

Language lateralization in children with pre- and postnatal epileptogenic lesions of the left hemisphere: an fMRI study

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ABSTRACT – Functional MRI was used to evaluate factors influencing hemispheric dominance for language in 34 children suffering from intractable focal epilepsy due to left hemispheric lesion of pre- (n = 19) or postnatal (n = 15) origin. Nineteen children (56%) exhibited pronounced left-hemispheric language dominance. Significant co-activation of the right hemisphere or a complete language shift to this hemisphere was present in 15 children (44%). Atypical language representation was detected in 6 children (31,6%) with developmental pathology and in 9 patients (60%) with acquired epileptogenic lesion. Younger age at epilepsy onset and longer duration of epilepsy correlated significantly with atypical language presentation ($p < 0,017$ and $p < 0,025$). Whereas lesser tendency of prenatal lesions to displace cortical language centers did not reach statistical significance in simple paired tests, multiple logistic regression analysis viewed positive interaction between language shift, etiology and age at epilepsy onset. In conclusion, the language network reorganization was strongly influenced by both, the age at epilepsy onset and duration of epilepsy, and to a lesser degree by the character of the epileptogenic lesion, either developmental or acquired postnatally.

Key words: language dominance, functional MRI, children, epilepsy, developmental lesions, acquired lesions

Language is predominantly a left-hemispheric function and the lateralization of language functions has been associated with handedness - more than 90% of the dextrals has the left hemisphere dominant for language (Knecht *et al.* 2000; Springer *et al.* 1999; Pujol *et al.* 1999). In healthy subjects, language centers can be occasionally found in the right or both hemispheres. This variability has been

observed in about 20-27% of healthy sinistrals (Knecht *et al.* 2003; Wood *et al.* 2004). As children grow older, their language and speech skills become more lateralized to the left hemisphere (Booth *et al.* 1999; Byars *et al.* 2002; Gaillard *et al.* 2003) and finally have a similar activation pattern to adults. In children, the current techniques, intra-carotid amobarbital procedure (IAP) for language dominance, and

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cortical electrostimulation mapping (ESM), are invasive and risky. Functional magnetic resonance imaging (fMRI) is an alternative method for noninvasive functional mapping, which can be used in young patients.

It is widely assumed that various structural lesions of the left hemisphere may induce a reorganization of neuronal networks and have significant impact on language function. Neuroimaging studies have indicated that the non-dominant hemisphere is able to sustain language functions in various clinical situations, *e.g.* early perinatal lesions, cortical malformations, stroke or brain tumors (Holland 2000; Schirmer *et al.* 2001; Heller *et al.* 2005; Fair *et al.* 2006). Also, patients suffering from epilepsy demonstrate more frequently atypical language presentation (Adcock *et al.* 2003; Springer *et al.* 1999; Sabbah *et al.* 2003; Yuan *et al.* 2006).

Following early damage to the left hemisphere, language functions are likely to reorganize and develop in other parts of the same hemisphere or shift into the non-dominant hemisphere. However, few data concerning correlation of language lateralization and the time of lesion formation, localization of the lesion, age at epilepsy onset and duration of epilepsy in children, are available. In absence of epilepsy, developmental lesions originated from the prenatal period or lesions acquired during the first years of life rarely result in relevant language disorders (Muter *et al.* 1997; Vargha-Khadem *et al.* 2000; Fair *et al.* 2006). Some authors found that atypical language presentation is more frequent in early lesions infringing Broca's or Wernicke's language areas compared with more remote lesions (Isaacs *et al.* 1996; Lazar *et al.* 2000). By contrast, other investigators have shown that developmental lesions or tumors involving critical areas of the left hemisphere need not implicitly induce inter-hemispheric language shift (DeVos *et al.* 1995; Duchowny *et al.* 1996; Anderson *et al.* 2006).

Several studies on language networks distribution in children and adults have demonstrated that right-sided or bilateral language localization is significantly more frequent in early left-hemispheric lesions, originating in the period of intensive language development, *i.e.* before the age of 5-6 years. However, criteria used by various investigators to determine "early brain injury" were considerably different. Some authors relied on radiological findings, other preferred the clinical history or onset of seizures as a indicator for age of lesion formation. Lesions originated before the end of the critical period for language development were mostly considered as early, however, the age limit used by investigators has been estimated between one and six years of age (Springer *et al.* 1999; Staudt *et al.* 2002).

Recently, we have not been able to assess exactly the significance of various factors for language networks reorganization. Does the lesion contribute to language shift or is it chronic epilepsy? There remains some controversy concerning the potential of both developmental or acqui-

red lesions to interfere with language formation. Similarly, the impact of lesion site on language distribution following early damage remains to be elucidated.

The aim of present fMRI study was to evaluate the language organization in children and adolescent with intractable epilepsy caused by left-hemispheric lesions. The study should give us information on how frequent the atypical representation of cortical language centers in these patients is. Moreover, the impact of developmental *versus* postnatally acquired lesions, age at epilepsy onset, duration of epilepsy and distance of the lesion to Broca's area were studied in this group of patients. This information could help us to define the critical period of language development and should give us a better understanding of how neuronal plasticity works during different developmental stages and how these mechanisms could be modified by epileptogenesis. Clarifying this issue helps to avoid possible postoperative language deficiencies in children who are candidates for epileptosurgery.

Patients and methods

Patients

The group consisted of 34 children, aged 7-18 years (mean 13 years), 16 female and 18 male, with epileptogenic lesions of the left hemisphere without any structural abnormality in the right hemisphere on MRI. All patients suffered from intractable focal seizures and were admitted to our department as candidates of epileptosurgery. Their average age at epilepsy onset was 7,7 years (5 months - 15 years) and epilepsy duration 5,5 years (6 months - 14 years).

The epileptogenic lesions detected on MRI were divided into two categories according to their origin: prenatal (developmental) and postnatal (acquired). In 20 cases, the MRI pathology could be confirmed histologically from resected tissue. Prenatal lesions were found in 19 individuals (55,9%) and included focal cortical dysplasias (FCD), congenital tumors and hamartoma. Fifteen patients (44,1%) presented with postnatally acquired lesions (mesiotemporal sclerosis MTS), focal and regional post-traumatic or post-inflammatory changes, cavernomas and low-grade gliomas. Three cases with double pathology (mostly MTS with FCD or hamartoma) were included in the developmental category.

The localization of the lesion was temporal in 20 children, frontal or fronto-central in 11 patients, parietal or parieto-occipital in 2 and multilobar in 1. The distance to Broca's area was estimated from the nearest part of the lesion (*table 1*).

All children underwent neurological, video-EEG and neuropsychological examination and structural MRI with detailed protocol. According to extensive neuropsychological assessment, all the patients except three were right-

Table 1. Patients' data (n = 34).

Patient	Sex	Age (years)	Epilepsy duration (years)	Age at epilepsy onset (years)	Etiology	Localization of lesion	Lesion origin	Distance to Broca (cm)	Handedness	Language presentation
1	f	17	10	7	DNET	Fronto-central	A	1	Right	Right
2	m	18	14	4	DNET	Temporal	A	4	Right	Right
3	f	14	12	2	FCD	Fronto-central	A	0	Right	Right
4	f	11	8	3	FCD	Fronto-central	A	0	Right	Right
5	f	10	5	5	LG glioma	Frontal	P	2	Right	Bilat
6	f	10	2	8	Cavernoma	Temporal	P	6	Right	Bilat
7	m	13	9	4	Post-traumatic	Temporal	P	3	Right	Bilat
8	m	15	1	14	LG glioma	Temporal	P	2	Right	Bilat
9	m	13	12	1	MTS	Temporal	P	4	Right	Bilat
12	f	10	6.5	3.5	Post-inflammatory	Frontal	P	1	Right	Bilat
11	f	7	4.5	2.5	MTS + FCD	Temporal	A	2	Right	Bilat
12	f	13	8	5	Cavernoma	Parietal	P	6	Right	Bilat
13	f	18	3	15	LG glioma	Temporal	P	1	Right	Bilat
14	m	18	6	12	MTS	Temporal	P	4	Left	Bilat
15	m	7	6.5	0.5	FCD + hamartoma	Temporal	A	0	Right	Bilat
16	f	13	6	7	FCD	Fronto-central	A	4	Right	Left
17	f	17	9	8	MTS	Temporal	P	4	Right	Left
18	m	9	2	7	Ganglioglioma	Temporal	A	1	Left	Left
19	f	11	2	9	FCD	Temporal	A	6	Right	Left
20	f	8	2	6	FCD	Fronto-central	A	4	Right	Left
21	m	17	3	14	Post-traumatic	Frontal	P	0	Right	Left
22	m	10	4	6	FCD	Multilobar	A	0	Right	Left
23	m	9	4	5	Ganglioglioma + FCD	Temporal	A	2	Right	Left
24	m	18	3	15	Ganglioglioma + FCD	Temporal	A	2	Left	Left
25	m	14	10	4	MTS + FCD	Temporal	A	2	Right	Left
26	m	12	10	2	Tuberous sclerosis	Temporal	A	1	Right	Left
27	f	13	1	12	Post-traumatic	Temporal	P	2	Right	Left
28	f	12	0.5	12	Ganglioglioma	Temporal	A	2	Right	Left
29	m	15	0.5	15	DNET	Parietal	A	6	Right	Left
30	m	12	0.5	12	Cavernoma	Temporal	P	4	Right	Left
31	m	17	5	12	FCD	Frontal	A	4	Right	Left
32	f	18	10	8	Post-operative	Frontal	P	3	Right	Left
33	m	14	5	9	Post-traumatic	Temporal	P	5	Right	Left
34	m	14	3	11	DNET	Frontal	A	2	Right	Left

m = male; f = female; FCD = focal cortical dysplasia; MTS = mesiotemporal sclerosis; DNET = dysembryoplastic neuroepithelioma; A = antenatal; P = postnatal.

handed and their verbal IQ ranked from 77 to 118. Only 1 patient had right-sided hemiparesis. fMRI data from a verbal fluency task (see below) could be successfully obtained from all children in this group.

fMRI acquisition and analysis

All our measurements were carried out on a 1.5 T MR scanner (Siemens Vision 1.5T), equipped with EPI capable gradient system (maximal amplitude 25 mT/m and slew-rate 125 mT/m/ms), standard head coil was used. First, morphological images were measured with T2-weighted

turbo spin-echo (TSE) sequence (turbo factor of 11, TE = 99 ms, TR = 6 s, FOV = 230 mm, 27 slices, voxel size of 1.1 x 0.9 x 4 mm, measurement time of 2 min 47 s).

The same number of slices (24) and slice location was used for fMRI: a single shot gradient - echo EPI sequence (TE = 54 ms, TR = 4 s, flip angle = 90 °, FOV = 230 mm, matrix 128x128, voxel size of 1.8 x 1.8 x 4 mm). Twenty-four slices with thickness of 4 mm and no gap were oriented in AC-PC direction and covered almost the entire brain. Sixty four successive images (volumes of 24 slices) were acquired under alternating neurophysiological conditions, each time eight images (32 s) representing either

the period of rest or stimulation (block design of four rest and four stimulation periods).

For stimulation of fMRI measurements, a verbal fluency test was used. This paradigm has demonstrated good feasibility in children, requires less attentional and working memory, is amenable for young or mentally impaired children and has very good correlation with the Wada test (Muller *et al.* 1997; Holland *et al.* 2001; Hertz-Pannier *et al.* 1997).

Prior to the examination, the test was rehearsed to make sure that the child comprehended the task. In the Czech implementation of the verbal fluency test, the subject was instructed to silently count during rest and to generate words beginning with the letters V, R, S, N respectively during stimulation. The word frequency of the selected letters for Czech words is similar to the original English version.

Acquired data were evaluated using the correlation coefficients statistic and the general linear model in statistical parametric mapping (SPM) programme. In the pre-processing phase, realignment and spatial smoothing (FWHM of 8 mm) were done before applying the general linear model (HRF modified square-box function). In the case of visible lesion, manually defined mask to cut-off the pathological region was also used in normalization procedure.

In this study we did not calculate the classical lateralization index (LI) and decided to apply a simple semi-quantitative analysis. First, a second order group statistic was applied to create standard activation maps of verbal activity from ten healthy right-handed children and adolescents. Three clusters of activation as defined in group maps and cluster centers in the frontal lobe had the following Talairach coordinates: L1 = [51, 27, 11] (Broca), L2 = [50, 26, 24] and L3 = [53, 13, 35] in the left hemisphere, and R1, R2, R3 in the right hemisphere with the same coordinates but negative x-values. For the semi-quantitative assessment of the activation, we used the number of statistical significant voxels in the selected areas in frontal lobes. Individual statistic maps were thresholded using uncorrected $p = 0.001$ for all patients. The map for each patient was lateralized by blinded visual inspection and assessed in the context of the presence or absence of activity in all regions of interest (L1, L2, L3 and R1, R2, R3). This approach allowed us to divide patients

into three principal groups: left dominant, right dominant and bilateral activation. The bilateral and right-hemispheric dominance was assigned as atypical.

Statistical analysis

Non-parametric tests and multiple logistic regression methods were used to analyse acquired data. After patients were classified into left, bilateral or right dominance patterns, group differences were studied with χ^2 analyses. These analyses correlated etiology (prenatal or postnatal) with the dominance pattern.

To assess the relationship between language dominance, age at epilepsy onset, epilepsy duration and localization of the lesion, a non-parametric statistical procedure (Mann-Whitney U test) was used.

To identify factors associated with binominal variable of language lateralization (*i.e.* left hemispheric or atypical pattern), a multiple logistic regression (Wald's stepwise method) was used. Selected regressors were actual age, age at epilepsy onset, epilepsy duration and dichotomic variable etiology (prenatal or postnatal).

Results

Nineteen children (55,9%), including two of three left-handed individuals, exhibited pronounced left-hemispheric language dominance without significant activity in the opposite hemisphere at the R1, R2 or R3 level. Atypical (bilateral or right dominant) language presentation was detected in 15 out of 34 children (44,1%). Significant co-activation of the right hemisphere was present in 11 patients (32,4%), other 4 (11,8%) exhibited a complete language shift to this hemisphere (*table 1*).

Language lateralization correlated with age at epilepsy onset and epilepsy duration

In patients with left dominant language, the average age was 13,3 years. Their mean age at epilepsy onset was 9,2 years and seizures persisted for 4,2 years. The average age in patients with atypical language presentation was similar (12,9 years), but their epilepsy started earlier at the mean age of 5,7 years and lasted for a longer period of 7,2 years (*table 2*).

Table 2. Epilepsy history and etiology in children with atypical (*i.e.* bilateral or right-dominant) and left-dominant language pattern.

	Atypical pattern (n = 15)	Left dominant (n = 19)	P value
Actual age (years)	12.93	13.32	NS
Age at epilepsy onset (years)	5.73	9.16	$p < 0.017$
Duration of epilepsy (years)	7.17	4.24	$p < 0.025$
Prenatal etiology (%)	40%	68.4%	NS

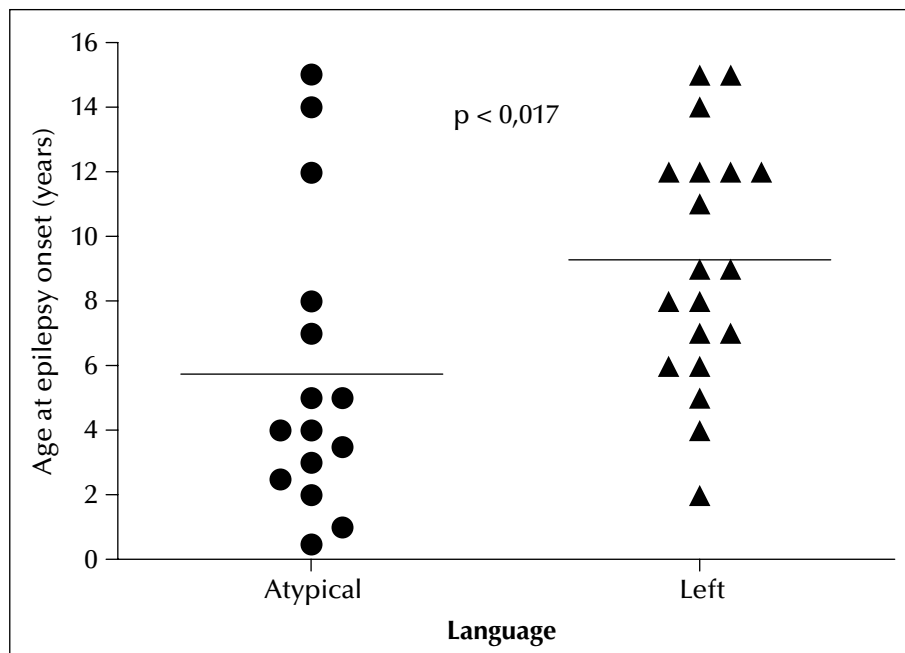


Figure 1. Age at epilepsy onset in children with atypical (right-dominant or bilateral) and left-dominant pattern.

To test for significant interaction between language reorganization and two main variables (age at epilepsy onset and epilepsy duration), we used a non-parametric statistical procedure (Mann-Whitney U test). Patients were classified in two dominance patterns: left or atypical (*i.e.* bilateral or right dominant) (*figures 1 and 2*).

The result of the Mann-Whitney U test [$Z(\text{Mann-Wh}) = -2,25$; $p = 0,017$] indicated a statistically significant impact of younger age at epilepsy onset on language networks reorganization. Similarly the language shift showed significant correlation with longer duration of epilepsy [$Z(\text{Mann-Wh}) = -2,25$; $p = 0,025$].

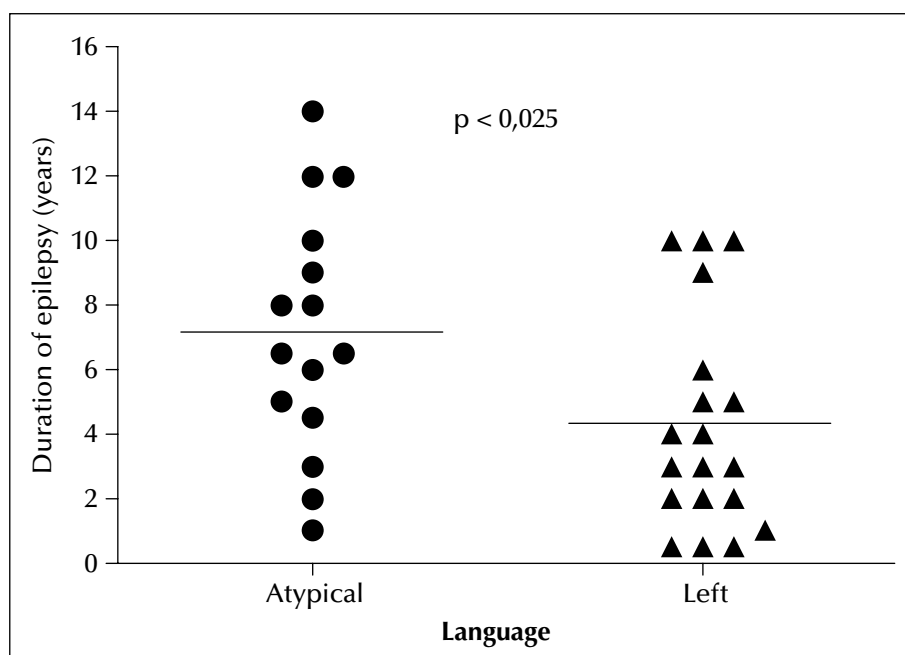


Figure 2. Duration of epilepsy in patients with atypical (right dominant or bilateral) and left dominant language pattern.

Language lateralization and etiology

Prenatal lesions had a remarkably lesser tendency to alter localization of cortical language centers than those of postnatal origin. Atypical language presentation was detected in six of 19 children (31,6%) with developmental pathology and in 9 of 15 patients (60%) with acquired epileptogenic lesions (despite the lower frequency of language reorganization among children with prenatal pathology all four patients with a complete shift were those with developmental pathology). However, the statistical correlation between language dominance shift and etiology was statistically weak [χ^2 (df=1)=2,75; $p < 0,097$]. Hypothetically, this correlation could become more significant in a larger group of patients.

Supposing that prenatal etiology may be related to earlier manifestation of epilepsy, we tried to determine, if there would be any interaction between etiology and age at epilepsy onset. Age of epilepsy manifestation and duration of epilepsy were similar in both groups, prenatal or acquired lesions (table 3).

In the next step, we used Wald's stepwise method of multiple logistic regression analysis to identify factors associated with binominal variable of language lateralization. We regressed language presentation (*i.e.* left hemispheric or atypical pattern) on selected actual age, age at epilepsy onset, epilepsy duration and dichotomic variable etiology (prenatal or postnatal).

With the stepwise analysis, the age at epilepsy onset had the strongest impact on language reorganization [$b(\text{OnsetAge}) = 0,32$; $p = 0.013$] and the persistence of left-

sided language dominance constituted a variable increasing with the age of epilepsy manifestation (table 4). The factor with significant additional influence on language dominance was the etiology [$b(\text{Etiol}) = -2,27$; $p = 0,028$]. The suitability of the regression model has been verified by Cohen's κ -coefficient (table 4), which indicates conformity assessment between observed and predicted categories of language presentation ($\kappa = 0,46$; $p = 0,007$).

In conclusion, the multiple logistic regression analysis showed – in contrast to non-significant paired dependence – a significant partial effect of etiology on language dominance and reciprocal independency of etiology and age at epilepsy onset. The probability of language shift induced by prenatal etiology was significantly lower than with acquired lesions.

Language lateralization and location of the lesion

Atypical language dominance was present almost equally and without any significant difference in five out of 11 (45%) children with lesions of the frontal lobe and 10 out of 20 (50%) patients with pathology of the temporal lobe.

The average distance of epileptogenic lesions from Broca's area was 1,25 cm in patients with right hemispheric dominance, 2,82 cm in those with bilateral language presentation and 2,84 cm in children with preserved left hemispheric language. Even this variable did not reach statistical significance.

Table 3. Epilepsy history and language presentation children with prenatal (developmental) and postnatally acquired lesions.

	Prenatal (n = 15)	Acquired (n = 19)	P value
Actual age (years)	12.42	14	NS
Age at epilepsy onset (years)	6.84	8.70	NS
Duration of epilepsy (years)	5.63	5.40	NS
Atypical language presentation (%)	31.57	60	NS

Table 4. Multiple logistic regression analysis with language presentation as dependent variable. Regressors are age at epilepsy onset and etiology (classification table^a).

Observed		Predicted		
		Language dominance		Percentage correct
		Atypical	Left	
Step 1 Language dominance	Atypical	10	5	66.7
	Left	4	15	78.9
Overall percentage				73.5

^a The cut value is ,500.

Discussion

The purpose of this study was to examine lateralization of cortical language functions in children with epileptogenic lesions of the left hemisphere. The main conclusions are as follows: a) atypical language representation could be found in a significant proportion of 44% in our patients; b) the younger age of epilepsy manifestation and the longer persistence of seizures are statistically significant factors for language reorganization; c) in developmental lesions, the probability of interhemispheric language shift is lower than with acquired lesions; d) neither lobar localization of the lesion nor its distance from Broca's area was significant for language presentation.

Neuroimaging studies on language distribution in healthy children and adults provide similar rates for language dominance to the left hemisphere. A higher proportion of atypical language representation has been observed in both adult and children with focal epilepsy (Springer *et al.* 1999; Janszky *et al.* 2003; Liegeois *et al.* 2004; Yuan *et al.* 2006). In this study, a partial or complete language shift to the right hemisphere was detected in 44% of children with refractory focal epilepsy and epileptogenic lesion of the left hemisphere. We do not assume that the inclusion of a small number of sinistrals significantly influenced the final results of our study because two out of three had the left hemisphere dominant for language.

The incidence of atypical language patterns seems to be higher in children with lesional epilepsy compared with adult patients (Benson *et al.* 1999). Several authors have published studies on language reorganization associated with early lesions and childhood epilepsy, partly with different results. Recently, the impact of developmental and acquired lesions on atypical language presentation in epilepsy patients has been studied by some investigators. Nevertheless, the controversy concerning the potential of different types of early lesions to interfere with language formation remains. Duchowny *et al.* (1996) used ESM for mapping the language distribution in children with lesional epilepsy and found that developmental lesions and early-onset seizures do not displace the language cortex from prenatally determined sites, whereas lesions acquired before the age of five may cause language shift in circumstances in which the language cortex had been destroyed. Anderson *et al.* (2006) studied expressive language distribution in a group of 35 children with cerebral lesions using fMRI and, in some of them ESM and IAP, and found atypical language presentation in 9 subjects. They stated that neither lesion lateralization, patient handedness, nor developmental versus acquired nature of the lesion was associated with language lateralization. The results of this study could be influenced by inclusion of right-sided and bilateral lesions. In a study of Liegeois *et al.* (2004), 5 out of 10 children with early epileptogenic lesions exhibited bilateral or right language lateralization. Briellmann *et al.* (2006) found atypical lateralization in

27% of patients with epileptogenic lesions localized in the temporal lobe and language lateralization was not different between patients with acquired lesions compared with those with developmental pathology.

In our study, the factor of etiology had only limited significance for language shift. While the lower probability of language shift with developmental lesions was not statistically significant in non-parametric tests [χ^2 (df = 1) = 2,75; $p < 0,097$], the same etiological factor exhibited some significance in multiple logistic regression [$b(\text{Etiol}) = -2,27$; $p = 0,028$].

Paradoxically, developmental lesions tended to behave "in extremes", all 4 patients with a complete right shift were those with developmental pathology.

Next, we found a statistically significant correlation between younger age at epilepsy onset and language network reorganization. The association between these two variables was confirmed in the non-parametric test [$Z(\text{Mann-Wh}) = -2,25$; $p = 0,017$] as well as the multiple logistic regression [$b(\text{OnsetAge}) = 0,32$; $p = 0,013$]. The positive correlation between longer persistence of seizures and language shift showed significance to a lower degree in non-parametric testing [$Z(\text{Mann-Wh}) = -2,25$; $p = 0,025$]. The impact of early epilepsy manifestation found in this study is consistent with the results of several other studies proving that language shift can be observed after early injury rather than late damage sustained after 5-6 years of age (Springer *et al.* 1999; Janszky *et al.* 2003; Adcock *et al.* 2003). Our results give evidence that the factor of epilepsy course, in particular younger age at epilepsy onset, had a stronger predictive value for language shift compared with etiology. The data embedded in table 3 demonstrate the reciprocal independence of these two variables, showing similar course of epilepsy in both groups, whether with prenatal or with acquired lesions. Moreover, the independence of age at seizure onset and etiology was confirmed by multiple logistic regression analysis. The same statistical method confirmed a negative correlation between speech reorganization and age of epilepsy manifestation, *i.e.* that persistence of left-sided language dominance constitutes a variable increasing with the age of epilepsy onset. We did not find any clear-cut age limit for language shift.

The factors that have been thought to influence language presentation, such as lesion lobar localization or its proximity to language regions, did not show a significant predictive value in our study. Several investigators demonstrated a similar proportion of patients with atypical language and lesions localized in the left frontal as well as temporal lobe (Muller *et al.* 1999; Janszky *et al.* 2003). According to some authors, early lesions near or within Broca's area should be at higher risk for language shift (Isaacs *et al.* 1996). This hypothesis seems valid in acquired destructive pericentral lesions, but not in so much in lesions of developmental origin (Duchowny *et al.* 1996; Liegeois *et al.* 2004; DeVos *et al.* 1995), which can lead to

intra-hemispheric shift or develop language in structurally abnormal cortical areas.

Our results did not demonstrate any difference between a lesion localized in the frontal or temporal lobe respectively. Similarly, the proximity of pathology – either developmental or acquired – to the frontal language area did not predict the language shift. However, in 4 children with a complete language shift to the right hemisphere, the average distance to Broca's area was noticeably (but not significantly) shorter than in other patients. All these lesions were of prenatal origin and 3 were within or close to Broca's area.

Finally, some methodological issues are to be discussed. We are aware that the use of simplified designations such as left-dominant, right-dominant and bilateral can, under concrete conditions, lead to loss of information. Because the language lateralization is thought to be a continuously variable phenomenon (Springer *et al.* 1999), the classical LI is more appropriate for quantification of language networks laterality. However, there is no complete agreement concerning the lateralization of language functions in different cohorts of patients, clinical conditions or – in children – during different developmental periods. While some authors noted an age-dependent increasing tendency to language lateralization into the left dominant hemisphere in healthy children (Holland *et al.* 2001; Brown *et al.* 2005; Szaflarski *et al.* 2006), others did not find any correlation between age and distribution of cortical language functions (Wood *et al.* 2004; Gaillard *et al.* 2000; Gaillard *et al.* 2003). In a study of Yuan *et al.* (2006), the lateralization of language function increased with age in the group of healthy controls, but this correlation with age was not significant in pediatric epilepsy subjects. This finding could indicate disruption of maturation patterns in epilepsy patients.

Moreover, the variability of LI may be due to various methodological and statistical factors, e.g. differences in categorization of patients, different tasks or task presentation used for stimulation of language centers, methods of signal thresholding and processing or defining ROI (Szaflarski *et al.* 2006; Roux *et al.* 2003; Rutten *et al.* 2002; Jansen *et al.* 2006). The number of voxels accepted as statistically significant can vary in time and between repeated examinations of the same subject (Rutten *et al.* 2002; Lohmann *et al.* 2004; Jansen *et al.* 2006) found that LIs based on an active voxels count processed with a fixed statistical threshold and on unthresholded signal intensity changes, are neither robust nor reproducible. Some studies of fMRI reproducibility show that the BOLD signal change could be a more relevant parameter in this aspect, compared to the number of voxels or statistically activated volume (Balsamo *et al.* 2006; Schapiro *et al.* 2004).

The hemisphere dominance in children was investigated using a verbal fluency test. This paradigm appears to be very valid and robust in the adult population, but the examination of children poses some procedural and tech-

nical challenges (Liegeois *et al.* 2002). The level of cooperation is usually lower in very young patients, sometimes also due to decreased comprehension or problems with alphabetical knowledge. It has been demonstrated that brain activation in Broca's area and Wernicke's areas is weaker and more dispersed in children with epilepsy (Yuan *et al.* 2006). If the brain activation is decreased due to the above-mentioned reasons (small number of significant voxels), LI tends to suffer with very low SNR and the value of LI cannot properly reflect the real situation of hemispheric dominance. Therefore, we omitted the LI for quantification of the dominance in this study and decided to prefer the semi-quantitative analysis. □

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