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## **Focal polymicrogyria in children: contribution of invasive explorations and epileptogenicity mapping in the surgical decision.**

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## **Abstract**

*Objective:* Report of the contribution of invasive EEG (iEEG) and epileptogenicity mappings (EM) in a pediatric cohort of patients with epilepsy associated with focal polymicrogyria (PMG) and candidates for resective surgery.

*Method:* Retrospective pediatric case series of patients presenting focal PMG-related refractory epilepsy undergoing an invasive exploration (iEEG) at Fondation Rothschild Hospital. We reviewed clinical data, structural MRI, and visual analysis of iEEG recordings. Moreover, time-frequency analysis of SEEG signals with a neuroimaging approach (epileptogenicity maps) was used to support visual analysis.

*Results:* Between 2012 and 2019, eight patients were selected. Five patients were explored with stereoelectroencephalography (SEEG) only, one patient with subdural exploration (SDE) only and two patients first underwent SEEG and then SDE.

The mean age at seizure onset was 40.3 months (range 3-120), and the mean age for the iEEG 10.8 years (range 7 to 15). The epileptogenic zone (EZ) appeared concordant to the PMG lesion in only one case, was larger in three cases, smaller in two cases and different in one case. Four cases were selected for tailored resective surgery and one for total callosotomy. Two patients remained seizure-free at their last follow-up (mean 32.6 months, range 7-98). Epileptogenicity mapping (EM) refined the qualitative analysis, showing in four patients an EZ larger than visually defined.

*Conclusion:* This study is the first pediatric study to analyze the value of iEEG and EM as well as operability in focal PMG-related refractory epilepsy. The results illustrate the complexity of this pathology with variable concordance between the EZ and the lesion and mixed response to surgery.

## **Introduction**

PMG is a malformation of cortical development, with an excessive number of abnormally small and partly fused cortical gyri with shallow sulci and abnormal cortical lamination [1]. PMG can be associated with other abnormalities such as corpus callosum dysgenesis, schizencephaly, periventricular and subcortical heterotopia, focal cortical dysplasia, or hemimegalencephaly [2]. The incidence of epilepsy is reported in up to 65-87% of cases. For most patients with PMG-related epilepsy, the onset occurs in childhood, and frequently becomes refractory to medical treatment [3]. Patients can also present a global development delay or motor deficit, depending on the extent and localization of the lesion. When focal, the localization is mainly perisylvian: in the largest imaging study, it is the region of maximal radiologic severity in 65% of patients [3].

Epileptogenicity of the PMG zone appears to be heterogeneous and complex. The epileptogenic zone (EZ) most frequently involves only a part of the PMG cortex sometimes with additional remote cortical areas [4]. It may also fully overlap or include only remote cortical areas, particularly mesial temporal structures or associated cortical malformations [5], [6], [7]. A well-conducted invasive intracranial study then appears warranted in most cases to delineate the EZ, while the neuroimaging studies are less reliable.

Surgical treatment has not been a frequent option so far due to the extent of the malformation and the presence of functional cortex within the lesion [8], [9]. However, recent studies, including a retrospective multicentric study of 58 patients, showed a good outcome after a complete disconnection/resection or tailored resection in well-chosen patients, with 50 to 72% achieving seizure freedom [5, 9], [6], [10], [11], [7], [12]. All those studies included adults or a mixed population of children and adults. A single article was exclusively pediatric [12]. The surgical treatment is likely to have a better prognosis with shorter epilepsy duration

[7]. We could then assume that those patients affected by PMG-related epilepsy should be considered for surgery during childhood as early as possible.

In this paper, we present a series of pediatric patients with focal PMG-related epilepsy referred for surgical considerations. The aim of this study was to assess the contribution of invasive EEG (iEEG) and epileptogenicity mappings (EM) in the evaluation of the EZ and the concordance with PMG in order to guide the feasibility of surgery. We also focused on surgical outcome and follow-up.

## **Patients and methods:**

### *Patients*

From our database, we retrospectively reviewed all the patients with focal PMG-related refractory epilepsy referred for potential resective surgery between 2012 and 2019. Over the same period, a total number of 271 patients underwent a focal surgery for drug-resistant epilepsy of various etiologies. All patients were referred by several neuropsychiatric departments in France and abroad but evaluated in a single centre (Rothschild Foundation) and operated on by two senior neurosurgeons (GD, SFS).

Medically refractory epilepsy was defined as the failure of adequate trials of two antiepileptic drugs appropriately selected and dosed for the patient's seizure type [13].

Inclusion criteria for our study were (1) age under 18 years, (2) diagnosis of PMG on magnetic resonance imaging (MRI), (3) refractory focal epilepsy and (4) evaluation by invasive procedure, either stereoelectroencephalography (SEEG) or subdural electrodes exploration (SDE).

A comprehensive medical history of epilepsy was obtained for each patient. They had pre-exploratory as well as pre- and post-surgical clinical examinations done by a pediatric neurologist. Cognitive abilities were determined based on the clinical examination. They were classified under normal, mild, moderate or severe intellectual deficiency, according to the

DSM V criteria. Every patient underwent a long-duration scalp video-EEG, the recording of all types of seizures being a requirement before iEEG. Information on localization of epileptic discharges and interictal abnormalities was collected. Characteristics of the PMG and other associated malformations were diagnosed by a neuroradiologist on structural brain MRI (3D T1 T2 Flair weighted sequences) in all cases and <sup>18</sup>F-FDG-PET images were analyzed and merged to MRI. If necessary and feasible, functional MRI (fMRI) for language lateralization and motricity was performed.

Based on the results of this work-up, our multidisciplinary team discussed indications and modalities of intracranial exploration and subsequent surgery.

IEEG was used to further delineate the EZ and/or identify a critical area when presumably embedded within the polymicrogyric cortex, either with SEEG or with SDE using few depth electrodes depending on the location of the suspected EZ [14].

A tailored surgery was guided by the results of the pre-surgical investigation, electro-clinical data and structural MRI, aimed at EZ resection. Subtotal resection was intentionally undertaken if the EZ overlapped with functionally eloquent cortex. A callosotomy was offered if necessary as palliative surgery.

Seizure outcome was assessed by the Engel's score [15]. Postoperative neurological deficits and surgical complications were identified for each patient. Patients were followed for three months in our institution, with routine EEGs, MRIs and antiepileptic drug adjustments according to seizure outcomes. They then received yearly check-ups at our outpatient clinic.

#### *Data analysis*

We retrospectively analyzed the patients' charts and contacted them to get the latest outcome. We reviewed all the video and EEG (scalp and invasive) data blindly to the neurophysiologist who wrote the report/completely blind to the neurophysiologist's report. Similarly, MRIs were blindly reviewed by a neuroradiologist experienced in epilepsy surgery. IEEG-recorded

seizures were also analyzed quantitatively using post-hoc Epileptogenicity Mapping (EM) [16]. EM of the explored volume aims at evaluating the propensity of the implanted regions to generate significant HFOs at seizure onset (ictal HFO). The frequency band of interest was visually tailored for every subject by selecting the highest band with significant change of early ictal power in high gamma band, defined within the maximum range of [50 - 170] Hz. After co-registering of electrodes with subject's MRI and local interpolation of iEEG spectral power on a 3 mm isotropic grid, the output of the EM processing [16], [17] is an epileptogenicity map that corresponds to the statistical image of the difference of logpower of ictal HFO between seizure onset and baseline (two-sample t-test). The threshold p-value was set at 0.05, family-wise error corrected for multiple comparisons. Baseline was defined as a period of 20 s devoid of artifacts or epileptic activity selected in a range between 10 and 60 s before the onset. Duration of onset period for EM analysis was set to 4 s.

## Results

From 2012 to 2019, eight consecutive patients were identified, five males and three females.

### *Seizure description (Table 1)*

The age range at seizure onset was 3 months to 10 years (mean 40.3 months).

Seizure frequency was highly variable, from barely one per month to 10 per day. Patients presented one to three different types of seizures. All patients had focal seizures, two of them presenting two different semiologies (patients 1 and 5). The second type was asymmetric spasms which were recorded in two patients (patients 1 and 6). A third patient had a history of spasms in infancy (patient 5). The third type was atypical absences with eyelid myoclonias which were recorded in patient 6. Three patients had focal seizures with evolution to bilateral tonic-clonic seizures (patients 3, 4 and 7). All patients had refractory epilepsy, resistant to at least three antiepileptic drugs.

### *Neurological examination (Table 1)*

Slight to moderate hemiparesis was observed in six patients (patients 1, 2, 3, 5, 6, and 7). All were, however, independently walking. Three patients (patients 5, 6, and 7) were able to use their hand while patients 1, 2 and 3 were limited to palmar prehension. No deficit was observed in case 8 but she had a mild amyotrophy of the left hand.

Two patients (patients 3 and 8) had normal cognitive abilities with learning difficulties in patient 3. Two patients (patients 5 and 6) had a mild cognitive delay and four had a moderate delay (cases 1, 2, 4 and 7). Three patients had an autistic spectrum disorder (patients 1, 4 and 5).

### *Images (Tables 1 and 2)*

MRI revealed unilateral multilobar PMG, with perisylvian involvement in five patients. It was located within the left hemisphere in four patients. In three of them, PMG involved the perisylvian region (cases 3, 5 and 6). In case 3, the PMG was more extended, also involving the central region (**Figure 1, left image**). One was restricted to the central region (case 2, **Figure 2, left image**). Four had right-hemispheric PMG: fronto-insular (case 1), perisylvian-precentral (case 4), fronto-parietal (case 7), and perisylvian-temporal (case 8).

Associated malformations included ventricular heterotopia (case 1), schizencephaly (cases 2 and 5), short corpus callosum (case 4) and focal atrophy (cases 4, 6, and 8). Six cases had no underlying etiology found. One presented an epidermal nevus syndrome with associated occipital lobe hypertrophy (case 7), and one had an unknown disease with progressive hemispheric atrophy associated with congenital PMG (case 8).

<sup>18</sup>F-FDG-PET was performed in four of our patients: the metabolic abnormalities were more extended than the PMG in three patients (patients 3, 4, and 5) and distinct from the PMG in the fourth (patient 8).



Functional MRI (fMRI) (**Table 3**) showed that motricity was located within the PMG zone in patients 2 and 3 and not in patient 6. In patients 2 and 6 there was also a contralateral representation. In the three patients with left-hemispheric PMG on whom an MRI was performed, speech lateralization was on the right (patients 3, 5 and 6).

#### *Scalp EEG (Table 1)*

Scalp video-EEG monitoring lasted two to five days. Interictal and ictal discharge localizations are summarized in Table 1. The ictal onset zone assessed by scalp EEG was concordant with the PMG (patients 1, 2, and 4) or overlapped with the PMG lesion (patients 3, 6, and 7). It was different in one patient (patient 8) and not informative in patient 5.

#### *Invasive explorations (Table 2)*

The mean age during exploration was 10.8 years (range 7 to 15). The mean duration of epilepsy before invasive exploration was 6.7 years (range 4-12.5).

Ten iEEG were performed in eight patients, two of them having been explored twice. Five patients were explored with SEEG only, one patient with SDE only (case 7) and two patients first underwent SEEG and then SDE (cases 2 and 3).

The implantation scheme and interictal and ictal abnormalities are summarized in Table 2. The interictal epileptic abnormalities were always multifocal and extended beyond the borders of the lesion, without clear limits. The EZ strictly corresponded to the lesion defined by the MRI in one case (case 2). The EZ was smaller than the lesion in two patients (patients 1 and 7). The EZ only partially involved the lesion and also included adjacent apparently normal cortex in two cases (cases 5 and 6). The EZ was different than the PMG cortex in case 8.

Three SEEG and one SDE were inconclusive either because no seizure occurred (SEEG in case 2 and SEEG and SDE in case 3) or because only unusual seizures could be

recorded (SEEG in case 4). Case 2 was explored using SDE the following year and seizures were recorded.

In three cases <sup>18</sup>F-FDG-PET abnormalities were more extended than the EZ (patients 2, 3, and 4) and in one it was coherent with the EZ (patient 8).

Results of EM are available for seven patients and presented in **Table 2**. In patient 4, the EZ defined by EM is more limited than in visual analysis, but the study was limited to unusual seizures. In patients 1 and 5, the results are identical with both methods and in patients 2, 6, 7 and 8, EM showed an EZ larger than what was visually assessed (**Supplementary Figure**).

Motor electrical stimulations (**Tables 2 and 3**) were performed in all patients and additional electrical stimulations in four only. When stimulating within the polymicrogyric cortex, two patients had a motor response (patients 2 and 3), none had any speech response, and three had primary somatosensory and insular responses (patients 3, 6, and 8). In patients 3 and 8, seizures could be evoked by stimulating within the EZ (one within and one outside PMG).

#### *Surgery (Table 4)*

Five patients had surgery. Four of them had a tailored resection (patients 1, 2, 3, and 7) and patient 6 had a total callosotomy.

Patient 1 had a total PMG resection in nonfunctional cortex (right fronto-insular disconnection, including motor opercular area). In patient 2, the EZ was concordant with the PMG and a total resection was advised. The motor cortex controlling the right arm had to be sacrificed, but the seizures were very disabling with falls and the child already had a moderate deficit. This decision was discussed with the patient and his parents to carefully weigh the benefits and risks. He therefore underwent a left central resection, sparing the motor cortex controlling the leg, although involved in the PMG. Unfortunately, on the post-operative MRI,

the deepest part of the lesion was left and a second surgery is presently being considered (Figure 2, right image). Patient 7 underwent a right frontal disconnection, sparing the precentral gyrus. Patient 3 had a left operculo-insular resection **(Figure 1, right image).** This decision was based on interictal abnormalities which were clearly focal and on the evocation of regular reported seizures from electrical stimulation in the inferior part of the precentral gyrus (**Table 2**). This zone was checked to be nonfunctional using electrical stimulations.

Patient 6 had at least two lobes implicated in the EZ, with motor cortex largely involved, but with a very discrete hemiparesia. Aggravating the deficit was not an option, so a callosotomy was performed in order to decrease the seizures with falls.

Three patients (62.5%) were deemed ineligible for surgery in our series. Patient 5 had four lobes implicated in the EZ, as the seizures could have different starting points. A left hemispherotomy was then proposed but refused by the family, because of the expected postoperative deficit of the hand. Patient 8 had a focal EZ located in the motor cortex without any motor deficit. Patient 4 did not undergo surgery because no regular seizures were recorded. This last situation was unexpected as the family had reported frequent seizures.

We summarized the results of invasive investigations and surgery in a flow chart (Figure 3).

The sole complication that occurred was in Patient 2. He presented vascular injury during surgery with a subsequent motor deficit of the leg which worsened and then recovered within four months following surgery with an ability to walk unaided. He kept an anticipated motor deficit of the hand.

Histological results were consistent with polymicrogyria in two cases (patients 1 and 7); for patients 2 and 3 the samples were too small to properly analyze cortical architecture and showed rare dysplastic neurons (Table 4).

Genetic tests were done in four patients (2, 3, 7, and 8). They were normal in three; only one patient (patient 7) carried PIK3CA pathogenic variants (p.Glu545Lys).

#### ***Outcome (Table 4)***

For the five surgical patients, the post-surgical follow-up is 32.6 months (range 7-98). Two patients (patients 1 and 3) achieved seizure freedom and improved regarding behavior and development. Patient 1 demonstrated better social interactions and improved language skills, and patient 3 improved academically. Patient 2 remained seizure-free for three months, but then the seizures reappeared with time and became stronger with a relapse of seizures with sudden falling. One year post-operatively, the clinical and EEG conditions were comparable to the presurgical situation. No change was noticed regarding his behavior and autonomy. Patient 7 showed no improvement after surgery. In patient 6, following the callosotomy, the seizures with absences and falls completely ceased; nevertheless, daily focal seizures occurred that were much less disabling. He showed dramatic improvement regarding motor autonomy and quality of life.

#### **Discussion**

In this article, we present eight children with focal PMG-related refractory epilepsy who underwent invasive exploration and, when appropriate, surgery. Our paper presents a small series; however, it is the largest pediatric group of focal PMG cases explored with iEEG. Indeed, Cossu et al. [11] had only five children explored with SEEG, Maillard et al. [7] two, and Jalloh et al. five children explored with SDE [12]. Moreover, we provide data about eloquent areas and their complex relationship with PMG. Lastly, it is the first article with a systematic use of EM in this pathology.

#### **1. Major contribution of invasive explorations in the identification of the EZ.**

Surgery can be performed without preceding iEEG in two particular situations, as reported in previous studies. The first situation concerns patients with extended or hemispheric PMG and

a pre-existing motor deficit. These cases can be treated successfully with a hemispherotomy[18], [19]. The second situation where iEEG can be bypassed concerns rare cases of small-sized unilobar PMG with fully concordant electroclinical findings. These patients are candidates for a direct resection of the lesion, with or without using intraoperative corticography [11], [12], [4]. Apart from these situations, invasive explorations appear warranted and this was the case for all of our patients probably due to the fact that we are a tertiary centre. In our population with focal epilepsies, a direct surgery could never be considered.

Both SEEG and SDE procedures are used in this indication. The advantages of these techniques are known to be complementary and choosing one of them can be challenging [14]. SDE offers the best coverage of the cortical convexity, which is particularly interesting in extended unilateral lesions like PMG to determine the borders of the EZ or its relationships with a functional area, in particular the speech area. This functional cortical mapping is useful in PMG with central or perisylvian localization. PMG indeed often involves motor cortex with preserved functionality but the anatomy of gyri appears malformed and hard to recognize in many cases. fMRI can help to understand the reorganization of functional cortical areas. Bilateral motor representation is also possible [20]. The sampling error related to SEEG can lead to overlooking eloquent cortices and makes SDE a better option in our experience. On the other hand, SEEG allows the exploration of deeper cortical structures often involved in the PMG and is preferred to help define three-dimensional epileptic networks. This is useful in PMG when the involvement of a remote located area is suspected. The strategy for SEEG should follow the general rules, i.e. implanting the suspected EZ, the neighboring regions and the adjacent potential eloquent areas as well as the alternative hypothesis with some electrodes within the lesion [14] . However, as PMG can be extensive, its complete exploration is not an option. Electroclinical data should play a particular role in targeting the

electrodes in the parts of the PMG potentially involved in the seizures. For instance, in patient 3 we only explored a small part of the PMG.

Our study supports the heterogeneous concordance between MRI-defined PMG and the EZ as already pointed out in previous studies, ranging from 0 to 50% [5], [10], [6], [7]. The EZ was fully concordant with the PMG lesion in only one case (12.5%), and was more extended than the PMG lesion with additional MRI-normal cortex in three cases (37.5%), comparable with 16% and 60% respectively in Maillard's series. The EZ was smaller than the PMG zone in two cases (25%) compared to 14% in Maillard's publication. Case 8 presented a very focal EZ apparently involving the motor cortex that appeared normal on MRI. The PMG was therefore not implicated in the seizure onset. Five (10%) similar cases were reported in Maillard's study. This lack of concordance was not predictable in any of our patients following only non-invasive explorations.

In PMG <sup>18</sup>F-FDG-PET seems to be of little help : the metabolic abnormalities showed the EZ in only 25% of our patients in whom it was performed and were so extended in the others that it was not even possible to properly explore all the involved zones. In the largest published study, PET was concordant with the EZ in only 29% of patients [7].

### **Relationship between focal PMG and eloquent cortex**

Coexistence of eloquent cortex and focal PMG is reported in the literature, as assessed by fMRI or electrical stimulations during invasive recording [8], [6], [7]. It was for instance the case in 34% of Maillard's series. Six of our patients had a mild to moderate hemiparesis. All together fMRI and electrical stimulations localized the motor area within the polymicrogyric zone in two patients. Regarding language evaluation, fMRI performed in cooperating patients with left-sided PMG showed a right-sided hemispheric specialization in all of them, and no speech deficits were evoked with electrical stimulation in the left hemisphere. Additionally, in three patients other functional responses were evoked with

electrical stimulations. One should, however, emphasize that electrical stimulations in children, in particular with developmental delays, are properly feasible for motor function only [21]. When children have an important speech delay and we cannot perform either fMRI or electrical stimulations, we hypothesize a right lateralization of speech in case of left-hemispheric epilepsy. Indeed, in the event of early unilateral injury, some authors found evidence of equipotentiality of the left and right hemispheres in the development of verbal and nonverbal abilities [22]. Our study, although comprising only a few patients, provides clues in favor of the previously reported presence of motor functions within the PMG whereas the language functions in all our left-sided PMG patients were shifted to the right hemisphere, illustrating brain plasticity in this specific etiology.

## **2. Focal PMG and surgery**

PMG, although being the most common brain malformation, represents only a small percentage of the patients operated on for epilepsy (in pediatric as well as in adult series). Of the 271 patients who underwent a focal surgery for drug-resistant epilepsy of various etiologies between 2012 and 2019 in our institution, only 3% were PMG patients. In a much larger series involving histopathological studies that spanned 25 years and included 2623 children operated on for all types of epilepsy, PMG was found in only 2.1% of the patients [23]. So the surgical rate is very low in PMG compared with other cortical malformations and acquired pathologies. In our study, only half of the patients were eligible for focal resection, which is low compared to our overall population with various etiologies: all together, we offer surgery in 78% of patients after SEEG [21]. Reasons not to operate on the patients of the present series were anatomico-electrophysiological discordances and the frequent involvement of functional eloquent area. Only two patients had clinical seizures compatible with a perisylvian onset while four had seizures suggestive of a central origin, which made them less accessible to surgery and most of them had widespread interictal and ictal scalp

EEG. In the literature, fewer patients with focal PMG (28 to 41%) were excluded from focal surgery after invasive explorations [5], [11], [7]. This can be related to a mainly adult population (80% in Maillard's paper) and a predominance of unilobar PMG while our patients all had multilobar PMG.

Of our five surgical cases, only two (40%) achieved seizure freedom (Engel I) which is a poor outcome compared to our global results in children explored with SEEG (67% Engel 1, [21]) or iEEG in general (68%, [24]). This is also low compared to the published articles, where Engel class 1 patients range from 50 to 75% [5], [6], [10], [11], [7], [12]. Authors reported outcomes considering partial versus total resection of PMG. According to the literature and our personal experience, the important issue is the total removal of the EZ, and not of the radiological abnormality. In our patients, the EZ was probably not sufficiently well-defined, which could explain surgical failures. Moreover, in one of our patients with a poor outcome, the planned surgery was unfortunately not completed. EM gives clues to the insufficiency of the visual analysis, as both patients who failed surgery had discordant results between quantitative analysis and visual analysis of the EZ. This suggests that this method should be systematically used in those difficult to analyze explorations. The other explanation is the reluctance of our team to create a post-operative deficit in order to cure the patient of his epilepsy. In the above series with successful surgical outcomes, 25 to 64% of patients had a new neurological deficit after surgery.

## **Conclusion**

Performing epilepsy surgery in pediatric patients with PMG-associated focal epilepsy is complex because of a double challenge: the first one is the difficulty in this specific etiology to adequately place the intracranial electrodes and the second is the frequent involvement of eloquent areas which complicates surgical decisions and feasibility. iEEG shows unpredictable concordance between the EZ and PMG, and frequent overlapping of



eloquent cortex, PMG and EZ exists. iEEG can lead to surgical abstention or insufficient resection because of functional risk. EM is of great help in those complex cases and should be systematically used to reach a surgical decision. Larger pediatric studies on selection of surgical candidates and invasive explorations are required.

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**Legends for figures:**

**Figure 1, patient 3:** MRI T1-weighted sequence in axial views showing left perisylvian PMG (left image) and left operculo-insular resection (right image).

**Figure 2, patient 2:** MRI T2-weighted sequence axial views showing left perisylvian PMG (left image) and MRI T1-weighted sequence in axial view showing incomplete left central resection (right image)

**Figure 3:** flow chart summarizing the results of invasive explorations and surgery.

**Supplementary Figure:** Epileptogenicity map (EM) of patient 7. The EM was computed on two seizures in the frequency band 110-170 Hz and is represented in the MNI stereotactic space (left: glass brain, right: subject's normalised pre-operative T1 MRI). Blue dots indicate co-registered electrode contacts. The EM map codes for the T values of the comparison between ictal onset and baseline. For display, the EM map was thresholded at  $T=4.15$ , which corresponds to  $p<0.001$  family wise error corrected for multiple comparisons.

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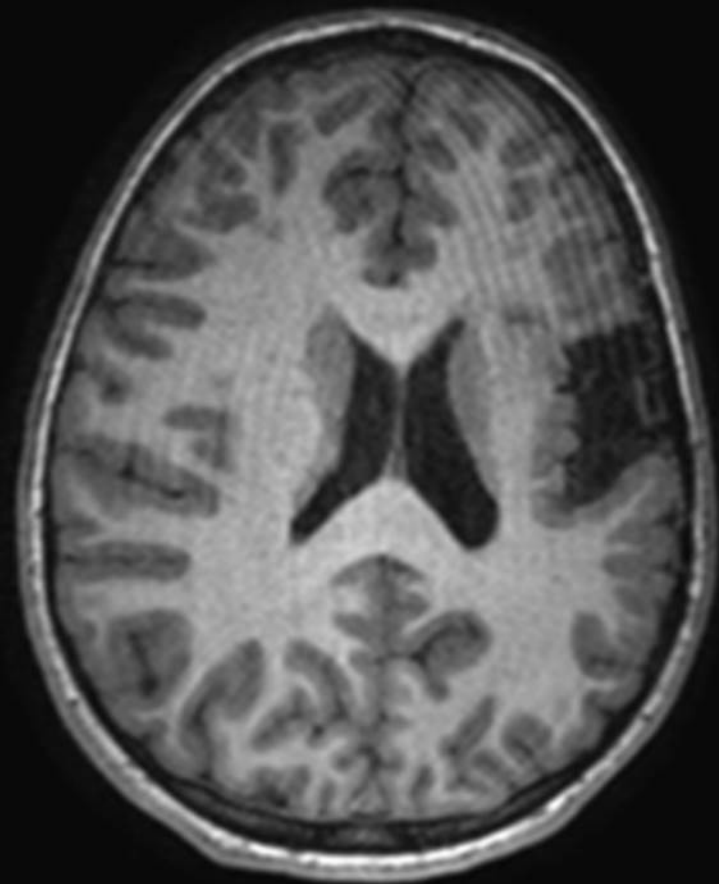
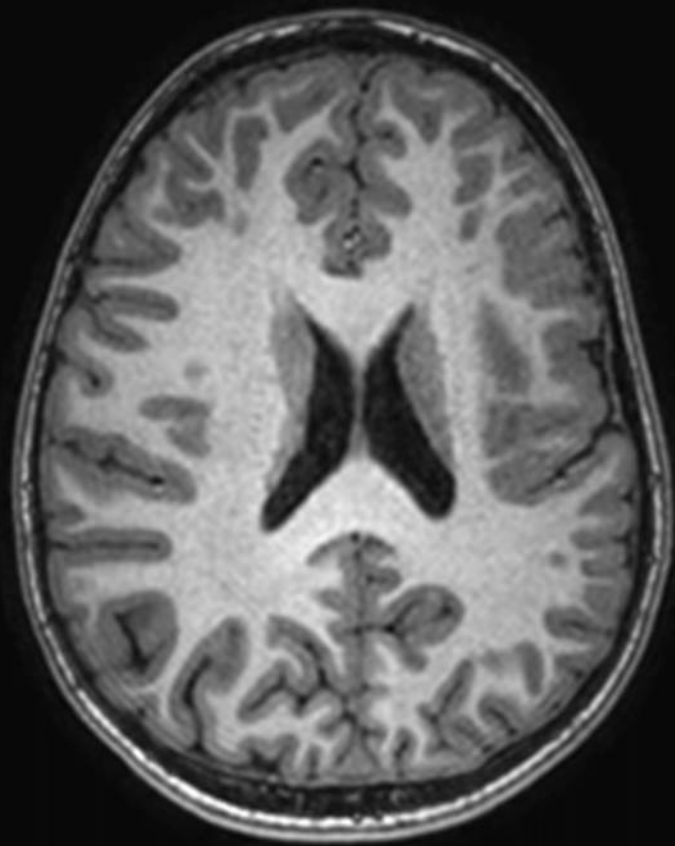
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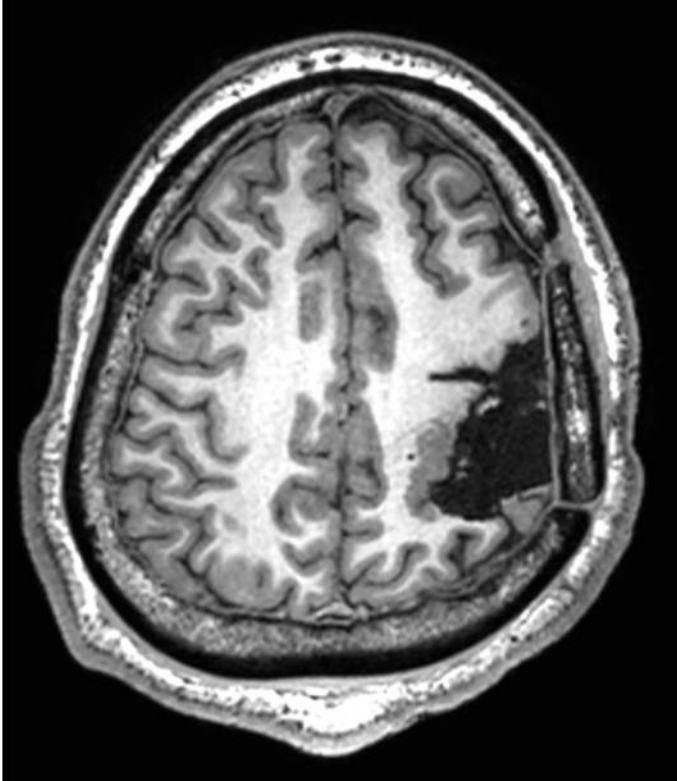
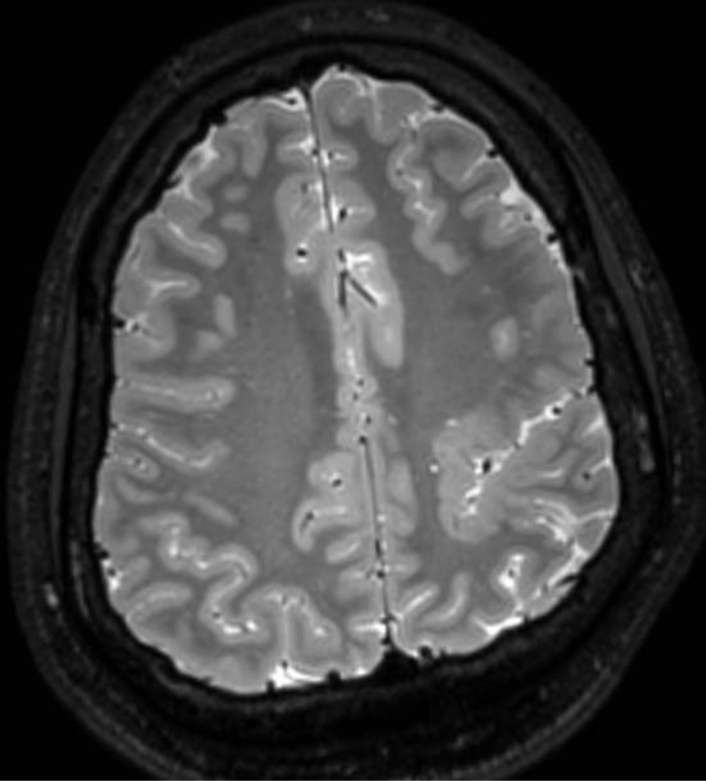
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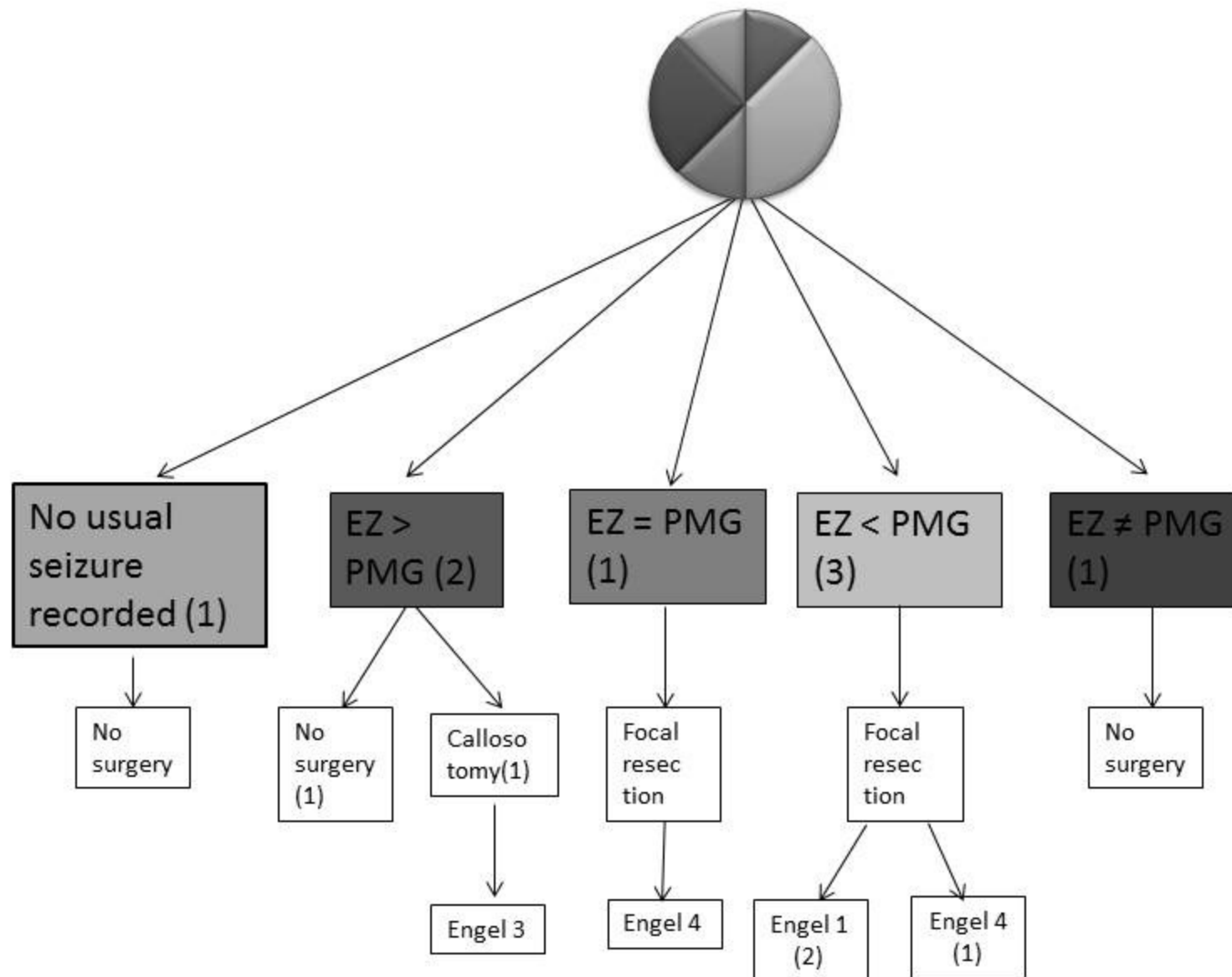
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**8 patients  
explored with  
SEEG**



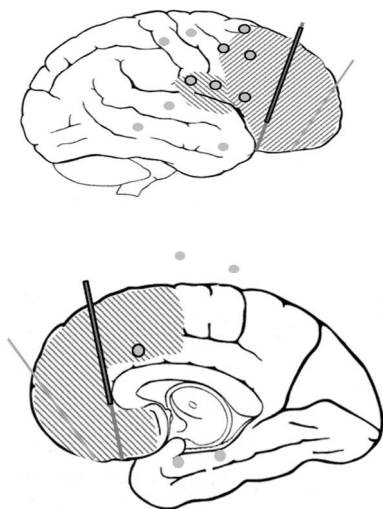
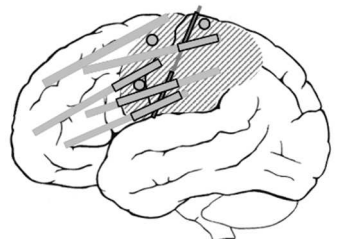


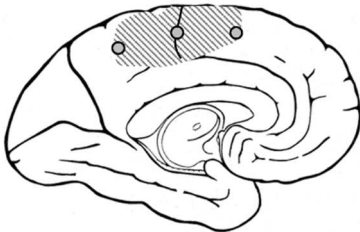
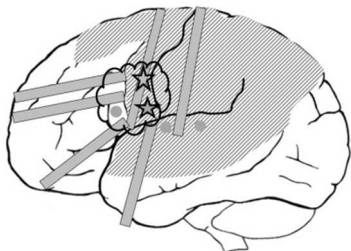

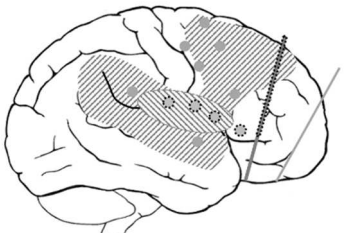
	Age at iEEG (y)	Sex	Duration of epilepsy (y)	Neurological examination at the time of iEEG	<u>Cognitive disabilities</u>	MRI-PMG	<sup>18</sup> F-FDG-PET
1	7	F	6.5	Moderate L hemiparesis with palmar prehension ASD	Moderate	R Fronto-insular	<u>NA</u>
2	15	M	9.5	Moderate R hemiparesis with palmar prehension.	Moderate	L Central (fronto-parietal)	<u>Frontal, central and temporal hypometabolism</u>
3	9	M	4.5	Slight R arm paresis with palmar prehension.	<u>No</u>	L Perisylvian (fronto-parieto-temporal) and central	<u>Extended L hypermetabolism, Frontal, central and parietal</u>
4	7	M	6.5	No motor deficit ASD	Moderate	R Perisylvian-insular-precentral	<u>R frontal, insular, central and anterior temporal hypometabolism</u>
5	13	M	12.5	Slight R hemiparesis, with palmar digital prehension ASD	Mild	L Perisylvian-insular	<u>NA</u>
6	14	M	4	Slight R hemiparesis with palmar digital prehension	Mild	L Perisylvian-insular	<u>NA</u>
7	12.4	F	12	Moderate L hemiparesis with palmar digital prehension	Moderate	R Fronto-parietal	<u>NA</u>
8	9	F	4	No motor deficit. Slight L hand amyotrophy	<u>No</u>	R Perisylvian-temporal	<u>hypometabolism of the R paracentral lobule</u>

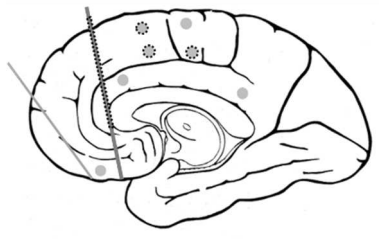
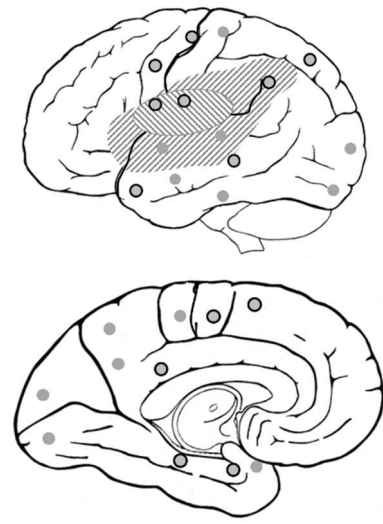
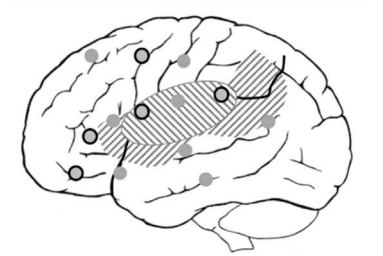
Table 1 : Children with polymicrogyria-related epilepsy who are candidates for surgery: clinical features, MRI and 1<sup>8</sup>F-FDG-PET

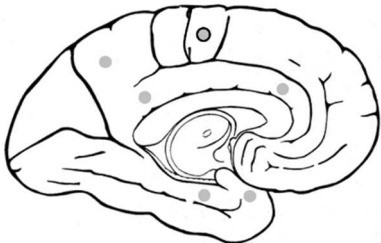
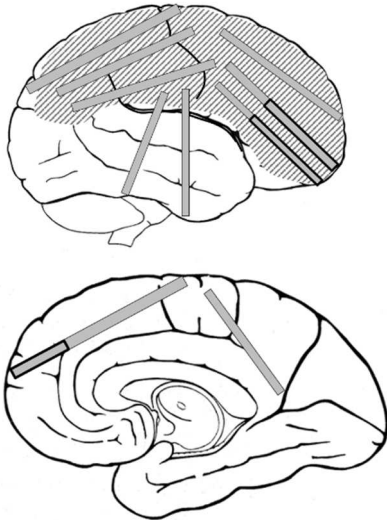
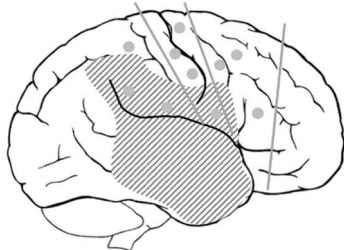
Abbreviations: iEEG: intracranial electroencephalography F: female, M: male, R: right L: left, Y: year, PMG: polymicrogyria, ASD: autistic spectrum disorders, NA: not available

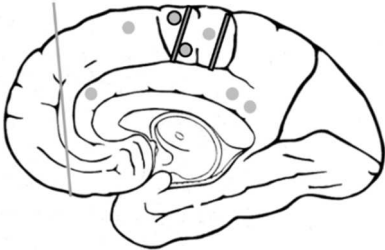
Table 2: Overview of invasive EEG in children with polymicrogyria-related epilepsy: schemas, invasive EEG findings and surgical resections

P a t i e n t	Implantation		Interictal	EZ and EM	PMG/EZ
1	<b>SEEG</b> Right side: Frontal 8e Temporal 3e Parietal 2e		<b>spikes:</b> external temporal, internal parietal and precentral. <b>CED:</b> Fronto-insular <b>LVRD:</b> Fronto-insular, SFG, operculum,	<b>Fronto-insular,</b> including motor operculum  <b>EM:</b> Frontal cortex (orbitofrontal, MFG, cingular anterior cingulum), temporal superior gyrus > paracentral lobule.	EZ<PMG
2	<b>SDE</b> Left side : Fronto-parietal (6 sde, 4e)		<b>spikes :</b> centroparietal ( <u>schizencephalic rim</u> ) <b>CED :</b> post-central gyrus,	Centro-parietal with rim of the schizencephaly  <b>EM:</b> Large frontoparietal	EZ=PMG

					
3	<b>SDE</b> Left side : Frontal : 5 <sub>e</sub> Temporal : 3 <sub>e</sub> Parietal : 5 <sub>e</sub> Operculum : 1 <sub>e</sub>	 	<i>Interictal zone represented by the cloud:</i> <b>CED:</b> parietal operculum, frontal inferior, insula	No spontaneous seizures recorded.  Two regular seizures induced by the electrical stimulations in the precentral gyrus <b>EM:</b> NA	EZ<PMG
4	<b>SEEG</b> Right side: Frontal : 10 <sup>e</sup> <u>Operculum</u> : 2 e Temporal : 1 e Parietal : 1 e		<b>Multifocal spikes:</b> insula, operculum, gyrus rectus, SFG, inferior parietal lobule...	Multifocal but only based on unusual paucisymptomatic seizures: frontal/ insular/ cingulum  <b>EM:</b> frontoparietal cortex around central sulcus.	?

					
5	<b>SEEG</b> Left side : Frontal: 4 e Parietal: 4 e Temporal: 5 e Occipital: 2 e		<b>Multifocal spikes:</b> occipital, parietal, temporal, frontal <b>CED:</b> precentral.	Multifocal : Fronto-insular/ paracentral/ parieto-temporal/ posterior cingulum  <b>EM:</b> large perisylvian involvement + frontoparietal cortex around central sulcus	EZ>PMG
6	<b>SEEG</b> Left side : Frontal : 6 e <u>Operculum</u> : 2 e Parietal : 2 e Temporal : 4 e		<b>CED:</b> insula, MFG, operculum, parietal, precentral gyrus, ITG	Multifocal : Frontal/ insula/ parietal/ temporal sup  <b>EM:</b> central gyrus> perisylvian (mainly IFG and operculum)> paracentral lobule>	EZ>PMG

				mesiotemporal	
7	<b>SDE</b> Right side: Fronto-parietal (10 sde)		<b>Spikes</b> : frontal	Prefrontal  <b>EM</b> : fronto-polar and extended from the frontal mesial region to the motor region	EZ<PMG
8	<b>SEEG</b> Right side: Frontal 7 e Parietal 6 e		<b>Multifocal spikes</b> : frontal, central and parietal <b>CED</b> : frontal anterior.	Paracentral lobule  <b>EM</b> : paracentral lobule, perisylvian region, anterior cingulum	EZ≠PMG

					
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**Legend :**

**CED** : continuous epileptic discharges, **IFG**: inferior frontal gyrus, **ITG**: inferior temporal gyrus, **e** : electrode, **EM** : epileptogenicity mapping, **EZ** : epileptic zone, **LVRD** : low voltage rapid discharges, **MFG** : medial frontal gyrus, **NA**: not available , **ND** : not done, **PMG** : polymicrogyria, **sde** : subdural electrodes, **SFG** : superior frontal gyrus

Figure key: Grey spots and rods represent SEEG electrodes and grid(s) positions. Black borders: epileptogenic zone, Hatched areas: polymicrogyric zone ; stars: areas of evoked seizures with electrical stimulations



**Table 3 : Functional results**

Patient	fMRI		Electrical stimulations			
	Motor	language	Motor area within the PMG	Language area within the PMG	Other functional responses within the PMG	Evoked seizures
1	NA	NA	Not relevant	NA	NA	
2	Activation within PMG; contralateral activation	NA	yes	NA	no	
3	Activation within PMG	R	yes	no	Somatosensory, insular response	Yes, within the PMG
4	NA	NA	no	NA	NA	
5	NA	R	no	no	no	
6	Bilateral activation outside the PMG	R	no	NA	Somatosensory Insular response	
7	NA	NA	no	NA	NA	
8	NA	no	no	no	Somatosensory, insular response	Yes, outside the PMG

Abbreviations: NA: not done or not interpretable (lack of cooperation), PMG: polymicrogyria, R: right, fMRI: functional MRI.

Table 4: surgery and follow-up

	Surgery	<u>Histopathology</u>	Post operative neurological exam	Engel score	Follow-up duration (months)	Schooling
1	Right Fronto-insular disconnection	<u>polymicrogyria</u>	No deficit behavioural improvement	I	98	institution
2	Left Central resection	<u>dysmorphic neurons</u>	Expected right arm motor deficit R hemiparesis following ischemia.	IV	23	institution
3	Left Operculo-insular resection	<u>dysmorphic neurons</u>	No deficit	I	7	Regular school
6	Callosotomy		No deficit	III (no seizures with falls)	16	Special school
7	Right Frontal disconnection	<u>polymicrogyria</u>	Moderate aggravation of L arm and hand	IV	19	Institution