



## Clinical Research

## Language plasticity after hemispherotomy of the dominant hemisphere in 3 patients: Implication of non-linguistic networks



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## ABSTRACT

The neural networks involved in language recovery following hemispherotomy of the dominant hemisphere after language acquisition in children remain poorly known. Twelve hemispherotomized children (mean age at surgery: 11.3 years) with comparable post-operative neuropsychological patterns underwent multi-task language functional MRI. Three of them had recovered from an initial postoperative aphasia i.e., hemispherotomy was performed on the language-dominant hemisphere. Our main results revealed (1) perisylvian activations in all patients after either left or right hemispherotomy; (2) no differences in activations between groups regarding the side of hemispherotomy; (3) additional activations in pre-frontal (3/3) and hippocampal/parahippocampal and occipito-parietal (2/3) areas, when comparing language activation in each of the three subjects with hemispherotomy of the language-dominant hemisphere to the group of 9 non-dominant hemispherotomized patients. These neural networks support the stronger engagement of learning and memory during language recovery in a hemisphere that was not initially actively subserving language.

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### 1. Introduction

Hemispheric dominance for language proceeds from birth – even from the third trimester of gestation [1] – to adulthood and involves hemispheric specialization and cognitive plasticity. On the one hand, there is a significant increase in left hemispheric lateralization in the developing brain as a function of normal brain maturation [2,3]. On the other hand, there is a high incidence of functional reorganization for language in the event of early brain insult and the possibility of a language contralateral shift must be considered in pediatric epilepsy presurgical workup [4,5]. Assessing hemispheric dominance for language is critically important in children with severe epilepsy who are candidates for hemispherectomy. As hemispheric specialization for language progresses with age, hemispherectomy of the dominant hemisphere provides a unique opportunity to study the mechanisms of language organization in the remaining "single hemisphere" (i.e. contralateral to hemispherotomy) [6–13]. Among surgical procedures,

hemispherotomy is mostly used in children and easily performed in early age [14]. Hertz-Pannier et al. [11] reported the first serial language fMRI in a child with Rasmussen encephalitis (RE) with seizure onset at the age of 5.6 years after normal language development and who underwent left hemispherotomy when he was 9 years old. Preoperative fMRI at the age of 6.9 years had shown left hemispheric dominance. After hemispherotomy, the patient experienced aphasia but progressively recovered the capacity for speech. At the age of 10.6 years, post-operative language fMRI showed new activations in the perisylvian areas of the right hemisphere, indicating the ability of the right hemisphere to take over language functions even at a relatively late age, and certainly long after the so-called "critical period" for the acquisition of oral language. However, there is still a knowledge gap in investigating the neural networks involved in language plasticity after hemispherotomy of the language-dominant hemisphere.

Functional magnetic resonance imaging (fMRI), which is being increasingly used to study normal language development during childhood, has reported early left hemispheric specialization from infancy [15–18]. In a recent systematic computerized analysis of 39 fMRI studies of language development (mainly during late childhood: 8–12 years), Weiss-Croft and Baldeweg [19] confirmed that age-related activations differed according to task type (expressive or receptive) and input

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modality (auditory or written stimuli) and highlighted a progressive maturational change in the lateral perisylvian cortex. To date, only one study has focused on the neural basis of language explored during natural sleep in infants aged 1–3 years, which is considered a pivotal period for language acquisition [20]. The authors reported activations during receptive tasks in the classical superior temporal gyrus associated with greater activation in bilateral frontal, occipital, temporal and cerebellar regions and they suggested that interaction of brain regions takes place during the second year of life, leading to ordinary language development. Finally, the participation of the right hemisphere progressively decreases during childhood and adolescence [21,22], with regressive changes in frontal central and medial (cingulate gyrus) regions when language skills become automatized [19].

Language fMRI also offers the opportunity to describe the neural networks sustaining language plasticity after hemispherotomy/ectomy, but data remain scarce. Overall eight patients have been reported, including two investigated both before and after surgery [11,23] and six after surgery only [24]. All patients performed verbal fluency tasks and analysis focused on the inferior frontal gyrus (IFG). In all patients, fMRI disclosed activations in the right IFG after left hemispherotomy/ectomy. Only the posterior part of the right IFG was involved in one case [23] or with a more variable pattern within the IFG in five other cases [24]. In the longitudinal study reported by Hertz-Pannier et al. [11], new activations were found in the frontal, temporal, and parietal right cortex roughly mirroring those of the left hemisphere before surgery.

Our aim was to investigate the differential ability of the non-dominant hemisphere to sustain both expressive and receptive language functions in a group of children who had undergone hemispherotomy. We performed distinct whole brain analyses of fMRI language tasks to clarify the organization of the language network in these patients: (1) firstly, we investigated inter-individual variability in all patients; (2) secondly, we compared patient groups according to the side of hemispherotomy (Left versus Right); (3) finally, we performed case studies to refine our understanding of language neural organization after hemispherotomy of the language dominant hemisphere. Each dominant-hemispherotomized patient was compared to the non-dominant-hemispherotomized group to investigate the language plasticity of the non-dominant hemisphere.

## 2. Material and method

The local ethics committee approved the protocol and both informed consent from parents and assent from children were obtained prior to the fMRI study.

### 2.1. Patients

From our population of 83 children hemispherotomized over a period of ten years [14], sixteen French-speaking patients with at least 6 years of developmental age (as assessed by the communication score on the Vineland scale), able to comply with a 30-min fMRI procedure and with at least one-year post-operative follow-up, were selected. Twelve of them agreed to participate in this research (age at fMRI = 17.2 yo, range 13–21 yo) (Table 1). These 12 patients (7 females) had all presented with epilepsy (mean age at seizure onset 5.6 yo, range birth – 13.5 yo) due to either RE ( $n = 8$ ), or hemispheric malformation of cortical development, perinatal ischemic sequelae or Sturge–Weber syndrome ( $n = 4$ ). They had undergone hemispherotomy at a mean age of 11.3 yo (range 0.4–16.1 yo) on the left ( $n = 7$ ) or the right ( $n = 5$ ) side and had subsequently been seizure-free. Surgery consisted of a vertical para-sagittal hemispherotomy where the general principle is to achieve, through a posterior frontal cortical window, the same line of disconnection as with classic anatomical hemispherectomy, while leaving the majority of the hemisphere intact along with its afferent and efferent vascular supplies [14].

### 2.2. Neuropsychological assessment

#### 2.2.1. Clinical neuropsychological assessment

Neuropsychological findings are summarized in Table 1. All children underwent intelligence assessment with the Wechsler scale [25,26] including the digit memory span test (forward and backward). They also performed a receptive vocabulary test (Peabody) [27], a repetition task using pseudo-words (NEPSY), and a verbal fluency test (semantic and phonological word generation from the NEPSY battery) [28]. At the time of fMRI, the median Verbal Intelligence Quotient (VIQ) was 62 (range: 46–84). All children succeeded on the Peabody test with a mean of 87 (range: 72–115). All children but one (L8) obtained a mean score of over 8 yo of developmental age (DA) for the repetition of pseudo-words (range: 8–13), and over 6.5 yo for verbal fluency tests (range: 4.5–13). All children scored below 65 (percentile 93) on the Achenbach Child Behavior Checklist (CBCL) [29]. Right Hemispherotomy (R-H) and left Hemispherotomy (L-H) patients did not differ in terms of age at seizure onset, or at hemispherotomy (Table 1, Wilcoxon  $p > 0.05$ ). Mean verbal IQ, mean sub-scores of language abilities, and working memory tests using digit span did not differ between the two groups either ( $p = 0.12$ ) (Table 1).

#### 2.2.2. Expressive and receptive language tasks

Performance during training on the 3 tasks (Word Repetition – Sentence Generation – Word Generation) carried out the day before fMRI ensured that all patients were able to perform the tasks in the magnet (Table 2). Word Repetition and Sentence Generation were the easiest with relatively homogeneous performances (the mean of correct answers was respectively 98% and 90%), while Word Generation performance was more variable (mean =  $6 \pm 2$  words for “animals” and  $5 \pm 3$  for “food and drink”). Patient L8 obtained a poor score on this task and could therefore not perform the Word Generation task in the magnet. Nine patients were able to recognize over half the sentences on the recognition test performed immediately after the fMRI session, showing that they had participated well in the listening task. The performances were not significantly different between L-H and R-H groups.

### 2.3. Preoperative language dominance

All children underwent a presurgical evaluation at our institution with a precise clinical examination but an extensive preoperative neuropsychological assessment was not systematically performed. Two patients underwent pre-operative language fMRI (L1: right language dominant hemisphere/L3: left language dominant hemisphere). Patient L5 had a Wada test assessment (L5: right language dominant hemisphere). The whole population had moreover a systematic 3-month postoperative follow-up with clinical, EEG, and MRI examination by the same pediatric neurologist and neurosurgeon.

Three patients with (RE) were operated on their language dominant hemisphere and exhibited complete aphasia after surgery (two left L3, L8; one right R12). Patient L3 has already been reported by Hertz-Pannier et al. [11] and was evaluated here for the 3rd time at the age of 16.9 years.

Patient L8 started seizures at the age of 7.6 years and epilepsy worsened around 9 with daily seizures and cognitive deterioration. Left temporal lobectomy was performed at 11 years followed by language deficit but without relief of seizures. He finally underwent left hemispherotomy at the age of 13.5 years followed by post-operative aphasia but became seizure-free and all antiepileptic drugs were stopped. He was assessed with fMRI at the age of 15 years.

Patient R12 had his first seizures at the age of 2 years after an uneventful development. Neuropsychological evaluation at the age of 3.6 years showed left handedness (with a family history of left handedness) with normal intellectual efficiency (TIQ = 87), fluent sentences, and average lexical knowledge. After right hemispherotomy

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