



# Language Cerebro-cerebellar Reorganization in Children After Surgery of Right Cerebellar Astrocytoma: a fMRI Study

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## Abstract

Language processing depends on an integrated circuit involving the left supratentorial language areas and the right posterior lateral cerebellar hemisphere (lobule VI, lobule VII, Crus I, and Crus II). Reorganization of the language system after lesions of the cerebral language areas includes also cerebellar relocation. This is the first study assessing functional language reorganization after lesions concerning primarily the cerebellum, using a fMRI paradigm of phonological covert word production task in six children operated for right cerebellar astrocytoma and in 15 typically developing children. We found right cerebellar and left frontal activations in healthy controls and high variability of reorganizational patterns in patients with early right cerebellar lesion. Also lesions not located in the areas typically involved in language tasks (Crus I and Crus II) can cause reorganization between the two hemispheres or hemispheric language reinforcement of the original lateralization. We discuss the role of several variables in determining the reorganizational pattern such as the site, extension, and timing of surgery. No variables revealed as predictors, suggesting that co-occurring influence of other biological and/or pathological factors are not yet demonstrated. Lesions in the postero-lateral cerebellum seem related to less efficient language performances, as an indicator of the system's functioning.

**Keywords** Cerebellum · Language lateralization/reorganization · fMRI · Children · Covert fluency task

## Introduction

The cerebellum, by tradition considered an associative area mainly involved in motor coordination and execution, is in recent years considered also an integrative center for higher emotional and cognitive functions including language, even in the developing brain [1, 2]. Clinical and recent neuroimaging functional studies described a complex cerebro-cerebellar system of multiple anatomically segregated sub-circuits between the cerebellum and the supratentorial motor, paralimbic and association cortices as the neuroanatomical substrate of the nonmotor role of the cerebellum in cognitive and affective processing [3–5].

In particular, the idea of a “linguistic cerebellum” has been conceptualized to explain that the cerebellum is specifically involved in wide variety of neurolinguistic processes [4]; indeed several linguistic deficits are reported after cerebellar lesions, not all of these explained by limited motor coordination [6].

Language processing is known to involve an extensive distributed bilateral network of brain regions, in which the left hemisphere plays a predominant role: only about 4–10% of right handers show atypical right hemisphere language dominance [7].

The demonstration of reciprocal crossed neural pathways between the cerebellum and frontal areas of the left (or language dominant) hemisphere, including the Broca area and supplementary motor area (SMA) [8, 9], reinforced the notion that the cerebellum is implicated in language processing. Moreover, functional studies have shown that the left or right hemispheric cerebral dominance for language corresponds to contralateral activation respectively of right or left cerebellar hemisphere. The lateral cerebellum activation during language tasks has been demonstrated by verbal fluency tasks [10–12], semantic word retrieval [13–15], and verbal working memory tasks [16].

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Hubrich-Ungureanu et al. [17] and Jansen et al. [18] provided strong evidence that the right posterior lateral cerebellar regions (lobule VI, lobule VII, Crus I, and Crus II) are especially involved in linguistic processing as evaluated by letter-cued word generation in young adults with left hemisphere language dominance and that left postero-lateral cerebellar is activated in subjects with atypical right language dominance. These studies demonstrated that crossed cerebral and cerebellar language dominance can be considered a typical characteristic of brain organization [19, 20].

Also connectivity studies on animals and on humans [9, 21, 22] confirmed that the cerebellar structures receive inputs from several cerebral regions involved in cognition and affect, in agreement with the position asserting that cognitive and motor functions are segregated in the human cerebellum [23–25].

From a developmental point of view, an initially bilateral representation of language has been demonstrated in both typically developing children [26] and in children with congenital or early unilateral brain lesion [27–29]. This bilateral representation is necessary for the efficiency of the system and facilitates the plasticity and reorganization processes in case of brain damage.

Applying these developmental consideration to the cerebellum, it has been suggested that at a very early age the contribution of the cerebellum to language processing could be, as for cerebral hemispheres, bilateral [30]. The bilateral cerebellar participation to the linguistic system, as is already known for the cerebral language network [31, 32], has been confirmed by studies on children with cerebellar tumors (indifferent side) showing impairment in several cognitive functions including verbal fluency [33–35] and expressive language [36].

Moreover, increasing lateralization of language during childhood have been reported in fMRI [32] and MEG studies [37]; accordingly, some authors considered that the language specialization of the right cerebellum increases in parallel with the specialization of the left cerebral hemisphere, given their reciprocal strict cross-connections, and that functional lateralization behaves as a unitary feature of cerebro-cerebellar circuits [38].

The development of brain functional networks is known to first involve sensory-motor and subsequently associative areas [39] which seems to be complete around the age of 9 years, though partially operative even before, as confirmed by the neurocognitive deficits described precociously even in children with congenital [40] or acquired cerebellar lesions [33, 36].

Clinical reports in children and adults showing language impairments following right cerebellar lesions, with consequent reduced verbal fluency [4, 6, 33, 41] and agrammatism [6, 42–45], confirm functional neuroimaging findings that language is lateralized within the cerebellum. For what concerns children specifically, cerebellar lesions of different nature lead to language deficits (together with other

neuropsychological weaknesses), both in the case of congenital or later acquired lesions—mainly tumors [33, 34, 46–48]. However, only a few studies have paid attention to side-specific language deficits after resection of left or right cerebellar tumors [33, 49] and the obtained evidences confirmed a prevalent linguistic dysfunction after right cerebellar surgery also in children.

When the cerebral hemispheric damage occurs very early during development, the probability for a shift of language dominance to the right hemisphere is apparently very high [50] even when the damage does not affect cortical language areas. During this reorganization process, the intact right hemisphere develops a language network involving the topographically homotopic regions of the (normal) left language network. This right reorganization has been demonstrated in periventricular lesions [51], cortico-subcortical lesions of perinatal origin [52], and after hemispherectomy [53], even if other functional patterns after lesions have been described (i.e., intrahemispheric or bilateral reorganization) [54–56].

Atypical right hemispheric reorganization of language has been demonstrated in children with congenital or early left hemispheric lesions by dichotic listening tests [57–61], and by functional imaging studies [62–65]. However, the relatively few fMRI studies on cortical language reorganization after left hemisphere brain lesions showed that damage to the left hemisphere does not necessarily induce a shift of language representation to the right hemisphere [54, 65] and that location and size of lesions may influence on ipsilateral versus contralateral reorganization [66].

This plastic reorganization after damage has been shown not only for cortical supratentorial structures but also for the cerebellum, with the consequent possible shift from right to left cerebellar hemisphere. In 5 adolescents and young adults with congenital left cerebral hemispheric lesion, Lizdaba et al. [50] demonstrated a shift of activation from right to left cerebellar hemisphere and found that the extent of laterality of the cerebellar activation correlated significantly with the laterality of frontal activation. Right cerebral and left cerebellar activation to language tasks also increases during recovery after left hemispheric stroke in adult patients with premorbid left language cerebral dominance [67]. In children with epilepsy, a cerebellar language activation in left cerebellar hemisphere contralateral to cerebral language activation has been demonstrated in case of right or left cerebral language dominance [56].

To our knowledge, no studies have investigated until now the effects on cerebral language functional reorganization in adults or children with lesions primarily affecting the cerebellum.

The aim of this study was to investigate whether the surgical ablation of right cerebellar low-grade astrocytoma could induce change in the cerebro-cerebellar language system as a whole, i.e., intracerebellar reorganization and consequently cortical language regions.

To explore the reorganizational pattern within the cerebrocerebellar language network, we examined the fMRI data and lateralization indices (LIs) in response to silent verbal fluency (SVF) task in children who underwent complete surgery for astrocytoma tumor. We compared the LIs of the pathological sample with an age-matched control group of healthy children who underwent the same fMRI protocol.

Furthermore, using the same task of the functional study, we assess linguistic performance to be correlated with LIs of cerebellum and frontal cortex for each group and with lesion variables (i.e., lesion size and time between surgical intervention and neuropsychological assessment).

## Materials and Methods

### Subjects

**Control Group** Eighteen Italian-speaking healthy children with no history of neurological or psychiatric disease were recruited among the children of the medical and technical staff involved in the study. At the time of pre-processing fMRI analyses, after motion correction of functional scans, three subjects were excluded from the analyses, given the presence of relevant movement artifact occurred during MRI session. This led to a final sample of 15 control subjects (6 females, 9 males; mean age = 12.2 years, SD 1.11, range = 9–15 years). Patients and controls are age-matched ( $p = 0.414$ ).

**Patients** Six out of 12 subjects with acquired right cerebellar lesions agreed to participate to the present study. All of them were Italian-speaking patients (1 female, 5 males; mean age = 11 years, SD 3.8, range = 8–17 years) with stable cerebellar post-operative changes for 5 years following pilocytic astrocytoma (PA) resection (from 13/10/1995 to 17/02/2004) and no evidence of residual tumor. The surgical operation occurred between 23 months and 67 months of age (from 2 to 5 years and 7 months). None of the patients presented any reported post-operative speech or language disorders or motor deficits at any time after the operation, except subject nr. 6 who presented a slight pyramidal hemisindrome. Formal post-operative neuropsychological assessment is available for all patients. Table 1 shows demographic data and neuroradiological findings, displaying localization, side, and size of the cerebellar surgical cavity for each patient.

### Neuropsychological Assessment

**Handedness** Hand laterality was assessed in patients and controls by the Oldfield Handedness Inventory [68].

**Intelligence** All participants, except for 4 controls, performed the full Italian version of the Wechsler Intelligence Scale for

Children-III (WISC-III) [69, 70], supplying full-scale IQ (FIQ), verbal IQ (VIQ), and performance IQ (PIQ) data for each subject.

**Language** All participants had Italian as their first language and did not present speech or/and language disorders at the time of study. All participants performed a phonemic verbal fluency task [71]. Subjects generated as many words as they could which beginning with the letters F and S after a training trial with letter A; 60 s were allowed for each letter, and words for names were not allowed.

### MRI Data Acquisition and Functional Protocol

**MRI Data Acquisitions** Subjects were imaged on a Siemens Magnetom Avanto 1.5 T scanner, using an eight-channel phased-array head coil. Head movement was minimized with decompression cushions.

The imaging protocol included the following sequences: axial PD/T2-weighted images (TR = 3500 ms, TE = 17 ms/84 ms, FOV = 208 × 256 mm, matrix = 208 × 256, slice thickness = 5 mm); coronal turbo spin-echo T2-weighted images (TR = 4100 ms, TE = 143 ms, FOV = 324 × 384 mm, matrix = 324 × 384, slice thickness = 5 mm); sagittal volumetric T1-weighted magnetization-prepared rapid acquisition gradient-echo (MPRAGE) (TR = 1640 ms, TE = 2.48 ms, TI = 552 ms, FOV = 256 × 256 mm, matrix = 256 × 256, 160 sagittal slices, voxel size = 1 × 1 × 1 mm).

Functional images were acquired with a gradient-echo echoplanar sequence (TR = 3950 ms and TE = 50 ms). A series of 100 functional volumes, each of 25 4-mm oblique axial slices with 2 × 2 mm in-plane voxel size, aligned along the commissural axis and covering more than 90% of the cerebellar volume, the temporal and the frontal lobes, were acquired in interleaved order. The frequency-encoding direction was in the cranium-caudal way, while the phase-encoding direction was in the latero-lateral way. Prior to functional imaging, first- and second-level shimming were performed using the slice packet as volume-of-interest.

For patients, a senior neuroradiologist inspected each subject's structural MRI acquisitions to exclude the presence of residual tumor, as well as to assess the side, size, and site of the surgical cavity. The size of the lesion has been determined as the volume of the surgical cavity: the three maximum diameters (antero-posterior, lateral-lateral, cranio-caudal) were provided based on the structural MRI acquisitions and the volume has been calculated as the product of the three diameters. The site of the lesion was determined using the cerebellum anatomical atlas developed by Schmahmann et al. [72].

Supratentorial abnormalities such as ventricular dilatation or signal alterations were also assessed on visual inspection basis. Neuroradiological observations are summarized in Table 1.



MRI acquisitions obtained for healthy subjects were similarly reviewed.

### Functional Magnetic Resonance Imaging Stimuli and Protocol

The experimental paradigm consisted of 6 repeated cycles of two experimental SVF tasks followed by the rest task (block design, time-course series of 20 s each, total duration of the paradigm 6.40 min). Visual stimuli were generated and presented by the e-Prime software (Psychology Software Tools) and MR-compatible glasses were provided to each subjects during the acquisition. Luminance, color, shapes (Arial font), and size (font “96”) were carefully balanced between the language task and the rest condition. Participants were asked to silently generate a words beginning with a letter F-M-R-I-L-A (fonemic fluency). Stimuli were presented at 0.2 Hz (1/5 s), 6 stimuli per block, for a total of 18 stimuli for each paradigm. Rest condition consisted of passive watching of a string of capital× letters (XXXX) presented at the same time frequency as the task stimuli. All subjects received detailed instructions and a short training prior to the experiment.

### fMRI Data Analyses

fMRI analyses were performed using the software package Brain Voyager QX Version 2.0.7 [73]. For the control group, after the realignment of all volumes, the functional data were pre-processed (spatial smoothing, temporal filtering, slice scan time correction, motion correction. Smoothing was performed using an isotropic Gaussian kernel with a width of 5 mm) and were co-registered to the respective high resolution T1 anatomic images of each subject. Then, functional images were transformed into Talairach standard space for reporting locations of activated brain regions and for averaging data across subjects. Statistical analyses were performed at the single subject and at group level using a random effects approach, to ensure the generalizability of the results at the population level.

At the first level, the SVF blocks were modeled as predictors using a canonical hemodynamic response function and its time and dispersion derivatives. Six movement parameters were also included in the model as regressors. Parameter estimates were calculated and single-subject contrast maps were obtained. For the second-level random-effect group analysis, each subject’s contrast image was entered into a one-sample t-test to examine effects across the whole group. The significance threshold was set at  $p < 0.05$  (FDR corrected) and clusters smaller than 5 voxels were discarded.

Given our main interest on studying the frontal and cerebellar functional activation to language tasks, the whole group functional data were further processed performing ROI-GLM analyses, to examine more specifically the cerebellar and frontal activation patterns in both hemispheres. With this tool, the bilateral cerebellum and frontal lobe could be examined as

regions of interest (ROI) and specific activation clusters surviving  $p < 0.05$  (FDR corrected) significance threshold could be derived. To perform ROI-GLM analyses, we derived four anatomical VOI masks, one for each region for each hemisphere (left and right cerebellum, left and right frontal lobes); each mask originated by its respective ROI, manually drawn on a standardized anatomical image (see below for ROI drawing procedure). Each VOI mask was then entered into separated random effects group GLM, restricting the analyses to each specific region.

For the patients’ group, given the small number of subjects relative to the control group, fMRI analyses were limited to the standard pre-processing (motion and slice time correction, temporal filtering, spatial smoothing with a Gaussian kernel of 5 mm width) and first level contrast maps of activation to SVF task calculation, without intersubject averaging of data; thus, the normalization step was inappropriate [74]. Moreover, the patient nr. 6 reported a large post-surgical lesion (Fig. 5) leading to significant anatomical alterations that made the spatial normalization step unsuitable. Single-subject activation maps were than inspected and localized for each subject by a senior neuroradiologist (AE).

For both controls and patients, we performed a single subject ROI activations extraction in the cerebellum and in the frontal lobe of both hemispheres to derive single subjects LI.

### Extraction of Single Subjects’ Region of Interest Activations and LI Calculation

Anatomical ROIs were defined by manually tracing the structures on a standardized anatomical image (for ROI-GLM group analyses) and on each subject’s anatomical volume (for the LIs calculation). A stereotactic atlas (automated anatomical labelling; [75]) was used as anatomical reference and the good fit in each patient data set was verified through visual inspection.

The cerebellar region was defined by visualizing the anatomical T1-weighted image in the three planes and drawing in the axial plane. It included the cerebellar anterior and posterior lobes and the vermis. The two hemispheres were defined by dividing the cerebellar region along the medial plane. The frontal region was defined by visualizing the anatomical T1-weighted image in the three planes and drawing in the axial plane. For each hemisphere, the frontal ROI included the superior, middle and inferior gyrus, pars opercularis, triangularis, and orbitalis. The posterior boundary was set to the precentral sulcus.

Although language tasks have been mainly associated with the inferior/middle frontal gyrus activity, a recent meta-analysis of 28 fMRI studies investigated the cerebral correlates of SVF in healthy controls [76] and found the additional implication of left superior frontal gyrus, together with the inferior/middle frontal gyrus. For these reasons, also giving

the explorative nature of the present study, we decided to include all the above described regions in the frontal ROI.

For each ROI, the percentage of activated voxels weighted for the corresponding  $t$  value was calculated both at three significant thresholds ( $p = 0.05$  uncorrected;  $p = 0.001$  uncorrected;  $p = 0.05$  with FDR correction for multiple comparison), in order to confirm that the results were not due to a particular cut-off.

In order to assess the lateralization of the activations, for each ROI and for all the subjects, a lateralization index (LI) was calculated as

$$LI = [(x_{\text{left}} - x_{\text{right}}) / (x_{\text{left}} + x_{\text{right}})],$$

where  $x$  is the percentage of activated voxels weighted for the corresponding  $t$  value within a selected ROI for each threshold value. Positive or strongly positive LIs indicate that the activation is in the right hemisphere. Negative or strongly negative LIs indicate activation of the left hemisphere and sharp lateralization. The absolute value 0.20 is commonly used as threshold for definite lateralization, while values of  $|LI| \leq 0.20$  represent “bilateral,” or, rather, indefinite lateralization. Indices between +0.2 and -0.2 are generally considered as indicating bilateral language representation [77].

In the following results, LIs are shown at  $p = 0.05$  FDR activation threshold.

## Correlation Analyses of Lateralization Indices

Statistical analyses were employed by the SPSS Statistics 20 software [78]. Given the normal distribution of each variable, we investigated by Pearson correlation the association between LIs of cerebellum and frontal cortex for each group, and the association between LIs, neuropsychological performance and lesion variables (i.e., lesion size and time between surgical intervention and language test).

Independent sample  $t$  tests were performed to compare cerebral and cerebellar LIs between patients and controls. Statistical significance were considered at  $p < 0.05$ .

## Results

### Healthy Subjects

**Handedness** All healthy subjects were right handed except for two being left handed.

**Neuropsychological Performance** Verbal IQs (mean = 108; SD = 18) and phonological fluency test performances (mean = -0.29; SD = 1.11) were in the normal range.

**Group Activation to Language Task** As explained above, we investigated frontal and cerebellar activation by mean of ROI-masked GLM group analyses. ROI results confirmed the whole brain activation pattern (Fig. 1), showing frontal left sided activations in inferior frontal gyrus (IFG)—pars triangularis and opercularis—insula, precentral gyrus, and SMA, together with right-sided activation in the IGF/insula. Right sided activations in cerebellum were located in the lobule VI and Crus 1, together with the cerebellar vermis. Group activations by mean of ROI analysis are shown in Table 2.

**Lateralization Indices** Control subjects' language LIs based on the activated voxels at FDR corrected 0.05 showed a sharp left lateralization for frontal region and right lateralization for cerebellar region.

Two-tailed correlation and linear regression analyses between cerebral and cerebellar LIs in healthy subjects showed that the right lateralization in the cerebellum correlate with the left lateralization in the frontal lobe in SVF task (Fig. 2a: Pearson  $r = -0.78$ ;  $R^2 = 0.61$ ;  $p$  value = 0.001). No significant correlation was found between LIs and IQ or fluency test performance.

### Patients

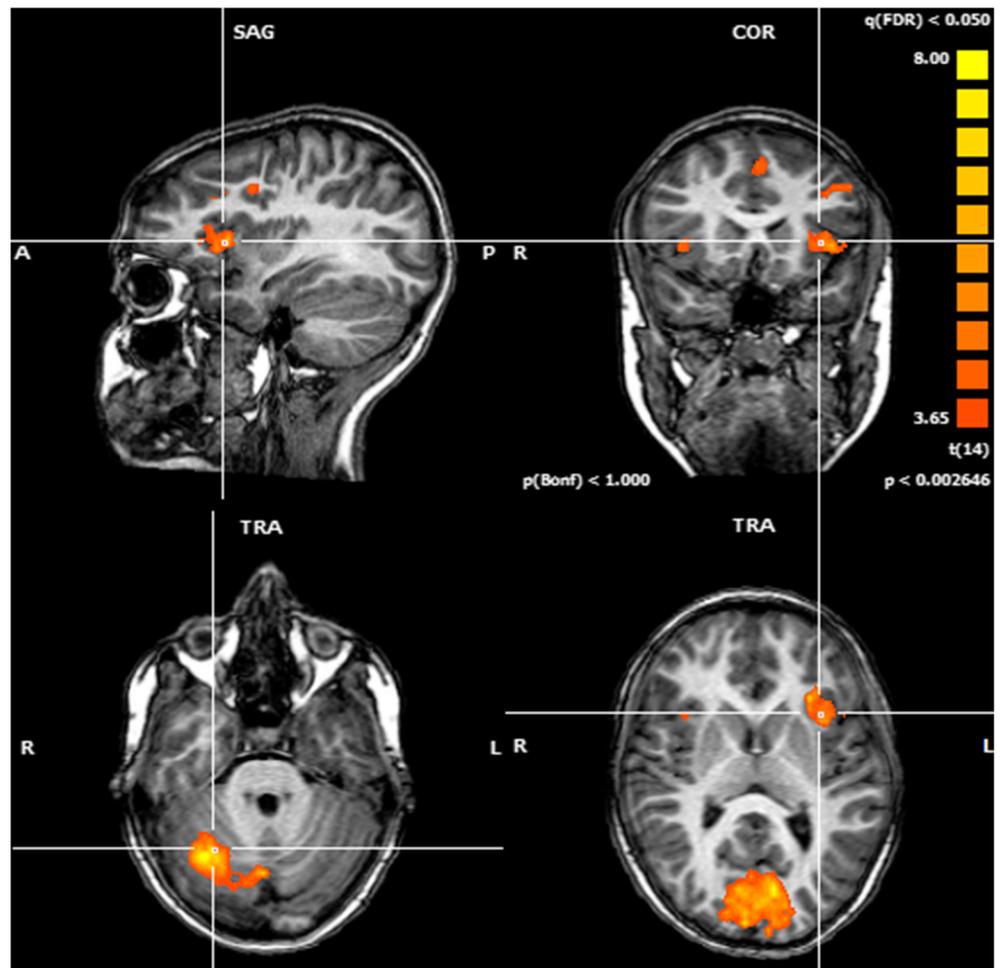
**Handedness** Four patients were right handed, one was ambidextrous (nr. 4) and one left handed (nr. 6). Patient nr. 6 prior of the intervention presented a right pyramidal syndrome due to perinatal asphyxia (Apgar 5/7—primary resuscitation), with subsequent pathological left handedness, in absence of a family history for left or mixed handedness. The other patients had no history of bilateral or left handedness in their families.

**Neuropsychological Performances** Table 1 shows for each patient verbal IQs and performance at language test together with fMRI LIs. Children had IQ ranging between 69 and 101. Performance at SVF task is expressed in  $z$  scores.

**Single Subjects Activation to Language Tasks** As explained above, given the small number of subjects relative to the control group, fMRI group analyses were inappropriate for the pathological sample. Here, we summarize the single subject activation to the SVF task as inspected by the senior neuroradiologist.

For what concerns the cerebellum, activations were recorded in right Crus I, Crus II, and lobule VI but also in the vermis (lobules IV, V, VI, and VII). Left cerebellum (Crus I; Crus II; lobules IV, V, and VI; and vermis lobules VI and VII) was activated in 5 patients. Two patients (nr. 1 and 2) showed a prevalence of activations in the right cerebellum and the patient (nr. 6) with largest

**Fig. 1** Brain activation to language task in healthy controls. Sagittal, coronal, and axial views of fMRI whole brain activation during silent verbal fluency task. Group activation map is superimposed on a standardized anatomical image. Bilateral activations in the visual cortices, left side activations in inferior frontal gyrus (IFG), insula, precentral gyrus, supplemental motor area (SMA), right-sided activations in the IGF/insula, and right-sided activations in cerebellum (lobule VI and Crus 1, cerebellar vermis). Results are displayed at  $p < 0.05$  FDR-corrected threshold



right cerebellar surgical cavity showed activations almost only on the left side (Crus I, Crus II, and VI lobule).

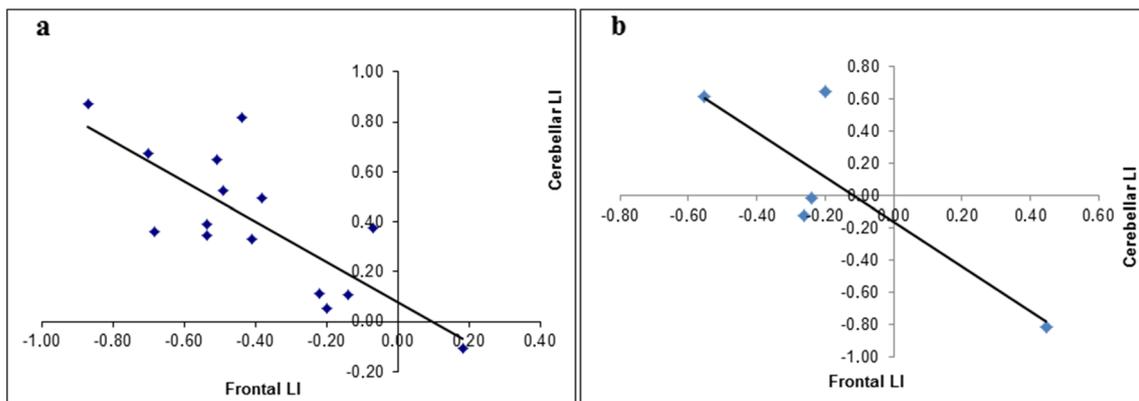
Left IFG (pars opercularis, triangularis, orbitalis) and insula and contralateral regions of the right hemisphere (although

**Table 2** Regions of interest's activation to language task in healthy controls

Brain structure and localization of peak voxels	<i>x</i>	<i>y</i>	<i>z</i>	<i>t</i> value	Cluster size (voxels)
<b>Frontal VOIs</b>					
Insula_L/Front_Inf_L	-27	26	7	8.96	1179
Front_Inf_Tri_L	-36	23	7	5.27	
Front_Inf_Oper_L	-45	17	4	4.26	
Precentral_L	-39	2	31	7.24	482
Sup_Motor_Area_L	-9	8	46	6.29	593
Insula_R/Front_Inf_R	39	17	4	4.69	136
<b>Cerebellum VOIs</b>					
Cerebellum R (peak at cerebellum_6_R)	30	-55	-29	9.89	10,413
Crus_1_R	33	-51	-29	6.65	
Vermis_6	0	-64	-26	8.43	
Vermis_9	3	-52	-32	4.77	406

Clusters and voxels peak of activations surviving (FDR corrected)  $p < 0.05$  threshold after masking for frontal and cerebellar VOIs (volumes of interest) are shown. Peak activation voxels are identified by Talairach Atlas coordinates

*L* left, *R* right



**Fig. 2** Correlation analyses between cortical and cerebellar lateralization indices in healthy controls and patients. Positive Lateralization Indices indicate right lateralization, while negative lateralization indices indicate

left lateralization. **a** Healthy subjects ( $N = 15$ ). **b** Patients ( $N = 5$ ). Results are displayed at  $p = 0.05$  FDR-corrected threshold

with lower intensity and extent than left side activations) were activated in all patients. Bilateral SMA, precentral gyrus, superior and middle frontal gyri, and anterior cingulate gyrus were also activated.

Figures 3, 4, and 5 show the pattern of activations superimposed on the anatomical image for each patient. Patient nr. 3 PnL is not displayed giving the absence of distinguishable activation to the language task in the cerebellum, likely for a poor adherence to the trial during the scan.

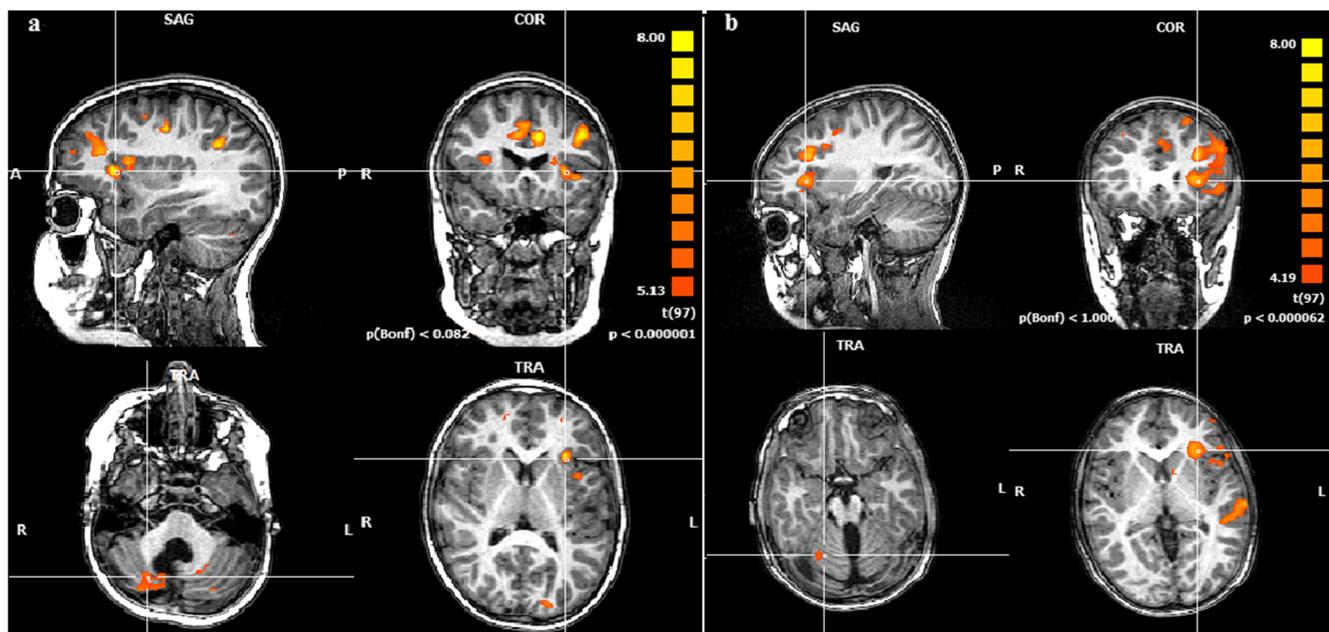
**Lateralization Indices** Table 1 shows the patients' LIs of frontal and cerebellar areas at  $p = 0.05$  FDR activation threshold.

In two patients, the typical pattern of right lateralization in the cerebellum and left lateralization in the frontal

lobe can be observed. Two other patients showed bilateral activation, while in patient nr. 6, the left lateralization in the cerebellum corresponds to right lateralization in the frontal lobe.

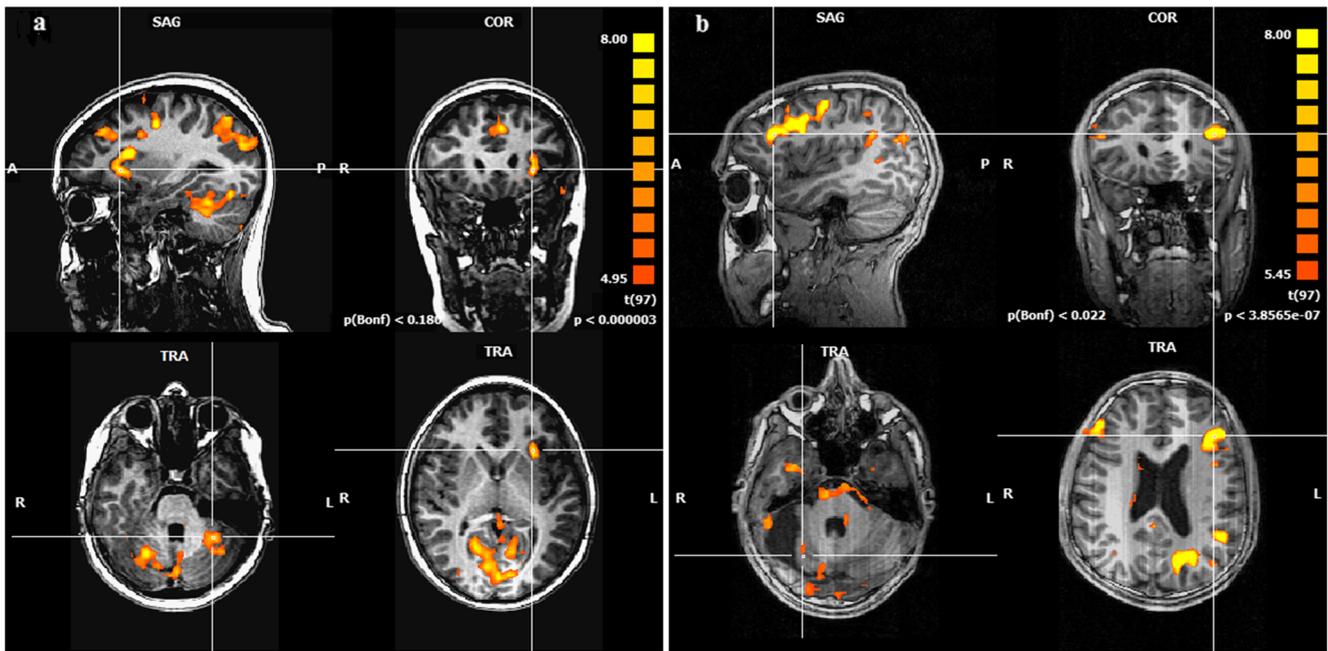
Patients' LIs two-tailed correlation confirmed that the right lateralization in the cerebellum correlate with the left lateralization in the frontal lobe with a trend to significance (Fig. 2b; Pearson  $r = -0.84$ ,  $R^2 = -0.71$ ,  $p = 0.07$ ).

**Correlation between LIs and Clinical Variables** No significant correlation was found between fMRI LIs and verbal IQ, language performances, age at neuropsychological evaluation, size of the lesion, and time passed between the neuropsychological test and the surgical intervention.



**Fig. 3** Brain activation to language task in patient AA and patient PdL. Sagittal, coronal, and axial views of fMRI during silent verbal fluency task in patient nr. 1 AA (**a**) and nr. 2 PdL (**b**). Activation maps are

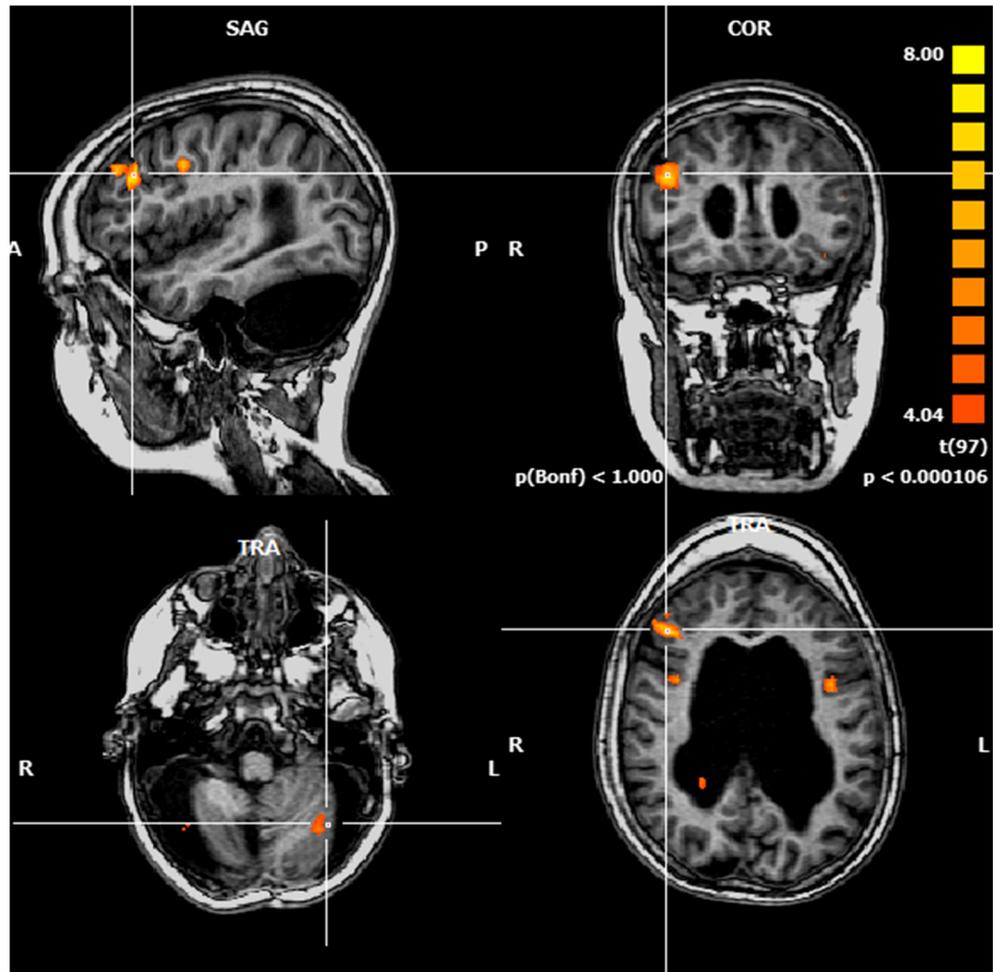
superimposed on T1-weighted image. Both patients show left lateralized language in frontal lobe and right lateralized activations in the cerebellum



**Fig. 4** Brain activation to language task in patient RE and patient MG. Sagittal, coronal, and axial views of fMRI during silent verbal fluency task in patient nr. 4 RE (a) and nr. 5 MG (b). Activation maps are

superimposed on T1-weighted image. Both patients show left lateralized language in the frontal lobe and bilateral cerebellar activation

**Fig. 5** Brain activation to language task in patient FS. Sagittal, coronal, and axial views of fMRI during silent verbal fluency task in patient nr. 6 FS. Activation maps are superimposed on T1-weighted image. Right lateralized frontal activations and left lateralized cerebellar activation



## Patients vs. Healthy Subjects Comparisons

**Neuropsychological Performances** Mean verbal IQ and phonemic fluency scores are significantly impaired in patients compared to controls (verbal IQ  $p = 0.02$ ; verbal phonemic fluency  $p = 0.02$ ). Only 2 subjects (AA1 and MG5) show a manifest impairment in phonemic fluency tasks (lower than 1.5 SD).

**Lateralization Indices** Mean (SD) frontal and cerebellar LIs in SVF paradigm were, respectively,  $-0.40$  (0.28) and  $0.40$  (0.28) for healthy subjects and  $-0.08$  (0.39) and  $0.06$  (0.60) for patients.

Comparisons between the two groups showed that cortical and cerebellar LIs differed between healthy subjects and patients (see Fig. 6). Specifically,  $t$  test analyses showed that frontal and cerebellar lateralization was lower in patients than in controls ( $p = 0.042$  and  $p = 0.289$  for frontal and cerebellar ROIs, respectively). In patients, a decrease lateralization in the operated cerebellar hemisphere seems to correspond to a decrease lateralization in the frontal lobe. High standard deviations reveal the wide variability in patients' reorganization pattern.

## Discussion

The present study provides for the first time insight about the cerebro-cerebellar language network reorganization after lesion primarily affecting the cerebellum, by conducting a fMRI investigation of six children with removed right cerebellar (five subjects) and vermian (one subject) low-grade astrocytoma, compared to 15 aged-matched controls.

By means of a fMRI paradigm of phonological covert word production, we demonstrated that (a) healthy children present right lateralized activation in the cerebellum and left

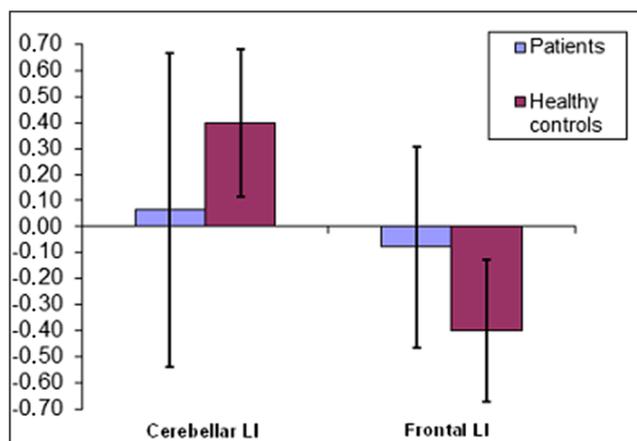
lateralized activation in the frontal lobe, as described in adults [17, 18], sustained by inverse correlation between frontal and cerebellar LIs; (b) functional reorganization of language network in patients presents highly variable LIs: one subject did not show significant cerebellar activation to the language task and presented right lateralized activation in the frontal lobe; three subjects showed a right intrahemispheric reorganization in the cerebellum, two of them maintained language representation in the right cerebellum and left cerebral hemisphere, one left handed maintained activations in the left cerebellum and right cerebral hemisphere; and two subjects showed a bilateral distribution of cerebellar activations, with a left frontal representation of language. LI pattern in the patients' group confirms the inverse correlation between frontal and cerebellar indices but show a general decreased LIs compared to controls in both frontal and cerebellar regions. No association has been found between LIs and age at surgery, age at neuropsychological evaluation, time passed between test and surgical intervention, language and IQ performances, and lesion size.

To discuss our results, we have to consider the typical developmental processes of specialization and lateralization of the language system, to evaluate whether the system have reached its stability to be sure to evaluate reorganizational and not developmental processes. This issue is particularly relevant given the age range of our subjects, between 8 and 17 years, and the even earlier age at surgery.

The crossed cerebro-cerebellar pattern of activation found in our sample of typically developing and intelligent subjects, without familial left handedness, has been demonstrated in several functional studies in healthy adults [4, 18] and children with epilepsy [56] and translates the organization of the cerebro-cerebellar network, in which cortical and cerebellar structures seems strongly related during development [38].

The absence of association between LIs and both chronological age and language performance is in contrast with previous results on typical children and adolescence [79], showing an increasing supratentorial lateralization from 8 up to 20 years and better cognitive performance related to magnitude of LIs. However, brain functional lateralization is not supposed to exactly mirror functional specialization: specialization might not only result from an enhancement of activation in some areas, but from a decrease of activation in others, possibly derived from the so-called pruning process occurring in developmental age [80]. The lack of these effects could be also ascribable to the small statistical power due to the small sample; on the other hand, it could confirm that the functional system is at the same maturational stage for all subjects and that we are looking at reorganization in patients rather than developmental processes.

It is well-known that cerebellar lateralization seems to mirror the developmental pattern of cortical regions involved in language function and that the cerebellar structures support the executive aspects of language (including verbal fluency)



**Fig. 6** Patients vs. healthy subjects comparisons of lateralization indices. Positive lateralization indices indicate right lateralization, while negative lateralization indices indicate left lateralization. Results are displayed at  $p = 0.05$  FDR-corrected threshold

sustaining the view that the two associative areas develop by neurogenetically tracking one another [38].

The growth of these regions in the human cerebellum may parallel the expansion of association cortex, including prefrontal cortex [81].

According to the focal network theory, the underlying neural network structure for language processing is generally well established by the age of 5 [82], with first evidence of network structure already in newborns [83]. Moreover, reciprocal connections between cerebellum and the cerebral cortex become active very early during development. Cerebellar activation is detectable by 4 years [30] and studies in pediatric population evidence cognitive deficits in cerebellar lesions since preschool age [19]. Moreover, the degree of intrinsic functional asymmetry of the cerebellum across individuals is significantly correlated with cerebral asymmetry and varies with handedness. In addition, cerebellar asymmetry estimated at rest predicted cerebral lateralization during an active language task. These results demonstrate that functional lateralization is likely a unitary feature of large-scale cerebro-cerebellar networks, consistent with the hypothesis that the cerebellum possesses a roughly homotopic map of the cerebral cortex, including the prominent functional asymmetries of the association cortex [38].

For what concerns the pathological sample, the absence of an association between age at surgery and age at testing and LIs, representing the level of specialization, despite biased by small numbers, reveals that the age at which the lesion occurred did not influence the development of language system. At a group level, patients' LIs are less lateralized compared to controls, but there is still a linear correlation between cerebellar and frontal indices, confirming that also in pathological conditions asymmetry is a unitary feature of the cerebro-cerebellar network.

Among patients, we evidenced three groups on the basis of different reorganization patterns of cerebro-cerebellar network after lesion: subjects nr. 1, 2, and 6 did not change their configuration after the lesion, while subjects nr. 4 and 5 showed a lateralization shifting with more bilateral (decreased) activation in both cerebellar and frontal regions.

Subject nr. 3 showed no activation in the both cerebellar hemispheres and right lateralization in the frontal lobe (still deriving from a very small activation area). This not very robust activation could simply translate as poor adherence to the trial during the scan. Alternatively, it could be interpreted as developmental immaturity of the automatization of speech initiation, as already discussed in previous fMRI studies on children [56, 84].

The sub-groups of patients showing different post-lesion configurations are heterogeneous both in terms of the cerebellar areas involved in the lesion, extension of the lesion, laterality, and age at the time of surgery. We found an unclear association between these variables in our sample, as the

reorganization pattern that follows different directions for each individual subject both in terms of contralateral shifting and linguistic functional outcomes. For example, among the patients who maintain the pre-intervention configuration, there are two right-handed subjects with lesions of medium size, involving different areas of the cerebellum (nr. 1 posterolateral, nr. 2 vermis)—one operated before 3 years of age and the other after 7 years—and a pathological left handed with a very extensive lesion (nr. 6), operated at a very early age (23 months). Only subject nr. 1 showed impaired verbal abilities, probably associated to the involvement of the linguistic cerebellum (lesion in lobule VII—divided into Crus I and Crus II). The absence of contralateral shifting despite the involvement of right relevant structures for language processing may be related to the partially interrupted contralateral connections from the cortex to the superior cerebellum, passing by the dentate nucleus [8]. In accordance, subject nr. 2 shows verbal abilities in the normal range, probably associated to the localization in the vermis, whose role in modulating linguistic processing is still under debate [31, 46]. For what concerns subject nr. 6, who present a surgical cavity so extended that the right cerebellum—including cognitive areas Crus I and Crus II—is almost absent, his pre-operative typical language representation in the right cerebellum and left frontal lobe has been strengthened, as confirmed by his strong LIs and good linguistic outcomes.

Among the patients who modified the pre-intervention lateralization pattern, we have a right-handed and a mixed handed subject, both operated around 5 years of age but with dissimilar lesions in terms of sizes and locations. The mixed handed patients nr. 4 has a lesion involving the sensorimotor (and not linguistic) cerebellum. Even if the lesion involves sensorimotor and not cognitive areas, we argue that the bilateral representation in the cerebellum could be derived by reorganizational processes after the lesion and that it is not correlated to mixed handedness, because the frontal LI is still left lateralized. A weaker cerebellar asymmetry compared to cerebral asymmetry has been described by Wang et al. [44]. In accordance with the authors, a possible explanation could be that functional asymmetry is primarily driven by the cerebral cortex, as the cerebellum simply echoes this specialization. Subject nr. 5 shows impaired linguistic performances coherent with the involvement of the linguistic cerebellum (right Crus I and Crus II) and the shifted LI pattern of bilateral cerebellum and left frontal LI, close to being bilateral.

In our sample, the post-injury shifting is not directly explained by lesion localization: the involvement of areas of the post-lateral cognitive cerebellum is present both in patients who maintain the initial configuration (nr. 1 and 6) and in those that show a bilateral shifting (nr. 4).

Moreover, in our subjects, the presence/absence of contralateral shifting does not seem to solely predict a preserved functional outcome, since low linguistic performance are

present in subjects both maintaining and shifting the pre-surgical lateralization pattern. We did not replicate in subjects with right cerebellar lesion the well-reported finding in subjects with left cortical lesions about better functional recovery of language with ipsilateral reorganization than with a contralateral shifting [27, 28, 85], probably as a result of the weak statistical power of our study.

Briefly, the reorganizational pattern of the cerebro-cerebellar system in case of right cerebellar lesion does not seem to follow predictive rules linked to the lesion site or size, or to handedness. This pattern is similar to what is described in left supratentorial lesions in which also a direct involvement of Broca's area does not necessarily shift to right language representation and the contralateral shifting does not completely derive by lesion characteristics or localization [54, 64, 65, 86, 87].

Liégeois et al. [54] investigated 10 patients with early left hemispheric lesions, finding that four out of five with lesions in or near Broca's area did not show interhemispheric language reorganization, but showed perilesional activation within the damaged left hemisphere, while lesions remote from the classical language areas were associated to non-left language lateralization in 4 of 5 patients; both handedness and site of electrophysiological abnormalities were not associated. Kadis et al. [86] confirmed this pattern in children with left insult, revealing an anterior language displacement within the frontal cortex. Finally, Raja Beharelle et al. [65] studied 25 children with pre- or perinatal left stroke and found activation in the same left inferior frontal regions that support language in normal children. All these studies sustain that in case of left injury, the language representation often shows intrahemispheric reorganization rather than contralateral shifting [50, 64]. By now, it is controversial whether this process could be referred also to lesions occurring in the cerebellum. As in left supratentorial congenital or early acquired lesions, also in the case of right cerebellar lesions, no variables exists that could constantly predict the contralateral shifting of language representation, and we could take into account not only the type, site, extension, and timing of lesion but also other biological and/or pathological factors that are not clearly evidenced [66].

As the cerebellum is part of the wide distributed language network, the same variability in the reorganization could be found in the cerebellum. In particular, the lesion's localization in cerebellar regions interconnected with supratentorial language areas does not constitute an index of contro-lateral shifting; on the other hand, lesions not located in language cerebellar regions may be associated to a reorganization involving the other hemisphere.

In line with what reported for supratentorial lesion, the localization in eloquent cerebellar area involved in language processing does not seem to have an impact on the

reorganizational pattern, but on the performance in the language domain, as an indicator of system's functioning.

In our sample, patients have significantly lower mean IQ and phonemic fluency scores compared to controls, confirming cognitive and linguistic impairments following right cerebellar hemisphere lesions well discussed above; moreover, only two patients have impaired performances compared to normative data, and this is the case of subjects where the surgical lesion involves Crus I and Crus II (subjects nr. 1 and 5). It is now well-known that cognitive impairments occur when posterior lobe lesions affect lobules VI and VII (including Crus I, Crus II, and lobule VIIIB), disrupting cerebellar modulation of cognitive loops with cerebral association cortices. In particular, a meta-analysis of neuroimaging studies revealed that the cerebellar regions more commonly identified during word generation tasks were the posterior lateral areas of the right cerebellar hemisphere and lobule VI, Crus I, and Crus II [3]. There is converging evidence from patient and neuroimaging studies that the left prefrontal cortex and right cerebellum are both involved in word generation tasks. Word generation deficits have been reported from clinical observations of cerebellar patients [41, 42, 88]. Studies on cerebellar patients with focal lesions have narrowed word generation to right Crus II [88]. Riva and Giorgi [33] found deficient verbal fluency task in children with right hemispheric astrocytoma tumors. These observations are in line with results in subjects nr. 2 and 4, who have good performances and a lesion not involving cerebellar regions implicated in language and cognition. Subject nr. 6 has good language performances despite the entire hemisphere has been disrupted, but was operated very early and thus could have reached an efficient reorganization. Briefly speaking, performances may be impaired if regions implicated in the language network are involved and if the reorganization is not strong enough.

The lesion size does not correlate with neuropsychological data (verbal IQ, fonemic fluency task), nor with LIs in the cerebellum and in the frontal lobe.

The absence of correlation between LIs and lesion size is in contrast with the idea that larger lesions, directly and indirectly affecting both cortex and white matter, would also affect a larger part of the language network and induce its reorganization [66]. However, several further factors are likely to influence the reorganizational pattern, such as lesion localization in cerebellar regions that are functionally involved in the language task. If we observe case by case our patients, in particular those with bigger lesions (nr. 5 and 6) that could influence the specialization shifting [27, 60, 66, 85], both involving Crus I and Crus II, it is evident that a strong contralateral reorganization is associated to good performances.

The current evidences about cerebro-cerebellar network reorganization in children with right cerebellar lesions should be replicated in future studies to overcome the present limitations. Our sample size is small, but recruitment of children

with a long story of illness is never easy, for them and their families, together with the need to exclude 6 subject who refused to participate. However, our sample size is comparable to those presented in other studies [50, 51, 53, 86]. Moreover, the recruitment of the controls among medical staff could have biased the results in neuropsychological testing, even though the mean group performance is still in the normal range. Another weakness is the fact that we could not check the compliance of the children during the covert condition, despite we used training trial and included the same task of laboratory condition in the fMRI paradigm. Finally, collecting fMRI scans before surgery would be useful to study post-surgical reorganization in the light of pre-surgery lateralization. Nevertheless, there also some strengths to the study such as the small range of age, which ensures that the cerebro-cerebellar language system has reached a comparable degree of specialization/lateralization among the subjects. Moreover, we selected children affected by the same pathology with no reported post-operative speech or language disorders or motor deficits (except the patient nr. 6 who presented a slight pyramidal right syndrome caused by perinatal asphyxia), excluding possible confounding factors [89].

## Conclusion

The results from the present study confirmed that functional lateralization of the cerebro-cerebellar language system is globally decreased in subjects with early right cerebellar lesion, though still following a typical pattern, and that also lesions not located in the areas typically involved in language tasks (Crus I and Crus II) can cause reorganization between the two hemispheres or hemispheric language reinforcement of the original lateralization. Furthermore, many variables interact in this reorganization making impossible to a priori predict the possible reorganization patterns. In this view, the investigation of functional connectivity networks (both task related and resting state) could help to find local and distant functional coupling between areas and better define cerebro-cerebellar functional and possible anatomical pathways after the reorganization process. In particular, resting state connectivity analyses would also partially overcome the cooperation limits occurring with subjects of developmental age. The analysis of connectivity networks goes beyond the objective of the present study but it could be an interesting issue to address in further investigations.

With regard to clinical implications, it seems essential to introduce early language rehabilitation programs in children with poor language performance and to refine surgical procedures to localize cerebellar regions involved in language, in order to give the same attention given up to now to cortical linguistic or motor cerebral regions and to minimize post-surgical deficits. Further studies on larger pediatric samples,

ideally undergoing fMRI before and after surgery, could improve our knowledge in this field.

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## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

**Ethical Approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed Consent** Informed consent was obtained by parents for all individual participants included in the study.

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