Intrinsic epileptogenicity in polymicrogyric cortex suggested by EEG-fMRI BOLD responses

Abstract—Polymicrogyria (PMG) is a widespread cortical malformation frequently associated with seizures and EEG spikes. Its epileptogenicity is poorly understood. Nine patients with simultaneous EEG and fMRI were studied to assess the blood oxygenation level-dependent response to spikes. Sixteen of 18 studies showed responses, with maximum activation involving the lesion in 61.5%, but often limited to a small fraction of that lesion, suggesting intrinsic epileptogenicity in small areas of the PMG cortex.

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Polymicrogyria (PMG) is a malformation of cortical development associated in 50 to 85% of patients¹ with epilepsy, which can be localization-related or generalized. EEG findings may be diffuse or focal, despite the usually extensive lesion. Epileptogenicity in PMG is still unclarified, and it is not known where the spike generator is located within the widespread lesion. In contrast to other developmental malformations where the epileptogenic focus can be identified and resected, clinical and experimental data do not encourage surgical treatment in patients with PMG. The main structural abnormalities may not be the main epileptic generator and the distribution of epileptic foci may vary with time.

Simultaneous recording of EEG and blood oxygenation level-dependent (BOLD)-fMRI is a new technique that allows evaluation of hemodynamic and metabolic changes related to spikes, and therefore indirectly provides localization of potentially epileptogenic areas.² Our objectives were to determine EEG-fMRI responses

to interictal spikes in patients with PMG and to correlate them with lesion boundaries.

Methods. We studied PMG patients with frequent interictal spikes on routine EEG. Diagnosis of PMG was established by MRI, according to the schema of Barkovich et al.³ Patients underwent a 2-hour recording session after signing informed consent. EEG was continuously recorded inside the scanner (1.5T Sonata, Siemens Medical Systems, Erlangen, Germany) using 21 MRI compatible scalp electrodes. Data were transmitted from an EMR32 (Schwarzer, Munich, Germany) or BrainAmp (Brain Products, Munich, Germany) amplifier via an optic fiber cable to the EEG monitor outside the scanner room. An anatomic acquisition (1 mm slice thickness, 256 × 256 matrix, echo time [TE] = 9.2 msec, repetition time [TR] = 22 msec, flip angle 30°) was performed for coregistration with functional images. BOLD-fMRI data were collected in runs of 6 minutes with the patient in the resting state (120 frames per run, 5 × 5 × 5 mm voxels, 25 slices, 64 × 64 matrix, TE = 50 msec, TR = 3 seconds, flip angle 90°).

EEGs were filtered using FEMR (Schwarzer) or Vision Analyzer (Brain Products) software. Spikes were grouped according to spatial distribution, and classified as focal (involving electrodes from one quadrant), bilateral focal (symmetric electrodes from the same quadrants), hemispheric (more than one quadrant, restricted to one hemisphere) and widespread (bilateral and diffuse). Each spike type from each patient constituted one study.

Maps of the *t* statistic (*t*-maps) were created using the timing of the spikes as events in the fMRI analysis.⁴ At each voxel, the maximum *t* value was taken from four *t*-maps created using four hemodynamic response functions with peaks at 3, 5, 7, and 9 seconds.⁵

Positive BOLD-fMRI responses were defined as activation and negative responses as deactivation. Significant responses were defined as five or more contiguous voxels with *t* > 3.1 or one single voxel with *t* > 4.8 (absolute values, corrected *p* = 0.05).⁶ Anatomic localization for each type of response was determined by coregistration of anatomic acquisition and *t*-maps. We looked at all areas with significant fMRI responses and determined the presence of activation and deactivation, and their concordance with spike location on the scalp and with the PMG lesion.

Results. We studied nine patients with sporadic PMG (five women, mean age, 36.5 years), two with a previous anterior callosotomy and two with a remote focal resection (table E-1 available on the *Neurology* Web site at www.neurology.org). Six patients had uni- or bilateral (*n* = 5) perisylvian PMG, one bilateral frontal PMG and two parietooccipital PMG. Six had more than one type of spikes (table E-2), and therefore a total of 18 studies were ana-

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Figure 1. (A) Anatomic MRI from a patient with bilateral perisylvian polymicrogyria (Patient 2, Study 3). Both activation (B) and deactivation (C) were observed, related to bilateral sharp and slow waves with left frontotemporal predominance. Activation has a larger volume and distribution, and the maximum response is in the left perisylvian region, with concomitant involvement of the homologous contralateral region. Deactivation is smaller and occurs in areas outside the lesion, with the maximum observed in the posterior cingulate gyrus bilaterally.

lyzed: 12 focal, two bilateral, one hemispheric, and three widespread. The number of spikes per study ranged from two to 266 (median, 22).

Sixteen studies (89%) showed responses: nine (56%) activations and deactivations (figure 1), four (25%) only activations, and three (19%) only deactivations (see table E-2). Studies with responses had a larger number of spikes than those with no responses for both activation (median, 76 vs 7) and deactivation (median, 56 vs 22). Also, studies with more widespread spike field seemed to be more likely asso-

ciated with BOLD responses, as four of the five studies with no activation and all six studies with no deactivation, were related to focal spikes (see table E-2).

Volumes of maximum activation ($12.16 \text{ cm}^3 \pm 16.48$) were larger than volumes of maximum deactivation ($4.18 \text{ cm}^3 \pm 6.80$) (nonparametric bootstrap t test, $p = 0.041$).

Twelve (92%) of 13 studies with activation involved the lesion (figures 1B and 2B, see also table E-2). Most studies had multiple areas of activation in or outside the PMG, but the maximum response occurred within the lesion in four,

Figure 2. Strong activation in the left frontotemporal perisylvian region related to F7T3 spikes (Patient 3, Study 5), and a smaller area of activation in the contralateral homologous region, both clearly involving the polymicrogyria (PMG) cortex, in a patient with bilateral perisylvian PMG. The activated areas extend beyond the cortical surface, and the maximum activation point is located in the meningeal and skull topography. No deactivation was observed for this study.

Figure 3. Widespread deactivation related to F7T3 spikes (Patient 7, Study 14), involving part of the lesion, characterized by bilateral (left predominance) frontal polymicrogyria and schizencephaly. The maximum deactivation is more posterior, in the parietal region (white arrow). This study also demonstrated activation, maximum in the left temporal region (not shown).

on the edge in four and outside the boundaries in five. Thus 8/13 (61.5%) involved the lesion. Twelve studies showed deactivation (see table E-2), but only five (41.5%) had deactivation in the lesion, the maximum involving the lesion in only two studies from the same patient (figure 3).

Discussion. We analyzed the localization and nature of BOLD responses related to different types and locations of spikes in PMG patients. We could noninvasively assess the possibility of multiple generators related to the lesion. The localization of seizure foci in PMG is usually not possible based on EEG and clinical findings, and no evidence of intrinsic epileptogenicity of the lesion has been demonstrated. Visual analysis of spike distribution is not precise enough to indicate whether the spike originates in or outside the lesion. Modeling of spike generators (dipolar or distributed) is difficult to apply because we do not know the number or extent of generators. EEG-fMRI makes no assumption regarding spike generators but simply measures the metabolic activity resulting from spikes. Animal PMG models using the glutamatergic agonist ibotenate and freezing lesions suggested widespread hyperexcitability outside the lesional area itself.⁷ An imbalance between excitation and inhibition is proposed, with an increase in the excitatory afferents projecting to the perilesional areas.

It is notable that 89% of studies showed BOLD-responses, mostly with activation and deactivation. Focal spikes were less frequently associated with BOLD-responses, as compared to widespread and bilateral spikes. This is in agreement with the more frequent responses in generalized discharges⁸ than in focal discharges.² Activations were more likely than deactivations in areas involving the lesion, and volumes were larger for maximum activation than deactivation. For both responses, only part of the lesion was involved, concomitantly with extralesional areas. In 61.5% of studies with activation, the maximum involved the lesion. Because the BOLD

response results from the spike itself, this finding strongly suggests that the PMG cortex can trigger epileptic activity.

PMG is not histologically uniform, and two patterns are recognized: unlayered and four-layered.⁹ The two types may coexist in contiguous cortical areas, indicating that they may form a continuum, and thus the PMG lesions may be heterogeneous. This heterogeneous histology correlates with variable degrees of hyperexcitability within PMG cortex, which may be associated with different metabolic demands. It may explain why the BOLD-responses do not always involve the lesion in a homogeneous manner, within and across patients. There is evidence that PMG may be secondary to vascular insults. The persistence of fetal meningeal vasculature over the PMG cortex sometimes reported,⁹ and MRI evidence of abnormal vessels in PMG lesions and adjacent white matter, may be relevant for fMRI studies.

The significance of BOLD responses distant from lesions remains unclear, but is consistent with findings from other functional studies. For instance, PET has shown that the few cases that presented hypometabolism had a heterogeneous pattern, including the lesion and areas outside the PMG cortex. MR spectroscopy has shown a reduction of neuronal N-acetylaspartate variable with respect to the lesional, perilesional, and normal brain areas.¹⁰

Using EEG-fMRI for localization of epileptogenic regions in PMG may provide valuable data about epilepsy secondary to such extensive lesions. In this group of patients, we were able to demonstrate that fMRI can measure BOLD responses related to epileptic activity generated by PMG cortex.

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NeuroImages

Figure. (A) Postcontrast axial fluid-attenuated inversion recovery (FLAIR) image demonstrates paranasal sinusitis, an abscess in the left ethmoid sinus adjacent to the left superior orbital fissure involving the oculomotor nerve. (B) Postcontrast T1 coronal image reveals left frontal and parasagittal subdural collection and meningeal enhancement (single arrows). The abscess with air-fluid level is seen in the left ethmoid sinus (double arrows). (C) Diffusion-weighted image shows hyperintensities of subdural empyema accumulated in the left frontal cortex and the para-central gyrus.

Ethmoid abscess with findings simulating Weber syndrome

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A 49-year-old right-handed man was admitted to the hospital because of generalized convulsions. On examination, he was somnolent with mild nuchal rigidity and right hemiparesis. His left eye deviated laterally with dilated pupil and impaired pupillary

light reflex. Brain MRI revealed a left subdural empyema with associated meningitis and an abscess in the left ethmoid sinus and paranasal sinusitis (figure, A, B, C). A craniotomy and nasal endoscopy with maxillary antrostomy and ethmoidectomy were performed. The cultures grew α -hemolytic streptococcus. His hospital course was complicated and he died 1 month later. The patient's initial neurologic signs were clinically indistinguishable from that of Weber syndrome, with ipsilateral oculomotor nerve palsy and contralateral hemiparesis.^{1,2}

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