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Late plasticity for language in a child's non-dominant hemisphere

A pre- and post-surgery fMRI study

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Summary

The ability of the right hemisphere to sustain the acquisition or the recovery of language after extensive damage to the left hemisphere has been essentially related to the age at the time of injury. Better language abilities are acquired when the insult occurs in early childhood (perinatal insults) compared with later occurrence. However, while previous studies have described the neuropsychological pattern of language development in typical cases, the neural bases of such plasticity remain unexplored. Non-invasive functional MRI (fMRI) is a unique tool to assess the neural correlates of brain plasticity through repeated studies, but the technique has not been widely used in children because of methodological limitations. Plasticity of language was studied in a boy who developed intractable epilepsy related to Rasmussen's syndrome of the left hemisphere at age 5 years 6 months, after normal language acquisition. The first fMRI study at age 6 years 10 months showed left lateralization of language networks during a word fluency task. After left hemispherotomy at age 9 years, the child experienced profound aphasia and alexia, with rapid recovery of receptive language but slower and incomplete recovery of expressive language and reading. Postoperative fMRI at age 10 years 6 months showed a shift of language-related networks to the right during expressive and receptive tasks. Right activation was seen mainly in regions that could not be detected preoperatively, but mirrored those previously found in the left hemisphere (inferior frontal, temporal and parietal cortex), suggesting reorganization in a pre-existing bilateral network. In addition, neuropsychological data of this case support the hypothesis of innately more bilateral distribution of receptive than expressive language. This first serial fMRI study illustrates the great plasticity of the child's brain and the ability of the right hemisphere to take over some expressive language functions, even at a relatively late age. It also suggests a limit for removal of the dominant hemisphere beyond the age of 6 years, a classical limit for the critical period of language acquisition.

Keywords: language; dominance; plasticity; functional MRI; child

Abbreviations: BA = Brodmann area; fMRI = functional MRI; SPM = Statistical Parametric Mapping

Introduction

The ability of the non-dominant hemisphere to sustain language functions has been studied in various clinical situations. In patients with early lesions of the left hemisphere, acquired either prenatally or in early childhood (such as large infarcts or extended angiomatosis in Sturge–Weber disease), the right hemisphere can support nearly normal development of language, provided there is no associated epilepsy (Isaacs *et al*., 1996; Muter *et al*., 1997), but with subtle differences compared with non-lesioned children (Vargha-Khadem *et al*., 1994). In patients with lesions occurring after language acquisition, language recovery highly depends on individual pre-lesional lateralization,

Table 1 *Neuropsychological data/fMRI timing*

	Before surgery		After surgery	
Age	6 years 9 months	7 years 8 months	9 years 3 months	10 years 6 months
Time/surgery	–2 years 3 months	–1 year 4 months	+3 months	+1 year 6 months
fMRI	Study 1	Failure	NT	Study 2
Attention/behaviour	Impulsivity	Familiarity Mild attention deficit	Apathy Marked attention deficit	Slowness
IQ	118	96	NT	64
Performance IQ	128	102	67	80
Verbal IQ	107	91	NT	48
Oral production	Normal	Hypospontaneity	Few words	Short sentences
Word repetition	m	m	NT	m
Non-word repetition	m	m	NT	–2 SD
Digit span	m	m	NT	–2 SD
Verbal fluency	+1 SD	m	NT	–2 SD
Naming	m	–1 SD	NT	–3 SD
Semantic comprehension	m	m	–3 SD	–3 SD
Syntactic comprehension	m	–1 SD	–3 SD	–5 SD
Reading	m	m	NT	–3 SD

IQ = intelligence quotient; m = mean for that age group; SD = standard deviation; NT = not testable.

which is difficult to assess in clinical practice. In adults, the functional role of the right hemisphere in aphasia recovery might be limited compared with that of peri-lesional structures in the left hemisphere (Weiller *et al*., 1995; Karbe *et al*., 1998*b*; Samson *et al*., 1999). The best situation for studying plasticity of the right hemisphere for language is a situation of late onset lesion, involving the left hemisphere in right-handers previously tested for language and resulting in isolated right hemisphere.

Rasmussen's syndrome has a unique pathology, which fulfils these conditions. Partial seizures typically appear between 4 and 13 years of age in normally developed children, and are refractory to medical treatment. Cortical atrophy, hemiplegia and mental deterioration appear progressively, and complete disconnection of the hemisphere using either hemispherectomy or hemispherotomy (i.e. complete hemispheric disconnection without removing the hemisphere) is needed to control epilepsy (Andermann *et al*., 1993; Vining *et al*., 1997; Delalande *et al*., 2000). But surgeons are often reluctant to disconnect the dominant hemisphere after 6 years of age, a limit proposed as the end of the critical period for language acquisition (Woods and Teuber, 1978; Woods and Carey, 1979; Marcotte and Morere, 1990). However, recent reports clearly demonstrate the capacity for the right hemisphere to acquire language later. One boy with Sturge–Weber disease *de novo* developed a well-structured language from 9 years of age, following left hemispherectomy at the age of 8 years 6 months (Vargha-Khadem *et al*., 1997). Six right-handed children with Rasmussen's disease recovered in a year their previous capacities for receptive language after complete aphasia immediately following left hemispherectomy performed between 7 and 14 years (Boatman *et al*., 1999).

Functional imaging such as PET and functional MRI (fMRI) provides a unique means of identifying the neuro-anatomical correlates sustaining such a plasticity of the non-dominant hemisphere. Because of the lack of ionizing radiations fMRI is largely preferred to PET in children. Both techniques have been used to localize the different brain areas activated in various productive and receptive language functions in adult volunteers (Petersen *et al*., 1988; Frith *et al*., 1991; Mazoyer *et al*., 1993; Rueckert *et al*., 1994; Frackowiak, 1995; Binder *et al*., 1997) and in patients (Weiller *et al*., 1995; Binder *et al*., 1996; Benson *et al*., 1999; Lehericy *et al*., 2000). Clinical applications of fMRI have been developed mainly to assess non-invasively language dominance before epilepsy surgery, showing an excellent ability to lateralize language networks when compared with the intra-carotid Amytal procedure (IAP, Wada test) in adults and children (Binder *et al*., 1996; Hertz-Pannier *et al*., 1997, 2001; Benson *et al*., 1999; Lehericy *et al*., 2000).

Imaging studies of post-lesional plasticity of language networks are scarce. In adults recovering from aphasia following left infarct, the areas activated during expressive tasks involve right hemisphere regions homologous to those usually found on the left side, leading to the hypothesis of 'reorganization of cerebral activity in a pre-existing bilateral language network' (Weiller *et al*., 1995; Thulborn *et al*., 1999). Similarly, in children with early-acquired large left-sided lesions, language tasks activate a right-sided perisylvian network, resulting from early specialization of the right hemisphere for language (Hertz-Pannier *et al*., 1999; Muller *et al*., 1999). However, none of these studies was performed in the ideal situation required for testing a 'naive' non-dominant hemisphere after language acquisition.

We report on serial pre- and post-surgical language testing, including neuropsychological and fMRI studies, of a child suffering from Rasmussen's syndrome who underwent complete disconnection of the left hemisphere at 9 years of age after previously normal and complete language development.

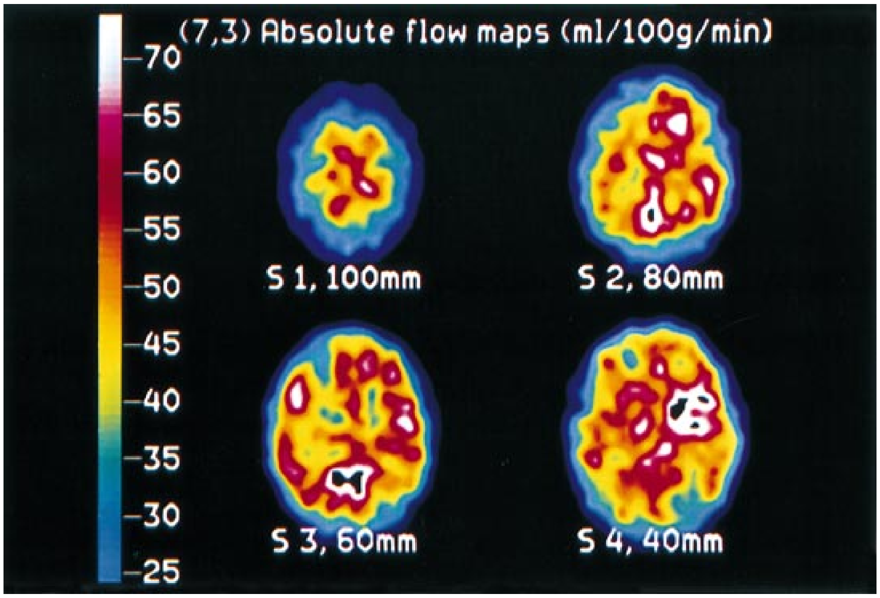


Fig. 1 Interictal ^{133}Xe single photon emission computed tomography before left hemisphere disconnection. Absolute flow maps show hypoperfusion in the left hemisphere compared with the right hemisphere, more pronounced in frontal regions (left hemisphere is on the left, right hemisphere on the right).

Case report

Patient history

The first seizures were experienced at 5.5 years in this previously normal boy, who was ambidextrous and had a family history of left-handedness (heterozygous twin). His epilepsy consisted of partial motor seizures of the right limbs and right epilepsia partialis continua, which were refractory to all antiepileptic drugs including high doses of corticosteroids. He was diagnosed as having Rasmussen's syndrome.

The boy was evaluated for the first time at 6 years 9 months (Table 1), when on 3 mg/kg/day of hydrocortisone. At that time, he presented with slight right hemiparesis and neglect, and some degree of behavioural disorder. However, he still had normal schooling; he could read, write and count normally and obtained high IQ scores (Wechsler, 1991).

Dichotic listening showed a clear right ear advantage, suggesting a relative predominance of the left hemisphere for language. The procedure consisted of a non-selective free recall of 36 sets of different monosyllabic digit pairs simultaneously delivered to each ear, after calibration of stimuli intensity during monaural presentation (100% good responses, i.e. no left ear extinction) and a practice run. The child was instructed to report heard digit pairs as accurately as possible. Because of an attentional deficit, he reported only one digit of each pair, with 66% correct responses for the digits delivered to the right ear versus 34% for those delivered to the left ear. Normal control children exhibit equivalent performances for both ears during such non-selective dichotic listening, probably due to a ceiling effect during this easy task (Duvelleroy-Hommet *et al.*, 1995). A forced listening condition (where children are instructed to recall what was heard in one given ear) is usually needed to reveal right ear advantage in right-handed children (88% correct responses versus 11% for the left ear) (Duvelleroy-Hommet *et al.*, 1995). Right ear advantage is also observed in 65% of normal left-handed children aged 8–9 years (Hugdahl and Andersson, 1989).

MRI was normal. Single photon emission computed tomography using ^{133}Xe, performed on a day when the child had no seizure discharge or myoclonus, disclosed left hemisphere hypoperfusion at rest (–2.2 SD), which was relatively more pronounced in frontal than posterior cortical areas (Fig. 1).

The first fMRI, performed at age 6 years 10 months, showed left lateralization of language networks during covert semantic word generation (Fig. 2, Table 2). Because right motor deficit was not complete, the child underwent subpial trans-section of the left motor strip at age 7 years 2 months, followed by resection of the left paracentral lobule at age 7 years 4 months, but both procedures failed to control seizures. At age 7 years 8 months, IQ scores had decreased by a mean of 22 points, mostly due to his behavioural disorders, but verbal abilities were still in the normal range (Table 1) (Chevrie-Muller *et al.*, 1981). An attempt to perform a second fMRI failed because of lack of co-operation and the presence of movement artefacts. The child was able to perform the tasks at pre-fMRI testing.

At age 9 years, the child had several seizures a day with speech arrest and falls, could no longer walk due to complete right hemiplegia and had deteriorated at the cognitive level. However, no formal neuropsychological testing was per-

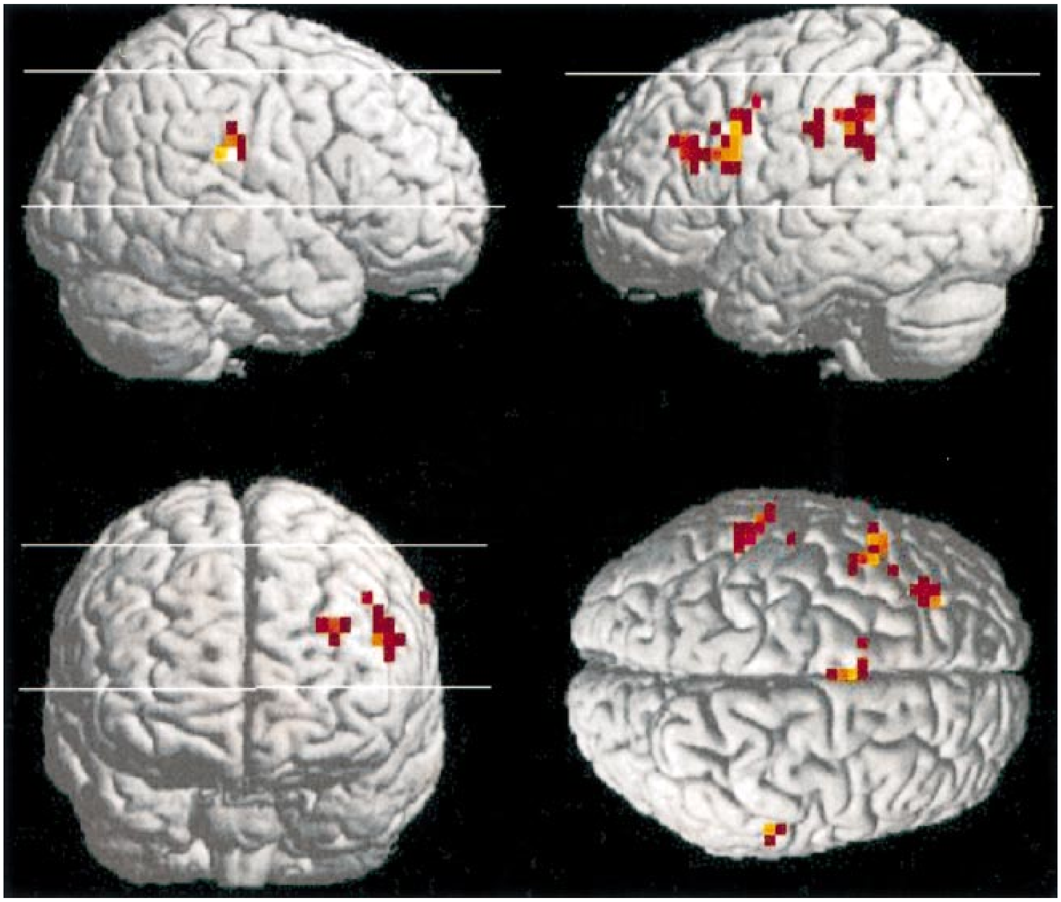


Fig. 2 Pre-surgery fMRI (Study 1). SPM map of word generation compared with rest, overlaid on the SPM template. White lines indicate the extent of slice acquisition. Height threshold $P < 0.01$ (uncorrected, at a voxel-level), with corrected extent threshold of $P < 0.227$ per cluster. Left-sided activated network involves inferior frontal gyrus, supplementary sensory-motor area and supramarginal gyrus ($P < 0.07$ in each cluster, $Z > 3.28$). Note that the activation in the right supramarginal gyrus does not reach cluster-level significance ($P = 0.227$, $Z = 4.26$) (see Table 2).

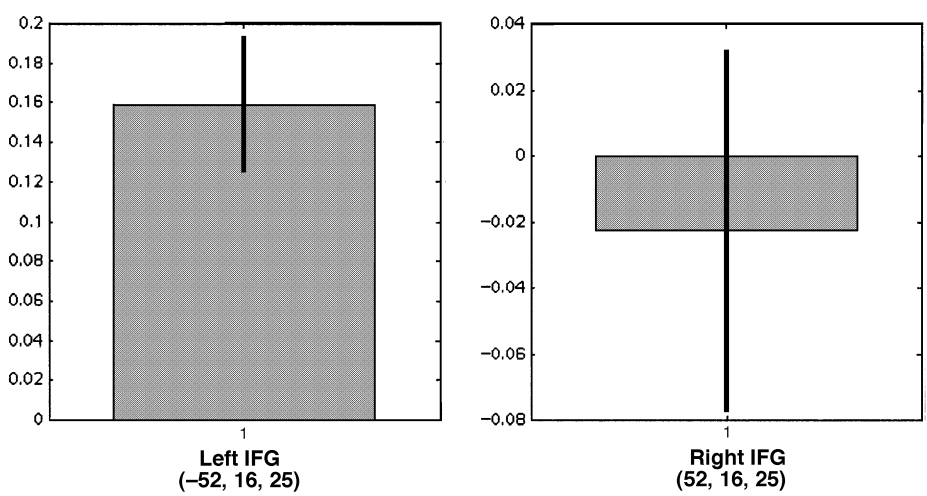


Fig. 3 Activation-related effect in left and right frontal regions in Study 1. The plots display verbal fluency minus rest contrast of the parameter estimates (relative size and standard error) in a typical activated voxel located in the left inferior gyrus (–52, 16, 25, $Z_{max} = 3.92$), and its right homologue (52, 16, 25). The magnitude of the activation-related effect is negligible (even slightly negative) on the right, with huge variability (error bar), and is ~16 times greater on the left. Similar results were found in all tested frontal lobe voxels.

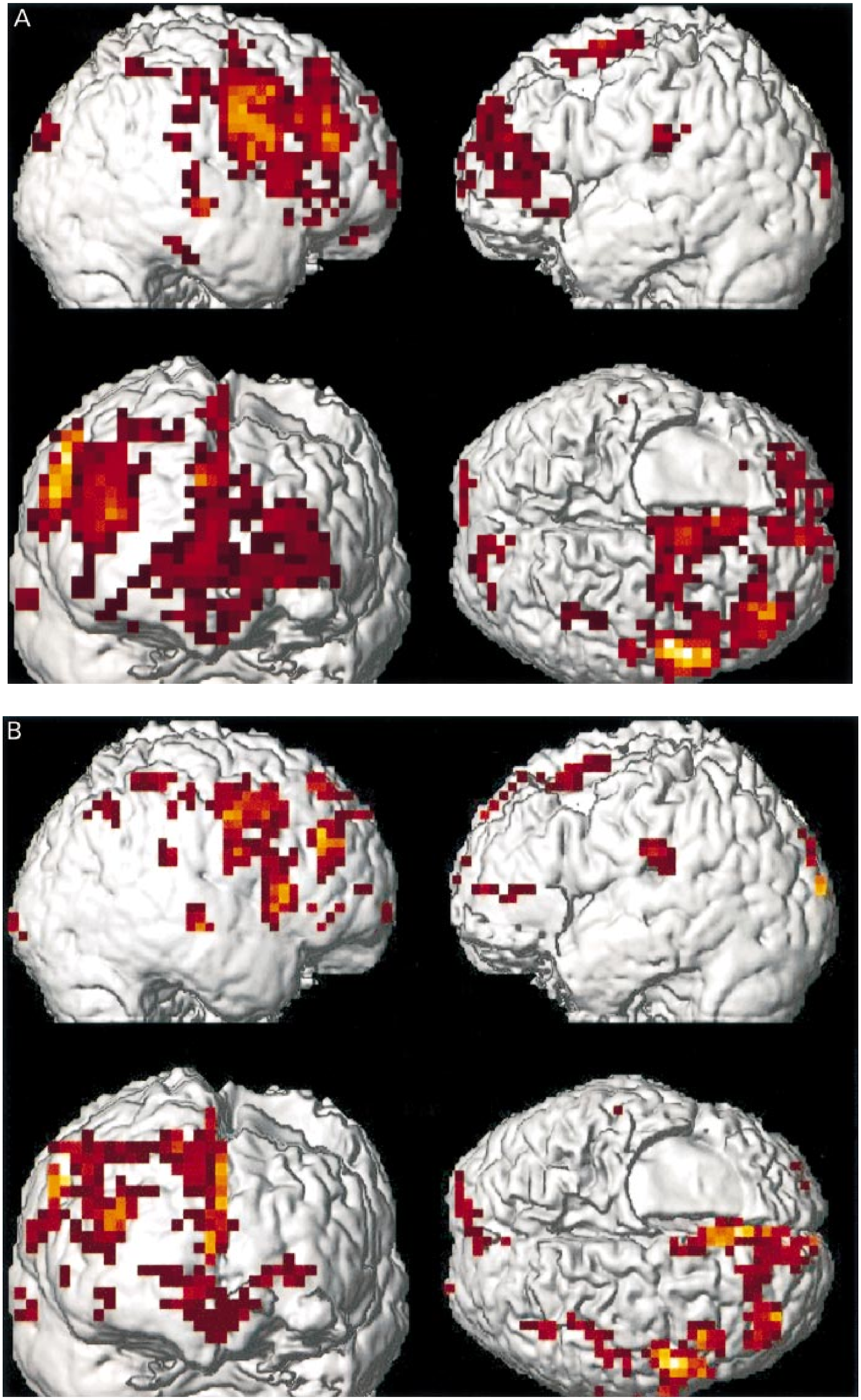
Table 2 *Longitudinal fMRI data*

Study 1 (P = 0.01 uncorrected)			Study 2 (P = 0.001 uncorrected)								
Word generation			Word generation			Sentence generation			Listening to sentences		
Area	P	Z_{max}	Area	P	Z_{max}	Area	P	Z_{max}	Area	P	Z_{max}
L SMA	$<10^{-4}$	4.99									
L IFG+ preCG	$<10^{-4}$	4.36									
L SMG	0.002	3.28	L SMG	$=10^{-3}$	4.80	L SMG	$<10^{-4}$	4.93			
	0.074*	3.85									
			L Insula	$<10^{-4}$	4.65	L Insula	$<10^{-4}$	4.66			
			L Fr	$<10^{-4}$	4.09	L Fr	$<10^{-4}$	4.26			
			L Occ	$<10^{-4}$	4.59	L Occ	0.001	4.26			
			R SMA	$<10^{-4}$	7.19	R SMA	$<10^{-4}$	4.78			
			R Cing	$<10^{-4}$	6.82	R Cing	$<10^{-4}$	6.98			
			R IFG	$<10^{-4}$	6.65	R IFG	$<10^{-4}$	5.39			
			R IFS	$=10^{-3}$	5.84	R IFS	$<10^{-4}$	5.56			
			R Insula	$<10^{-4}$	7.28	R Insula	$<10^{-4}$	6.05			
			R DLPFC	$<10^{-4}$	9.96	R DLPFC	$<10^{-4}$	5.97			
			R preCG	$<10^{-4}$	inf	R preCG	$<10^{-4}$	7.38			
			R caudate	$<10^{-4}$	5.01	R caudate	$<10^{-4}$	5.12			
			R Fr	$<10^{-4}$	4.26	R Fr	$<10^{-4}$	4.74			
			R postCS	0.01	3.92	R postCS	$<10^{-4}$	4.07			
R SMG	0.227*	4.26	R SMG	$<10^{-4}$	5.87	R SMG	0.03	3.92			
						R AG	$<10^{-4}$	4.63			
			R STS/STG	$<10^{-4}$	5.96	R STS/STG	$<10^{-4}$	5.03	R STS/STG	$<10^{-4}$	6.53
			R ITG	0.05	4.09				R MTG	$<10^{-4}$	4.99
			R Occ	$<10^{-4}$	4.64	R Occ	0.03	4.23			
			L cerebell	0.003	4.99						

P values are given for each cluster; Z_{max} corresponds to Z score of maximum local voxel; L = left; R = right; inf = infinite; SMA = supplementary motor area [Brodmann area (BA) 6]; IFG = inferior frontal gyrus (BA 44, 45); IFS = posterior part of the inferior frontal sulcus (junction between BA 8, 6 and 44); preCG = precentral gyrus, primary motor cortex (BA 4); postCS = postcentral sulcus (BA 7); SMG = supramarginal gyrus (BA 40); AG = angular gyrus (BA 39); Cing = cingulum (BA 24/32); DLPFC = dorsolateral prefrontal cortex (BA 9/46); Fr = frontal pole and mesial cortex (BA 10/11); STS = superior temporal sulcus (BA 22); STG = superior temporal gyrus (BA 41/42/22); MTG = middle temporal gyrus (BA 21); ITG = inferior temporal gyrus (BA 37); Occ = occipital cortex (BA 17/18). *Not significant.

formed. MRI disclosed peri-insular atrophy. Left hemispherotomy was performed, which consisted of extra-thalamic deep white matter disconnection of the whole hemisphere along with complete callosotomy and section of the anterior and posterior commissures, without removing the disconnected hemisphere (Delalande *et al.*, 2000). This procedure results in a normally perfused, but totally isolated left hemisphere, i.e. with no single connection left with both the right hemisphere and the descending pathways of the pons. Seizures immediately disappeared and treatment was discontinued at age 10 years. Neuropathological examination of a frontal fragment confirmed the diagnosis of Rasmussen's syndrome. Despite persistent right hemiplegia, the child could walk again. However, persistent and complete mutism with complete loss of reading and counting immediately followed surgery. Three months after surgery, while the patient had begun to recover, his semantic comprehension scored at a level of 6 years (Lege and Dagne, 1976) (Table 1), whereas he was only beginning to say a few words and failed in most oral verbal tasks (de Agostini *et al.*, 1998). He could count up to six, but could not read. He presented with severe attention deficit. Six months after surgery, his lexical stock had improved and he could recognize a few letters.

At age 10 years, the child was admitted in specialized schooling and benefited from orthophonic rehabilitation. The last evaluation was performed 6 months later, i.e. 1.5 years after surgery (Table 1). Attention was still fluctuating and Wechsler Intelligence Scale for Children sub-scores were strongly dissociated with a low verbal IQ. However, the child had substantially recovered as he could construct short sentences, name images, repeat words, read some words and perform simple additions. He was able to perform a third fMRI, which showed a right-sided activated network for the three language tasks tested (word generation, sentence generation and story listening) (Fig. 4A–C and Table 2), in locations that were not detectable on the first study. One year later, when he had progressively recovered spontaneous and intelligible fluent speech, although with persistent syntactic deficit according to his teachers and carers, he refused to submit to another fMRI study.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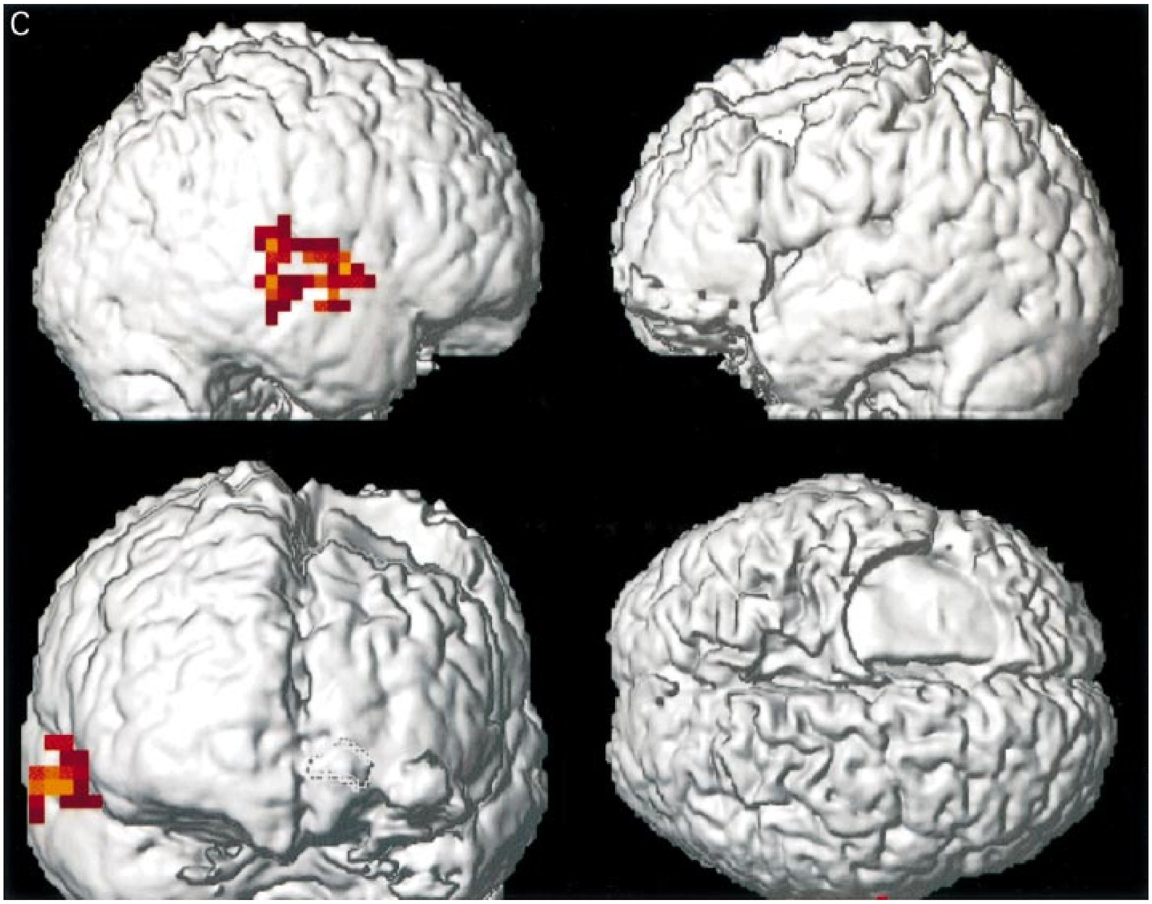

Fig. 4 fMRI after left hemisphere disconnection (Study 2). SPM maps of three language tasks compared with rest, overlaid on the normalized patient's brain surface rendering. Note left hemisphere atrophy and brain resection. Height threshold $P < 0.001$ (uncorrected at a voxel level), with corrected extent threshold of $P < 0.05$ per cluster. See Table 2 for statistics. (**A**) Word generation compared with rest. Right-lateralized activated network involves mostly frontal regions (inferior and middle frontal gyri, precentral gyrus, supplementary motor area) and a few superior and inferior temporal regions, as well as the supramarginal gyrus. Activation can be also observed on the left in the supramarginal gyrus, and bilaterally in occipital cortex and frontal poles. (**B**) Sentence generation compared with rest. During this task, the activated network is very comparable to the previous one, although less extended, with additional activation in the right angular gyrus. (**C**) Listening to sentences compared with rest. In this purely receptive task, activated network is restricted to right-sided superior and middle temporal regions.

fMRI

Data acquisition and task design

All fMRI procedures were performed after obtaining parental consent and child assent according to the ethical committee of Bicetre Hospital, on a 3T Bruker spectrometer, using gradient-echo echo-planar sequences and block paradigms. The child was trained carefully before the fMRI procedure and tested to ensure good understanding and performance of the tasks. Because of the long timespan between the examinations (3 years), the acquisition technique and paradigms differed slightly.

Study 1 (pre-surgical study). Covert word generation to concrete categories (animals, colours) was tested during two activation periods lasting 60 s each, interleaved with three rest periods of the same duration during which the child was asked to stop thinking of words and listen to the scanner noise. This paradigm was repeated twice during the acquisition of a total of 100 gradient-echo echo-planar images [TR (repetition time) = 6 s, TE (echo time) = 35 ms, voxel size = $3.7 \times 3.7 \times 5$ mm^3, 10 axial slices].

Study 2 (post-surgical study). Three language tasks were studied according to our ongoing protocol of expressive and receptive language (Hertz-Pannier *et al*., 1999). As in all fMRI language studies, all tasks were performed covertly to avoid head movements. (i) Word generation to concrete categories (similar to Study 1, using animals, colours, first names, food) during four activation blocks of 27 s duration each, interleaved with rest periods of the same duration, for a total of 3 min 54 s (TR = 3.5 s, 67 repetitions). (ii) Sentence generation from a concrete noun with the same experimental design as in the word generation paradigm (four activation and four rest periods). This task was chosen because it requires less attentional and working memory demands than covert word production, and is therefore more amenable to impaired children, while showing a good lateralization power (Muller *et al*., 1997). A concrete word was presented through the intercom every 7 s with four nouns presented in each activation period. The child was asked to make a simple sentence with the presented noun (such as subject—verb—object). No words were presented during the rest periods, during which the child was asked to listen to the scanner noise. (iii) Listening attentively to simple sentences (one sentence lasting a maximum of 2.5 s every 5 s, six sentences per activation block) presented through the scanner intercom without any explicit verbal production, compared with rest (similar to previous tasks), for a total duration of 4 min 15 s (TR = 5 s, 51 repetitions).

To avoid interference from the scanner noise and to ensure good comprehension of the auditory stimuli, we used a modified echo planar imaging sequence in which the slice acquisition gradients (loud beeps) are grouped over a 1.4 s interval to leave a silent interval within each repetition time, while maintaining proper RF (radio frequency) excitation (van de Moortele *et al*., 1998). The duration of silent intervals was adapted to the length of the stimuli (2.1 s for presentation of simple words within a TR = 3.5 s and 3.6 s for the presentation of the sentences within a TR = 5 s). Twenty-two axial slices (voxel size = $3.7 \times 3.7 \times 5$ mm^3) were acquired.

Data analysis

Data from both studies were analysed using statistical parametric mapping (SPM) (SPM99, Wellcome Institute for Cognitive Neuroscience, University College, London, UK). After motion correction, linear normalization of the images in the Talairach space, and spatial and temporal smoothing, data were analysed using voxel by voxel uncorrected threshold of $P = 0.01$ in Study 1 and $P = 0.001$ in Study 2. In both studies, we selected only the clusters with a probability of activation of $P = 0.05$ for each cluster (extent threshold). One major question pertaining to the mechanisms of brain plasticity during language recovery in this patient was whether we could detect *a posteriori* in Study 1, some activation (even below standard statistical thresholds) in the right frontal regions that were found activated in Study 2. Therefore, we re-analysed Study 1 at very low thresholds ($P = 0.1$ uncorrected) and used a threshold-independent approach. This involved comparing the verbal fluency minus rest contrast of the parameter estimates (relative size and standard error) in the 17 left frontal voxels that reached maximum Z scores versus their right homologues (Fig. 3).

For anatomical display, data from Study 1 were displayed on the SPM template because we could not acquire good anatomical data in this early study (standard MRI at 1.5 T was normal at that time). Data from Study 2 were displayed on the normalized surface rendering of the patient's brain.

Results

In Study 1, the SPM-activated regions during word generation were restricted to the left hemisphere (Fig. 2 and Table 2). They involved the left inferior frontal gyrus [IFG, Brodmann area (BA) 44, 45] and the lateral precentral gyrus (preCG, BA 4/6), the supramarginal gyrus (SMG, BA 40) and the supplementary motor area (SMA, BA 6). The only activation found on the right side, in the right supramarginal gyrus, did not reach cluster significance ($P = 0.227$, $Z_{max} = 4.26$). No activation could be detected in the right frontal regions, even at very low thresholds. In addition, the threshold-independent approach confirmed that the magnitude of the activation-related effect was negligible on the right, with huge variability, and that it was four to 16 times greater on the left. A typical left and right IFG voxel comparison is shown in Fig. 3. In this early study, temporal regions and cerebellum were not studied due to the limited number of slices.

In Study 2, activated regions were strongly lateralized to the right (Fig. 4A–C). They differed slightly according to the tasks. (i) During word generation, activated areas involved mostly right regions homologous to those found preoperatively on the left, namely the right inferior frontal gyrus (BA 44), anterior insula and precentral gyrus (BA 4/6), the right supramarginal gyrus (BA 40) and the right supplementary sensory-motor area (BA 6). Additional activation was found in the right dorsolateral prefrontal cortex (DLPFC, BA 46) and cingulum (BA 24/32), the right frontal pole, the right caudate and putamen, the right superior temporal sulcus and gyrus (STS, STG, BA 41/42/22), inferior temporal gyrus (ITG, BA 37), the right post-central sulcus (postCS, BA 7), the occipital cortex and the left cerebellum. Surprisingly, some activation was also found on the left side, in the anterior insula and frontal pole, the supramarginal gyrus and occipital cortex. (ii) During the sentence generation task, the activated network was strongly comparable with the previous one, with additional activation in the right angular gyrus (AG, BA 39), but no activation in the right inferior temporal gyrus and in the cerebellum. (iii) Finally, during sentence listening, activation was strictly restricted to the right superior temporal region, including primary and secondary auditory cortices (STG, BA 41, 42), as well as the superior temporal sulcus (STS, BA 22) and middle temporal gyrus (MTG, BA 21).

Discussion

In this serial fMRI study of language plasticity, we could compare for the first time pre- and postoperative data of language networks in a child who had had normal language development before undergoing complete disconnection of the dominant left hemisphere for severe epilepsy at age 9 years. The isolated right hemisphere was shown able to sustain late plasticity changes for language, thus indicating that it would be reasonable to consider surgical disconnection of the dominant hemisphere at least until 9 years of age in patients with intractable late onset seizures. Postoperative language fMRI studies demonstrated the redistribution of activated areas in the right hemisphere, mostly involving regions in which no activation was detectable before surgery, but were homologous with those found previously in the left hemisphere. This exemplary case demonstrates the physiological and clinical relevance of longitudinal fMRI studies of language, even in the difficult context of young patients with epilepsy, provided the tasks are adapted to individual abilities.

In the present case, language recovered substantially after surgery at 9 years of age, well beyond the age of 6 years proposed previously as the end of the critical period for language acquisition. Receptive functions recovered more quickly and completely than expressive ones, which remained limited to the production of simple sentences at 1 year postoperatively, but are currently improving dramatically at 2 years. Similar findings were recently observed in six children who underwent left hemispherectomy for late onset epilepsy between the ages of 7 and 14 years (Boatman *et al.*, 1999). After complete aphasia immediately following surgery, all patients recovered the ability to discriminate phonemes within 2 weeks and to understand words and sentences as well as to repeat words within 6 months, whereas naming was still severely impaired after 1 year. In this series, follow-up was too short to draw conclusions on long-term recovery of expressive functions. Another study that compared children and young adults who had undergone right or left hemispherectomy for intractable seizures after normal language acquisition showed that, although both groups had normal speech production with regards to their full scale IQs, left hemispherectomized patients were more likely to show syntactic comprehension and rapid-rate auditory processing deficits than the right hemispherectomized group (Stark *et al.*, 1995). Similar findings were also described in another short series, where left hemispherectomized patients showed mostly grammatical and lexical impairment (Vargha-Khadem *et al.*, 1991). Taken together, these data provide strong arguments for receptive language processing to be innately rather bilateral, and for functional resources necessary to sustain expressive functions to be at least partially acquired by the right hemisphere.

In adults, functional studies of language using either PET or fMRI rely on various tasks, including some degree of verbal production [e.g. silent word generation, silent naming, semantic tasks (Frackowiak, 1995; Binder *et al.*, 1997; Benson *et al.*, 1999)] and/or comprehension [e.g. listening to stories or short sentences (Mazoyer *et al.*, 1993; Dehaene *et al.*, 1997; Muller *et al.*, 1997)]. Expressive language tasks, which prove to be the most lateralized ones when compared with the Wada test (Benson *et al.*, 1999; Lehericy *et al.*, 2000), show left lateralized frontal activations in 94% of right-handed and 76% of left-handed normal volunteers, and in 78% of patients with epilepsy (Pujol *et al.*, 1999; Springer *et al.*, 1999). The left cortical networks sustaining expressive language as studied by verbal fluency tasks comprise Broca's area, premotor, prefrontal and supplementary motor areas as well as, less consistently, the superior temporal, middle temporal and supramarginal gyri (Frackowiak, 1995; Lehericy *et al.*, 2000). This large network reflects the complexity of such a task, which associates numerous cognitive components such as phonological and semantic processing, lexical retrieval, verbal memory and pre-articulatory processing. Comparable fMRI activation patterns were observed during covert word generation in normal school-age children and in children with epilepsy (Hertz-Pannier *et al.*, 1997, 1999; Gaillard *et al.*, 2000). However, some degree of right activation is almost always found both in adults (Pujol *et al.*, 1999; Springer *et al.*, 1999), and in children (Hertz-Pannier *et al.*, 1997, 1999; Gaillard *et al.*, 2000), making the respective functional roles of left and right fMRI activated regions difficult to assess.

In the present case, word generation elicited activation in the usual left network before surgery, without clear right activation. Only the right supra-marginal gyrus showed slight, but not significant activation, which was far less pronounced than in the homologous left region. The right ear preference at dichotic listening and speech arrest during left-sided seizures before surgery, along with the severity and duration of language deficit after left hemispheric disconnection (complete aphasia and alexia), clearly demonstrate the predominant role of the left hemisphere for language processing at the time of surgery, although the patient was firstly ambidextrous and had a family history of sinistrality. A partial preoperative shift to the right cannot definitely be ruled out because of the delay between the first fMRI and surgery, and the lack of quantification of language degradation during the year before surgery. However, if any right hemisphere participation had ever existed, it was not sufficient to sustain even rudimentary language function in the first months following complete left hemisphere disconnection.

After substantial, but incomplete, recovery of expressive functions in the first postoperative year, verbal fluency was supported by a right-sided network which was homologous with that previously observed on the left, with predominant activation in the inferior and middle frontal gyri, and supplementary motor area. The right supramarginal gyrus was also found activated in the same location as in preoperative Study 1. The sentence generation task yielded very comparable activation, in agreement with our previous studies (Hertz-Pannier *et al.*, 1999), thus increasing confidence that the results are not spurious.

The fact that this right frontal network could not be detected before surgery, even by threshold-independent methods, suggests it was recruited *de novo*. While fMRI cannot rule out the possibility of minimal right-sided neuronal activity without perfusion changes in Study 1, its specific distribution in Study 2 mirroring the initial left-sided one is a strong argument favouring a pre-existing bilateral network, with right-sided activation being normally inhibited by preferential left activation, similarly to that described for syllable discrimination (Boatman *et al*., 1998). The hypothesis of collateral inhibition of trans-callosal activity being responsible for functional brain asymmetries during expressive language processing has been documented using PET (Karbe *et al*., 1998*a*). In the case of complete hemispheric disconnection, such an inhibition would be suppressed, leading to expression of pre-existing contralateral networks, analogous to the recovery of motor functions in similar cases (Holloway *et al*., 2000). This hypothesis has also been raised to explain right hemisphere participation in functional recovery after stroke (Weiller *et al*., 1995).

Various methodological issues must be discussed in relation to this study. The choice of the task is a key point when studying young or debilitated children using fMRI, because task complexity limits feasibility. All tasks must be performed silently in the scanner to avoid head movements. Thus, special care was taken to train the child in selected tasks. These were tested by a neuropsychologist and practised overtly before fMRI to ensure good comprehension, to check the feasibility and to improve performance (Price and Friston, 1999). Word generation and sentence generation have demonstrated good feasibility in children, even with mild cognitive impairment, and excellent correlation with the Wada test (Hertz-Pannier *et al*., 1997; Hertz-Pannier *et al*., 2001). Word generation is known to explore semantic fluency, which proved to be normal before surgery (Table 1). Performance of this task does not necessarily reflect the level of daily propositional speech and may be impaired in non-aphasic patients with verbal memory deficits. At the time of postoperative fMRI, our patient showed global language impairment, but was able to perform the verbal fluency task (Table 1). Similarly, he could generate short sentences overtly at a rate of one sentence per 7 s, both during neuropsychological evaluation and immediately before fMRI. As for the receptive task, while the child showed impairment in both semantic and syntactic comprehension at neuropsychology, he easily understood the simple active non-reversible sentences presented during fMRI.

Interictal ^{133}Xe single photon emission computed tomography performed at the same time as preoperative fMRI Study 1 showed a hypo-functioning left hemisphere at rest, more pronounced in frontal regions, according to the clinical motor deficit, and in agreement with the literature (Yacubian *et al*., 1997). This left hypoperfusion, however, did not preclude the expression of activation-related haemodynamic changes in expected frontal locations, as demonstrated by fMRI Study 1. No perfusion abnormality was found in the right hemisphere.

In longitudinal studies, one would ideally wish to obtain similar sensitivities for the detection of activation. In the present case, the sensitivity of detection of activation cannot be strictly compared between both studies because of differences in data acquisition and task design (these explain differences in statistical power in addition to the obvious differences in cognitive abilities). However, the key issue was to demonstrate that no activation could be detected in the right hemisphere before surgery. Since one might question the statistical power of Study 1 owing to the limited number of slices and time points, we used a lower uncorrected threshold than in Study 2 (P = 0.01 versus P = 0.001). Moreover, the possibility that a threshold effect might have obscured right activations was investigated by a threshold-independent approach and proved negative. Finally, the Talairach coordinates of activated regions of both studies cannot be strictly compared despite normalization of all images, for two reasons: (i) in Study 1, the limited number of slices and lack of good anatomical images may have hampered the accuracy of spatial normalization; and (ii) in Study 2, the large anatomical changes secondary to both serial surgical procedures and left hemisphere atrophy resulted in a mid-line shift to the left and may have induced some distortion of normalized images.

Finally, two points need to be mentioned. The right-sided post-surgical activation is more extended and pronounced than the left-sided pre-surgical one. Beside differences in statistical power, which preclude rigorous comparison of the extent of activation between both studies—the child could have been more cooperative during the second than the first study. Another speculative hypothesis could relate to recent plasticity and learning effects that require more widespread networks, as suggested by fMRI studies conducted in normal children compared with adults (Hertz-Pannier *et al*., 1997; Gaillard *et al*., 2000), as well as in low-proficiency adult volunteers using a foreign language (Dehaene *et al*., 1997). In longitudinal developmental studies, the use of comparable tasks over time remains a problematic issue because of variability of performance either due to evolving cognitive abilities and strategies in normal children and/or cognitive consequences of treatment in patients. More surprising is the post-surgical activation of a few left regions, including the supramarginal gyrus, anterior insula and frontal cortex, and occipital cortex. Such an observation has not been reported previously and is not fully understood. Indeed, all hemispheric connections were cut during hemispherotomy, which included complete callosotomy, section of anterior and posterior commissures and peri-thalamic disconnection, and resulted in complete clinical seizure control. There were no residual head movement artefacts after image registration in either contrast (such artefacts usually present as mirror images in positive and negative contrasts, in the white matter, at the edges of the brain, the ventricles or the resection cavity). In addition, motion-related artefacts would be unlikely to create such regional and reproducible effects. Indeed, left-sided activation was very consistent during both word fluency and sentence generation (which are very close at a cognitive level) and involved cortical regions close to those normally activated by these tasks, but was not found during the listening task. Because the vascular supply to the left hemisphere was maintained, one may wonder whether some degree of regional vascular reactivity could be preserved without neuronal activity. Another hypothesis relates to residual activity of deafferented neurones in a disconnected hemisphere, by analogy with epilepsy patients in which infraclinical seizures can be recorded in disconnected megalencephalic hemispheres (unpublished personal data). But the mechanism by which this activity could be synchronized with contralateral activity remains unknown.

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