=92)	Controls (n=19)
1. Broca						
Right	12 (26.3%)	8 (28.6%)	3 (20%)	3 (75%)	26 (28.2%)	0 (0.0%)
Bilateral LI^+	1 (2.2%)	1 (3.2%)	1 (6.7%)	0 (0.0%)	3 (3.2%)	1 (5.3%)
Bilateral LI^-	2 (4.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.1%)	2 (10.5%)
Comp. Bil.	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.3%)
Total	15 (33.3%)	9 (32.1%)	4 (26.6%)	3 (75%)	31 (33.6%)	4 (21%)
2. SMA						
Right	5 (11.1%)	5 (17.9%)	3 (20%)	3 (75%)	16 (17.3%)	1 (5.3%)
Bilateral LI^+	4 (8.9%)	2 (7.1%)	0 (0.0%)	1 (25%)	7 (7.6%)	2 (10.5%)
Bilateral LI^-	2 (4.4%)	1 (3.6%)	1 (6.7%)	0 (0.0%)	4 (4.3%)	3 (15.8%)
Comp. Bil.	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.3%)
Total	11 (24.4%)	8 (28.6%)	4 (26.7%)	4 (100%)	27 (29.3%)	7 (36.8%)
3. SMG						
Right	30 (66.7%)	8 (28.6%)	4 (26.7%)	3 (75%)	45 (48.9%)	7 (36.8%)
Bilateral LI^+	4 (8.9%)	3 (10.7%)	1 (6.7%)	0 (0.0%)	8 (8.6%)	1 (5.5%)
Bilateral LI^-	2 (4.4%)	1 (3.6%)	0 (0.0%)	0 (0.0%)	3 (3.2%)	7 (36.8%)
Comp. Bil.	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (21.1%)
Total	36 (80%)	12 (42.9)	5 (33.3%)	3 (75%)	56 (60.8%)	19 (100%)
4. AG						
Right	28 (62.2%)	14 (50%)	9 (60%)	2 (50%)	53 (57.6%)	8 (42.1%)
Bilateral LI^+	3 (6.7%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	4 (4.3%)	6 (31.6%)
Bilateral LI^-	1 (2.2%)	1 (3.6%)	2 (13.3%)	0 (0.0%)	4 (4.3%)	1 (5.3%)
Comp. Bil.	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (15.8%)
Total	32 (71.1%)	15 (53.6%)	12 (80%)	2 (50%)	61 (66.3%)	18(94.7%)
5. STG						
Right	7 (15.6%)	3 (10.7%)	2 (13.3%)	2 (50%)	14 (15.2%)	0 (0.0%)
Bilateral LI^+	4 (8.9%)	1 (3.6%)	0 (0.0%)	0 (0.0%)	5 (5.4%)	0 (0.0%)
Bilateral LI^-	4 (8.9%)	1 (3.6%)	1 (6.7%)	0 (0.0%)	6 (6.5%)	0 (0.0%)
Comp. Bil.	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	11(57.9%)
Total	15 (33.3%)	5 (17.9%)	3 (20%)	2 (50%)	25 (27.1%)	11(57.9%)
6. MTG						
Right	10 (22.2%)	3 (10.7%)	3 (20%)	1 (25%)	17 (18.4%)	0 (0.0%)
Bilateral LI^+	2 (4.4%)	2 (7.1%)	1 (6.7%)	2 (50%)	7 (7.6%)	0 (0.0%)
Bilateral LI^-	3 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (3.2%)	1 (5.3%)
Comp. Bil.	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (26.3%)
Total	15 (33.3%)	5 (17.9%)	4 (26.7%)	3 (75%)	27 (29.3%)	6 (31.5%)
7. Cerebellum[a]						
Left	5 (11.1%)	5 (17.9%)	1 (6.7%)	0 (0.0%)	11 (11.9%)	1 (5.3%)
Total	5 (11.1%)	5 (17.9%)	1 (6.7%)	0 (0.0%)	11 (11.9%)	1 (5.3%)

Statistical analysis

Statistical analyses were performed using SPSS (version 14.0). A combination of non-parametric Mann-Whitney *U*, chi-square (χ^2), and *t*-test analyses was used. Since the distribution of LI in controls and patients was not normal, the Mann-Whitney *U*-test was used to evaluate group differences between and within the groups. Group differences in prevalence rates evaluated with χ^2 test (or Fisher's exact test in situations with cell counts less than 5). A non-parametric correlation analysis was used to identify numerical variables associated with LI in each group. A probability value less than 0.05 was considered to be statistically significant.

Results

Activations in controls

The LI analyses revealed that the most extensive and prominent activation in all healthy controls was observed in the left IFG and MTG. A less prominent cluster of activation was also seen in the left SMA. As expected with binaural presentation, bilateral STG activations (left>right) were observed. Inferior parietal lobule (IPL) including SMG and AG activations tended to be bilateral but more on the right (Table 2).

With reference to the IFG, the control subjects showed left-sided predominance in their IFG activations, and only four control subjects (21%) showed bilateral IFG activations (left>right in two and right>left in the other two) (Table 3). In the MTG, again we observed the expected left-sided predominance; 13 controls (68.4%) showed left-sided activations. In the SMA, left-sided activity was observed in 12 healthy subjects (63.2%) and in six showed bilateral activations with a left-sided predominance. In only one control did we observe right-sided SMA activations. As expected, in the majority of the controls the STG (59.7%) was activated bilaterally, while 42.1% displayed greater left-sided STG activation. Bilateral activations were seen in 63.2 and 57.8% of the controls with respect to the SMG and AG, respectively. The cerebellar activations contralateral (right hemisphere) to the left IFG activation were observed in 11/19 controls (57.9%) and 7/19 (36.8%) activated the cerebellum bilaterally but with a right-sided predominance. Only one control (5.3%) showed left-sided (atypical) cerebellum activation.

Activations in patients

Analyses of LIs showed little consistency in the findings across the patients (Table 2). The global maximum of activation was observed in the right-sided IFG and SMA. In the SMG and AG, bilateral activations were seen with the right-sided dominance. Bilateral activations with the left-sided dominance were observed in the STG and MTG. Cerebellar activity was generally right-sided.

Table 4 Factors thought to be associated with inferior frontal gyrus (Broca) lateralization

Factors	Typical (n=61)			Atypical (n=31)			p value
	n	%	LI	n	%	LI	χ^2
Age at onset							
Early (≤5)	8	13.1	0.35	9	29	−0.50	0.03
Late (>5)	53	86.8	0.47	22	70.9	−0.33	
Sex							
Male	25	40.9	0.48	16	51.6	−0.36	0.22
Female	36	59.0	0.44	15	48.3	−0.39	
Duration (year)[a]	8.72	13.9	***0.01***				
Language deficit							
Yes	11	18.0	0.66	5	16.1	−0.51	0.53
No	50	81.9	0.41	26	83.8	−0.35	
Types of lesion							
Tumors	38	62.2	0.49	20	64.5	−0.34	0.28
Cortical dysplasia	10	16.3	0.40	8	25.8	−0.51	
Vascular	13	21.3	0.41	3	9.6	−0.26	
Localization							
Frontal	30	49.1	0.46	15	48.3	−0.39	0.07
Temporal	19	31.1	0.43	9	29.0	−0.42	
Parietal	11	18.0	0.50	4	12.9	−027	
Insular	1	1.6	0.26	3	9.6	−0.33	

[a] Non-parametric correlation analysis (Spearman)

Table 5 Characteristics of the 12 patients with tumors who were scanned twice (*Aty. Activ.* atypical activation, *LI* laterality index, *MWU* Mann-Whitney *U*-test)

Case no.	Age/sex	Interval (months)	PET_1/PET_2	$Broca_1$ (LI)	$Broca_2$ (LI)	*p* value[a]
			Aty. Activ.			MWU
Frontal						
1	25/F	144	Yes/no	0.18	0.33	
4	32/F	84	No/yes	0.77	−0.64	
5	23/M	48	No/no	0.77	0.77	
8	52/M	12	No/no	0.79	0.33	
13	22/F	12	No/yes	0.51	−0.17	
16	34/M	3	No/yes	0.75	−0.54	
37	36/F	2	No/yes	0.35	−0.36	
Mean	32.0±10.4	43.5±53.3	–	0.58±0.2	−0.04±0.5	0.02
Temporal						
7	31/F	36	No/no	0.35	0.22	
10	31/F	60	No/yes	0.47	0.17	
23	29/M	48	No/yes	0.43	−0.24	
Mean	30.3±1.1	48.0±12.0	–	0.41±0.06	0.05±0.25	0.05
Insular						
1	46/F	60	Yes/no	−0.18	0.44	
2	43/M	60	Yes/yes	−0.13	−0.13	
Mean	44.5±2.1	60.0±0.0	–	−0.15±0.3	0.15±0.4	0.22
Total	33.6±9.2	47.4±40.2	–	0.42±0.33 (Typical)	0.01±0.4 (Atypical)	0.01

[a] The *p* value was analysed between LIs of $Broca_1$ and $Broca_2$

When patients were assigned to a group according to lesion location, analyses of the mean LIs in each group again revealed variability in the findings (Table 2). With reference to the IFG ROI, only the parietal group showed the typical left-sided activation (LI=0.29). The temporal (LI=0.16) and frontal (LI=0.17) groups had bilateral activations in the IFG with a left-sided dominance. In the insular group, the IFG was activated bilaterally (LI=−0.18) with a right-sided dominance. Regarding the SMA, activation was more left lateralized again for the parietal group (LI=0.25), while the frontal and temporal groups showed bilateral activation with left-sided dominance. The insular group again showed bilateral activation with right-sided dominance (LI=−0.13). The SMG activations were bilateral with left-sided dominance in the parietal group, bilateral with right-sided dominance in the temporal group and right lateralized in insular and frontal groups. Regarding the AG activations, the left lateralization in the parietal group was less evident, the temporal and insular groups showed bilateral lateralization, while the frontal group showed bilateral activation that was more right-sided. With

Table 6 Characteristics of the four patients with tumors who were scanned three times (*AA* atypical activation, Int_1 scanning interval between the first and second PET, Int_2 scanning interval between the second and third PET)

Case no.	Age/sex	Int_1 (months)	Int_2 (months)	$PET_1/_2/_3$	$Broca_1$ (LI)	$Broca_2$ (LI)	$Broca_3$ (LI)	*p* value[a]
				A A				**MWU**
Frontal								
6	25/F	48	12	Yes/yes/yes	0.18	0.14	0.14	
7	36/F	12	36	Yes/yes/yes	0.18	−0.70	−0.70	
11	46/F	48	12	No/yes/yes	0.44	−0.18	0.18	
12[b]	29/M	12	72	No/no/yes	0.39	0.29	−0.12	
Mean	34.0±9.2	30±20.7	33±28.3	–	0.29±0.1 (Typical)	−0.11±0.4 (Atypical)	−0.21±0.3 (Atypical)	0.02

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[a] The *p* value was analysed between LIs of $Broca_1$ and $Broca_3$

[b] This patient had four PET studies

reference to the STG, activity was left lateralized for the temporal (LI=0.37), parietal (LI=0.36), and frontal (LI=0.31) groups, but it was bilateral with right dominance for the insular (LI=−0.02) group. In the MTG, all patient groups showed left lateralized activations but in the insular group the activity was bilateral with a left-sided dominance [from more to less left lateralization: temporal (LI=0.43)=parietal (LI=0.43)<frontal (LI=0.22)=insular (LI=0.05)]. In the cerebellum, more right-sided activations were noted for the insular group (LI=−0.44), followed by the temporal (LI=−0.39), frontal (LI=−0.37), and parietal (LI=−0.27) groups.

For patients with atypical language lateralization, we observed specific patterns that were dependent upon lesion location. The majority of patients with IPL lesions showed atypical activations [61 patients (66.3%) for AG and 56 patients (60.8%) for SMG]. Among the four patient groups, frontal lesions were the main cause to lateralize the PET activations in both the AG and SMG. Atypical IFG activations were the second most common, which rated 33.6% (31 patients). In the IFG, the right-sided activation was most commonly observed for patients with insular tumors (75%), followed by frontal (33.3%) and temporal (32.1%) lesions. In the SMA, atypical activations were seen in 29.3% of the patients and again patients with insular lesions (100%) most commonly showed atypical SMA lateralization, followed by temporal, parietal, and frontal lesions. A considerable number of the patients also demonstrated atypical temporal lobe activations, with atypical temporal activation most commonly observed in patients with insular and frontal lesions. Finally, left cerebellar activations were found in 11 (11.9%) patients and most of these patients had frontal and/or temporal lesions. Table 3 demonstrates the number of the patients who had atypical PET activations in each ROI.

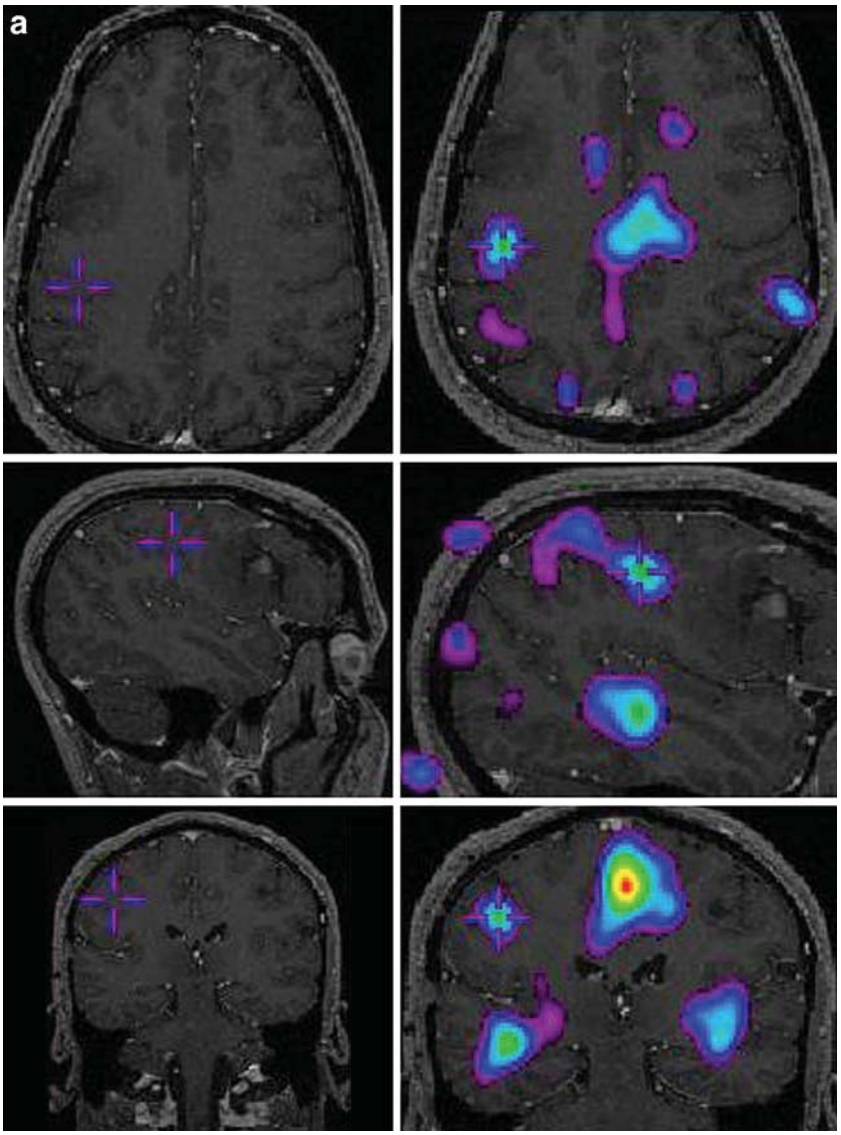
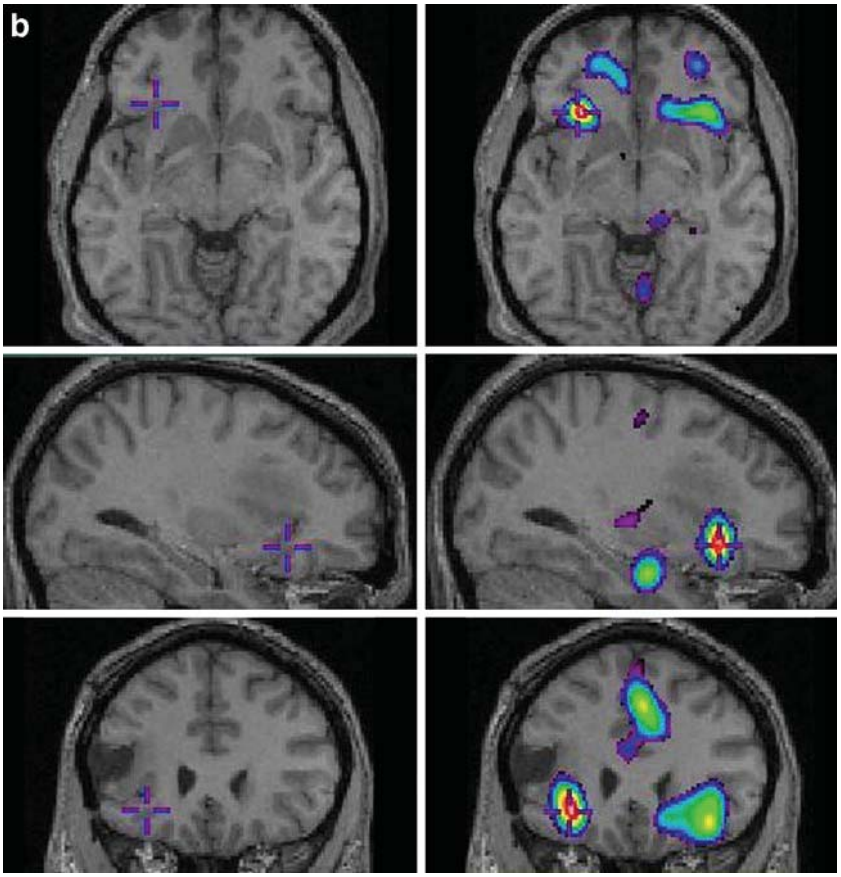


Fig. 1 In this patient with left frontal operculum tumor, there was one focus of speech activation immediately above the lesion in the left side but nothing in the right Broca in the first PET before the first surgery (**a**). Subtotal removal was performed and the diagnosis was oligodendroglioma-II. At the time of the second PET (before the second surgery and 14 months after the first PET study), the tumor had progressed and the speech activation was seen below the tumor in the left Broca (**b**). Furthermore, there was also activation in the right Broca (**c**), which was not seen in the first PET. In the third PET (before the second surgery and 21 and 7 months after the first and second PET studies, respectively), the speech activation in the left Broca was split by the tumor; one above (**d**) and one below (**e**). Again, we had also activations in the right Broca (**f**). In the second surgery, subtotal removal, again was performed and the diagnosis was the same: oligodendroglioma-II. In the fourth PET study (7 years after the first surgery and first PET study), strong activity was observed in the right Broca (**g**), with little activity being evident in the left frontal gyrus, particularly near the lesion (**h**). The histopathologic diagnosis after the third surgery was glioblastome multiforme

Fig. 1 (continued)



Comparisons

There were no statistical differences in mean age and gender between the patients and controls (age: *t*-test; $p=0.05$; gender: χ^2 test; $p=0.5$) or between the patient groups (age: *t*-test; $p>0.05$; gender: χ^2 test; $p>0.05$). Mean seizure onset was not significantly different within the four patient groups (*t*-test; $p>0.05$) but mean seizure duration was found to be significantly longer in patients with insular lesions compared with patients with frontal (*t*-test; $p=0.01$) and temporal lesions (*t*-test; $p=0.001$). Comparison between the patient ($n=92$) and control groups ($n=19$) revealed more left-sided lateralization for the control group (Table 2). In specific analyses comparing patients and controls with reference to the ROIs, no differences in LI were noted in the IFG (Mann-Whitney *U*-test; $p=0.19$), SMA (Mann-Whitney U test; $p=0.45$), the SMG (Mann-Whitney *U*-test; $p=0.16$), AG (Mann-Whitney *U*-test; $p=0.0.97$), STG (Mann-Whitney *U*-test; $p=0.07$), MTG (Mann-Whitney *U*-test; $p=0.79$). In the cerebellum, LIs tended to show more right-sided lateralization in the patients but the difference between the two groups was not significant (Mann-Whitney *U*-test; $p=0.18$). Comparisons of each lesion group with controls separately revealed significant differences in only a few comparisons. The frontal lesion group showed less typical (left-sided) lateralization (Mann-Whitney *U*-test; $p>0.05$) than controls. The temporal group showed stronger left-sided STG lateralization than controls (Mann-Whitney *U*-test; $p=0.03$). In the parietal group, LIs of the SMG showed significant difference in a comparison with the controls (Mann-Whitney *U*-test; $p=0.07$) with bilateral activation with right-sided dominance.

Comparisons of each patient group with each other also did not reveal significant differences regarding LIs in the majority of selected ROIs. The frontal and temporal group comparisons showed significant differences in only MTG (Mann-Whitney *U*-test; $p=0.02$) and SMG (Mann-Whitney *U*-test; $p=0.02$) activations and these two ROIs tended to be more atypical in the frontal group. The insular group showed stronger right-sided SMA lateralization than the frontal (Mann-Whitney *U*-test; $p=0.006$) and the temporal (Mann-Whitney *U*-test; $p=0.02$) groups. And finally, the insular group again showed strong right-sided IFG lateralization than the parietal group (Mann-Whitney *U*-test; $p=0.04$).

Factors associated with Broca lateralization

In this study we analysed several variables, including age at onset, sex, duration of seizure, presence of language deficits, types of lesion, resection type, localization of the lesion, as to whether they were associated with atypical

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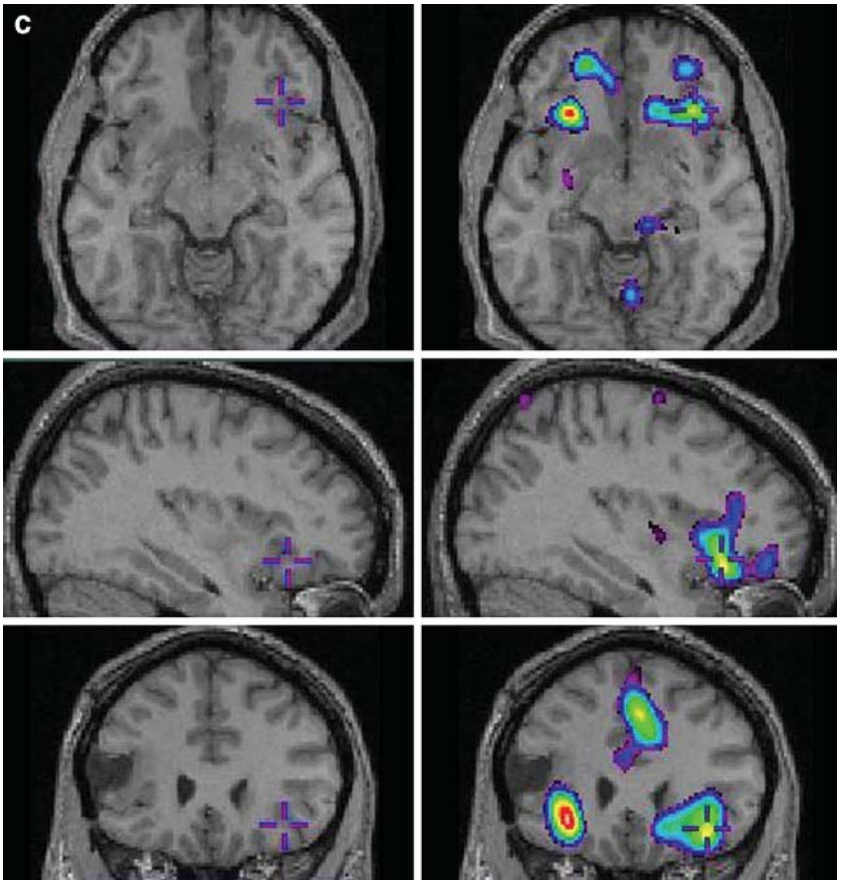
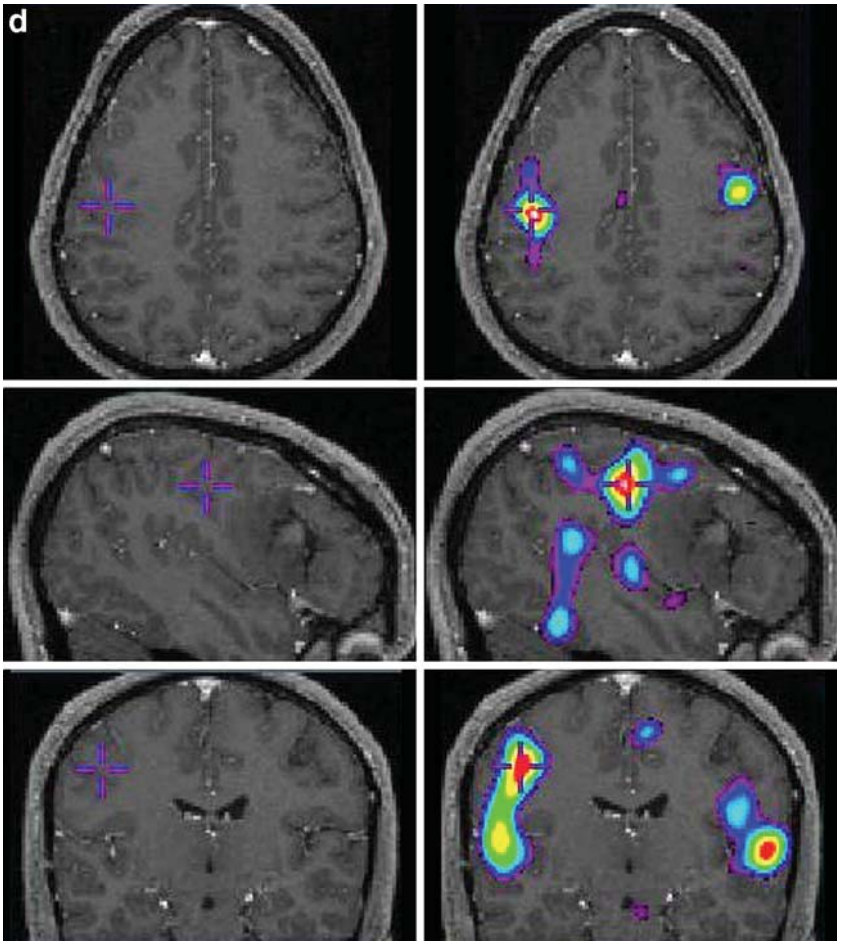


activations (Table 4). Here, we defined "early onset" if the seizure started at age of 5 years or less (17 patients), since it has been accepted that the language lateralization is generally completed until age of 5 (cut-off age) [44]. A significantly greater proportion of the group with early seizure onset had atypical (bilateral or right) language dominance (Spearman's correlation; r=0.21, p=0.03). Furthermore a significant difference between typical and atypical language lateralization was found to be related to the mean duration of seizure: the longer the duration, the higher the rate of atypical language lateralization (Spearman's correlation; r=−0.26, p=0.001). There were no significant differences between typical and atypical lateralization related to gender (χ^2 test; p=0.22), presence or absence of a language deficit (χ^2 test; p=0.53), histologic type of lesion (χ^2 test; p=0.28), and anatomical location of lesion (χ^2 test; p=0.07).

Interhemispheric compensation

A review of 12 patients who underwent PET scanning twice and four patients who had three PET scans allowed for examination of changes in CBF over time. Tables 5 and 6 show the clinical characteristics of the 12 and four patients, respectively. Six (50%) of the 12 patients showed a change in IFG activity from the first scan with greater atypical activation being present at the time of the second scan. The mean value of LIs of the 12 patients in the first PET scanning showed complete left-sided (typical) activations while the second PET showed greater bilateral activation with left-sided dominance, the difference was found to be significant (Mann-Whitney U-test; p=0.01). Strikingly, seven patients with frontal lesions showed bilateral activation with right-side dominance at the time of the second PET and LIs in this group were significantly low in comparison with the LIs obtained in the first PET. Likewise, two (50%) of the four patients who had PET scanning three times showed atypical language lateralization in the second and/or third PET which was not seen in the first PET scanning session. All four of these patients had frontal lobe lesions close to the IFG. Complete left-sided (typical) lateralization was observed in the first PET scan, bilateral with right-sided dominance was observed at the time of the second PET, and at the time of the third PET scanning session, complete right-sided lateralization was observed (Mann-Whitney U-test; p=0.02). Figure 1 demonstrates the progression of the language activation from typical (left) to atypical (right or bilateral) lateralization.

Fig. 1 (continued)



Discussion

The results for the healthy control subjects using the synonym-generation task are in good correspondence with previously published PET studies using word-generation tasks [33, 34]. The main pattern observed in controls is left-hemisphere IFG and SMA activation, together with bilateral, left-hemisphere dominant STG activation. Bilateral IPL activation is also observed. In controls, activity in the cerebellum is right-sided and a reciprocal pattern of left IFG with right-sided cerebellar activity is observed. Atypical IFG activation is uncommon, with only 4% of normal subjects showing bilateral activity and none showing clear right hemisphere dominance. Our patient group showed activations in the same ROIs as the controls, but with a high degree of interindividual variability. The most striking difference between the patient and control group was the frequency of atypical (right or bilateral) IFG activations observed. The LIs of the frontolateral activations in the patient group showed bilateral with right-side dominance; with right-lateralized IFG activation in cases of insular lesions, followed by temporal and frontal lesions. The most important finding in our patient sample was the high percentage of subjects who displayed atypical language lateralization indices (33.6%). Interestingly, five out of the 16 patients showing strong right IFG activations also had language deficits, suggesting that atypical (non-dominant) activation may not necessarily reflect hemispheric reorganization and may be related to a compensatory recruitment of the homologous region when deficits are present. Interestingly, in our patients, the cerebellum was atypically (left) activated (11.9%) together with atypical (right and bilateral) speech activation in the IFG. In healthy controls, this crossed laterality of cerebral and cerebellar dominance has been demonstrated in PET and fMRI studies. The anatomical basis for this crossed cerebellar activation is the prefronto-pontine (cortico-pontine) tract [4, 29, 47] and cerebellar diaschisis has been used to explain these findings [48]. It has been postulated that destruction of the fronto-pontine and cortico-rubral fibers by a lesion in the left frontal lobe decreases the excitatory influence of the left frontolateral cortex onto the right cerebellar hemisphere (crossed cerebellar diaschisis). Simultaneously, the lesion leads via transcallosal disinhibition to an increase of right

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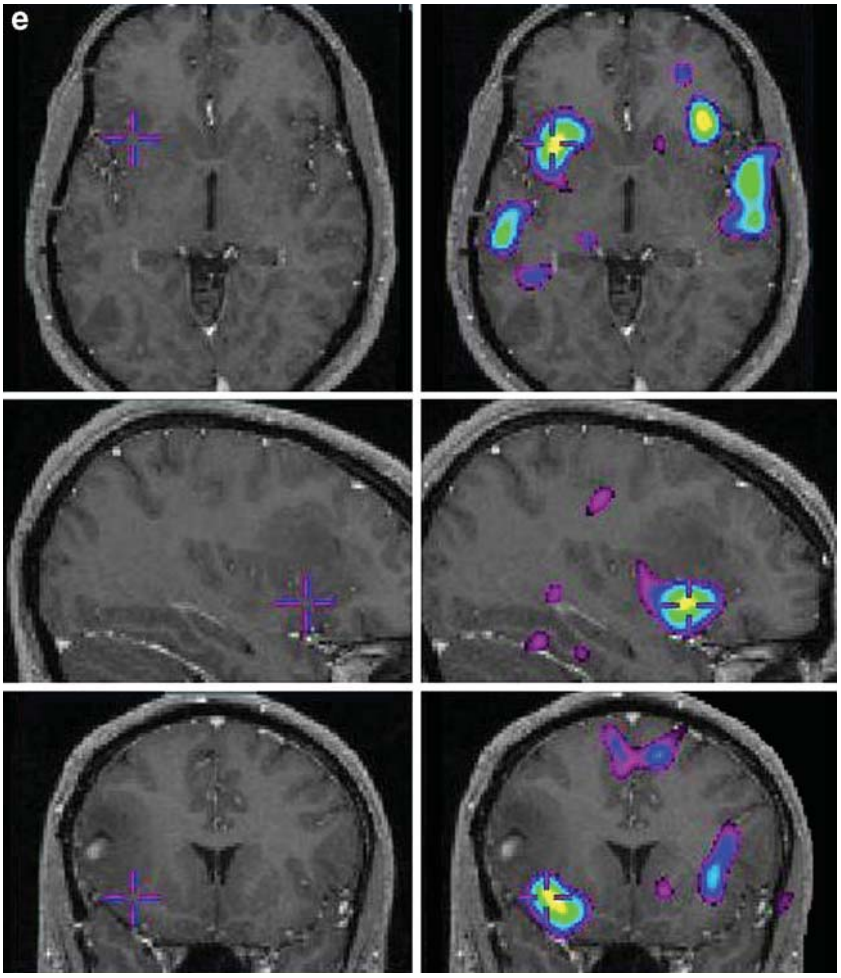

frontolateral activation, which causes an increase of left cerebellar activity, as indicated by significantly more left cerebellar activations [31]. This influence has already been demonstrated during resting conditions where a strong correlation between ipsilateral frontal lobe and contralateral cerebellar metabolism was reported [29]. Consistent with these earlier findings, our sample shows that lesions in the frontal, posterior temporal and inferior parietal regions results in strong right-sided IFG activations and left cerebellar activity.

Language lateralization was not strongly associated with sex, presence of language deficit, and types of lesion (Table 4). Location of lesion showed nearly significant association with atypical lateralization: the more the frontal location, and the more the atypical activation. Among the variables analyzed in the present study, duration of seizure and early seizure onset showed a strong relationship with atypical speech lateralization. In our sample longitudinal study of patients revealed that three of the four patients with insular tumors showed right IFG activation, suggesting that the percentage is relatively high compared with other regions. However, given the small number of patients included in the insular lesion group, it is difficult to conclude that the insular tumors are most likely to cause atypical IFG activations. The significant predictors of atypical lateralization in our patient group were age of onset and duration of seizure.

Our results support earlier studies [26, 44] which suggest that patients with early brain lesions tend to have greater atypical speech representation. In our study the relationship between LIs and duration of seizure was strong, reflecting the fact that recurrent seizures represent a more definitive marker of permanent brain dysfunction. Several mechanisms, from microscopic to macroscopic level, underlying brain plasticity have been defined. In the microscopic level, modulation of synaptic strength [8], synchrony within the functional network [35], unmasking of latent connections and network [28], modulation of neuronal activity by glia [24], modulation of neuronal activity by extracellular matrix [11], neuronal and glial phenotypic modifications [55], and neurogenesis [25] have been described. It has been assumed that these ultrastructural changes may lead to

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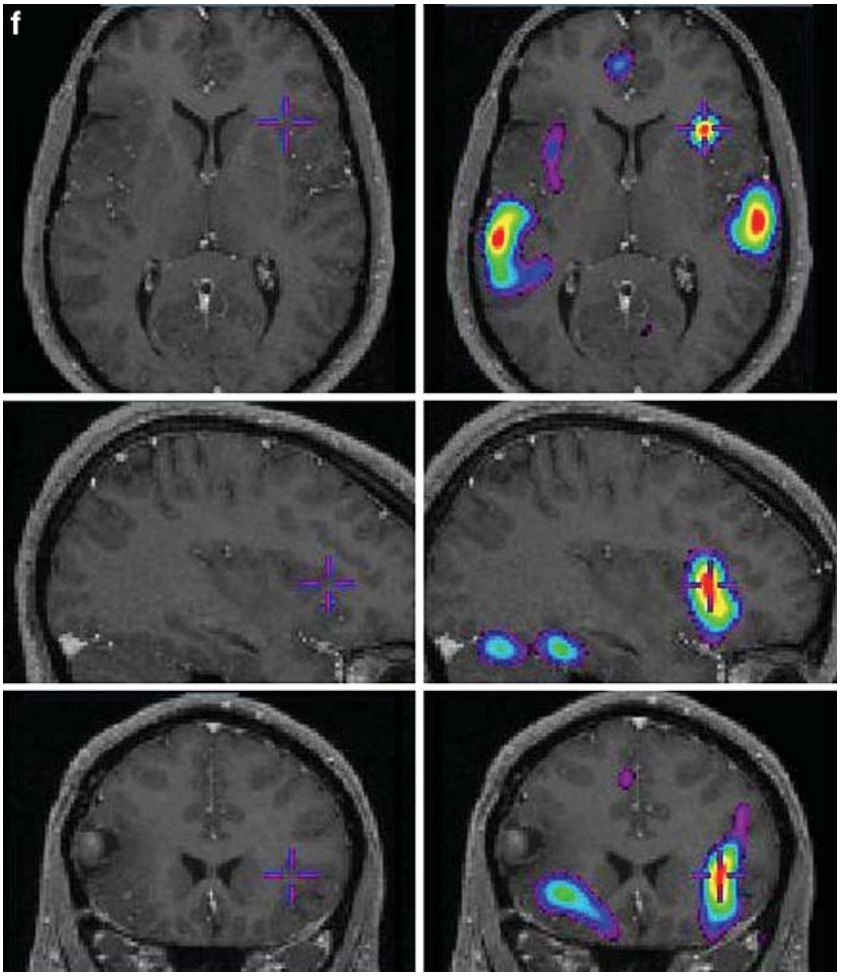

functional reorganization and compensation strategies at the macroscopic level. Diaschisis [48] is the functional changes in structures remote from the damaged area and its secondary resolution may participate in spontaneous functional recovery. Reorganization within the functional network is another macroscopic modification [19]. In especially wide lesions involving crucial areas, other regions within the functional network may be recruited, such as first perilesional areas; if the compensation is still insufficient, remote ipsilateral structures can take over the function. Finally, due to suppression of transcallosal inhibition, functional homologous structures in the contralateral hemisphere may also be recruited [13]. Cross-modal plasticity was recently defined as a compensatory strategy. When a lesion destroys many centers within a functional network, recruitment of structures initially not belonging to this circuit is possible [3, 13, 16]. For example, in humans, PET and fMRI studies have shown that posterior visual areas are active during somatosensory processing in the blind, and that auditory areas are active during visual and somatosensory processing in the deaf [7, 37]. Although we did not evaluate the relationship between size of the tumors and LIs, there was some evidence from our sample which suggest that patients who had progressive lesions tended to have more atypical activations. In a total of 16 patents we were able to get PET scans more than once (two scans in 12 patients, three scans in three patients, and four scans in one patient). In nine of the 16 patients (56.25%), inter-hemispheric compensation or atypical IFG lateralization were observed in the second or subsequent PET scans as the tumor progressed (Tables 5, 6). However, one can argue that the mass effect from tumor and peritumoral edema could have produced mechanical arteriolar constriction, which in turn would have eliminated or dampened the vascular response expected during functional brain activation (synonym generation here) or since the synonym generation tasks may engage not only classical language-related areas but also areas involved in executive frontal functions, a certain amount of right frontal activations could be eliminated. Thus, future studies are needed in order to provide more accurate data related to functional significance of the regions where atypical activations are found in patients with left-sided lesions.

The hypothesis of collateral inhibition of transcallosal activity has gained popularity to explain right hemispheric

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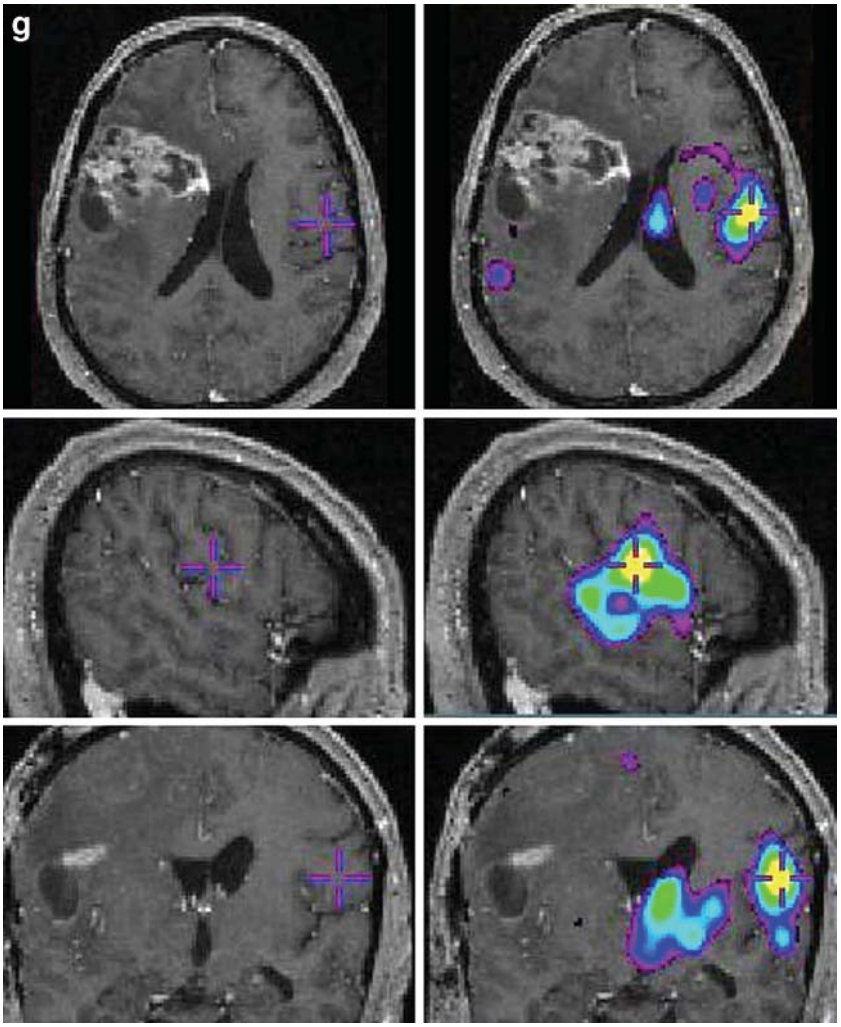

activations in right-handed patients with left-sided lesions. According to this theory, the two hemispheres are relatively equipotential with respect to their language capacity at birth, and that lateralization evolves gradually during the early years of development [30, 49]. Thus, crucial areas of activity in the left hemisphere continuously inhibit homologous regions in the right hemisphere. Destruction of one of these areas is sufficient to release right frontal activations, which were suppressed during language development [30, 53]. Taken together, the concept of brain plasticity depending on the above-cited studies have tought us that there is a large interindividual variability in the functional organization of the brain [39] and also proven the existence of great plasticity within the central nervous system in children as well as in adults.

In this study we present results from a large dataset of patients which clearly indicate a greater incidence of atypical language organization in patients with left hemispheric lesions. However, some important questions remain to be resolved. (1) If the undamaged hemisphere or undamaged parts of the damaged hemisphere take over language function, why do some patients overcome language deficits but others remain impaired? (2) During the language tasks, some right hemisphere activations are observed. How can one interpret these non-dominant activations? (3) In the case of bilateral activations, does either side contribute to language function independently; or rather, are both hemispheres necessary? (4) Finally, and more importantly, because neuroimaging studies can never prove whether a certain brain region is essential for the performance of that task, can we safely remove essential language areas involving the lesion safely when we demonstrate activity contralateral to the dominant hemisphere lesion?

Surgical implications from this study

Integration of functional brain mapping into neurosurgery has enabled neurosurgeons to perform the total removal of tumors (especially LGG) located within crucial functional areas, which have in the past been considered inoperable. In some recent studies, multistage surgery has been offered in patients with LGG involving eloquent areas because of the suggestion of long-term

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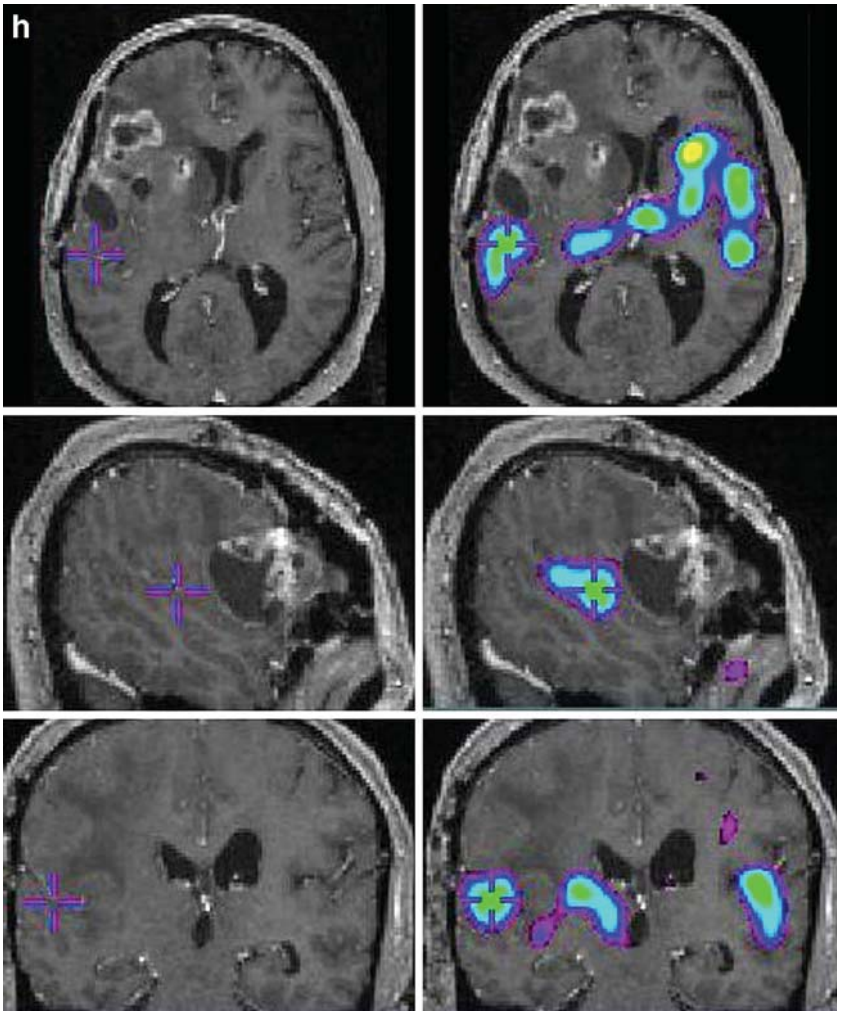

brain plasticity [12–20, 45]. Application of the concept of brain plasticity (intra- or inter-hemispheric reorganization) to neurosurgical strategies has shown improved functional outcome and almost 95% of patients who had staged surgery returned to a normal socio-professional life [12]. In our sample, inter-hemispheric reorganization is well-demonstrated in individuals who had consecutive PET studies (Tables 5, 6) as the tumor progressed, and in some patients reshaping took place several years after the first PET study or first surgery. Thus, multistage surgical application in low-grade gliomas (LGG) seems to be feasible, but larger patient series are required to improve our understanding of the individual mechanism(s) of the inter-hemispheric activations and whether this, in fact, reflects brain plasticity.

Limitations

Our results depend on PET studies, together with review of the patient charts and follow-up of the post-operative course of the patients. On the basis of these findings we cannot determine whether the regions activated that are atypical are essential for language function; moreover, only one language task was sample, that of word fluency (generation), so that future work would need to show that these findings generalize to more language processes. Secondly, age of onset of a seizure does not reveal the exact onset of the brain injury which could have started due to a tumor or cortical dysplasia before the seizure episodes had begun. Thus, defining onset at age 5 years or less as "early" could have caused a bias.

Conclusion

Our PET results with a large group of patients clearly showed that right-handed patients with left-sided lesions are more likely to have atypical speech representation compared with healthy subjects. In our study the shift of laterality index from the left to the right hemisphere is strongly correlated with seizure duration and early onset.

We conclude that understanding the brain plasticity or cortical organization and lateralization of language as focused on in this study is important for the planning of surgery in patients with dominant side lesions. Although results suggest that cerebral plasticity might be present not only in children but also in adults, future studies will be necessary to determine what extent the right hemisphere contributes to language function, and such knowledge will definitely have an impact on surgical strategy.

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Comment

The authors performed language mapping in 92 right-handed patients harboring a left-sided lesion and in 19 right-handed healthy volunteers using positron emission tomography. They found atypical language lateralization, strongly correlated with duration of seizure and early age of onset. Their results provide further arguments in favor of inter- and intra-hemispheric plasticity related to language function. The rationale of this study is original, and based on a clear review of the literature. The methodology is robust, and well exposed by a team with extensive experience in this field. The results are well presented and well discussed. Currently, the potential of cerebral plasticity is under-estimated and under-used in neurosurgery. Thus, this paper may have both important fundamental and clinical implications.

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