Epilepsia, 54(2):296–304, 2013
doi: 10.1111/j.1528-1167.2012.03667.x

FULL-LENGTH ORIGINAL RESEARCH

Intracranial evaluation of the epileptogenic zone in regional infrasylvian polymicrogyria

***Georgia Ramantani, †‡§Laurent Koessler, †‡Sophie Colnat-Coulbois, †‡§Jean-Pierre Vignal, ¶Jean Isnard, ¶Hélène Catenoix, †‡§Jacques Jonas, #Josef Zentner, *Andreas Schulze-Bonhage, and †‡§Louis Georges Maillard**

***Epilepsy Centre, University Hospital Freiburg, Freiburg, Germany; †University Hospital of Nancy, Neurology Department, Nancy, France; ‡CNRS, CRAN, UMR7039, Vandoeuvre, France; §Faculty of Medecine, Lorraine University, Vandoeuvre, France; ¶Functionnal Neurology and Epileptology Department, Pierre Wertheimer Neurological Hospital, Lyon, France; and #Department of Neurosurgery, University Hospital Freiburg, Freiburg, Germany**

Summary

Purpose: To define the relationship between the epileptogenic zone and the polymicrogyric area using intracranial electroencephalography (EEG) recordings in patients with structural epilepsy associated with regional infrasylvian polymicrogyria (PMG).

Methods: We retrospectively reviewed the medical charts, scalp, and intracranial video-EEG recordings, neuroimaging findings, and neuropsychological evaluations of four patients with refractory temporal lobe epilepsy related to PMG who consequently underwent resective surgery.

Key Findings: High-resolution magnetic resonance imaging (MRI) revealed temporal lobe PMG in all cases, accompanied by hippocampal malrotation and closed lip schizencephaly in 3/4 cases, respectively. In intracranial recordings, interictal spike activity was localized within the PMG in only 2/4 and within the amygdala, hippocampus, and entorhinal cortex in all cases. In the first patient, two epileptogenic networks coexisted: the prevailing network initially involved the mesial temporal structures with spread to the anterior PMG; the secondary network successively involved the anterior part of the PMG and later the mesial temporal structures. In the second patient, the epileptogenic network was limited to the mesial temporal structures, fully sparing the PMG. In the third patient, the epileptogenic network first involved the mesial temporal structures and later the PMG. Conversely, in the last case, part of the PMG harbored an epileptogenic network that propagated to the mesial temporal structures. Consistent with these findings a favorable outcome (Engel class I in three of four patients; Engel class II in one of four) at last follow-up was obtained by a resection involving parts of the PMG cortex in three of four and anteromesial temporal lobe structures in another three of four cases.

Significance: Infrasylvian PMG displays a heterogeneous epileptogenicity and is occasionally and partially involved in the epileptogenic zone that commonly includes the mesial temporal structures. Our results highlight the intricate interrelations between the MRI-detectable lesion and the epileptogenic zone as delineated by intracranial recordings. Seizure freedom can be accomplished as a result of a meticulous intracranial study guiding a tailored resection that may spare part of the PMG.

KEY WORDS: SEEG, Intracranial recordings, Malformations of cortical development, Epilepsy surgery, Outcomes, Polymicrogyria, Schizencephaly.

Malformations of cortical development (MCDs) reportedly give rise to 8–12% of medically intractable structural epilepsy (Sisodiya, 2000) and constitute the underlying etiology in 7.2% (16 of 222) of patients with temporal lobe seizures (Lehéricy et al., 1995). Infrasylvian polymicrogyria (PMG), alone or combined with schizencephaly (SZ), is rare compared to other malformations (1 of 222, 0.4%) (Lehéricy et al., 1995) and presents with a high degree of histopathologic variability that mirrors its pathophysiologic heterogeneity (Ferrer, 1984; Guerrini et al., 1997; Takano, 2011). Recent advances in imaging and molecular biology have promoted the identification of genotypes giving rise to diverse spatiotemporal distributions of PMG (Barkovich et al., 2005) that in turn result in distinct electroclinical phenotypes (Kuzniecky et al., 1994; Guerrini et al., 1997; Barkovich et al., 1999). Although 78–87% of patients with PMG are diagnosed with epilepsy (Guerrini & Filippi, 2005; Leventer et al., 2010) and 65% present a refractory course (Guerrini & Filippi, 2005), results of epilepsy

Accepted July 30, 2012; Early View publication September 18, 2012.
Address correspondence to Georgia Ramantani, Epilepsy Center, University Hospital Freiburg; Breisacher Str. 64, 79106 Freiburg, Germany. E-mail: georgia.ramantani@uniklinik-freiburg.de

surgery are poor; only 50% of patients achieve seizure freedom (Chang et al., 2011). Apparently, the issue of epileptogenicity within these complex infrasylvian malformations has not been resolved to date.

Although electroclinical phenotypes in PMG have been studied extensively during the last years, observations commonly derive from scalp recordings, and very few cases explored with depth electrodes have been reported so far (Guerrini & Barba, 2010; Takano, 2011). In particular, data from intralesional recordings in regional infrasylvian PMG are limited to two cases associated with SZ, with intrinsic epileptogenicity established in the PMG cortex surrounding the cleft and the epileptogenic zone extending beyond the visible abnormality (Chassoux et al., 2008). The authors report a favorable seizure outcome following a resection of the entire PMG as well as of cortical areas beyond its magnetic resonance imaging (MRI) margins, so that the outcome does not allow definite conclusions as to the heterogeneous epileptogenicity of different areas within the malformation. In contrast, the coexistence of both epileptogenic and electrophysiologically normal cortex within a regional PMG has been highlighted in a recent case report combining Stereoelectroencephalography (SEEG) and electrical source imaging (ESI), with seizure freedom accomplished by partial resection of the PMG and of cortical areas beyond its MRI boundaries (Maillard et al., 2009).

This study aims to explore the correlations between functionally and morphologically affected regions, that is, between the epileptogenic zone and the MRI-detectable lesion in four cases of regional infrasylvian PMG by means of the gold standard of intracerebral EEG recordings and surgical outcomes.

Methods

We retrospectively reviewed the medical history, presurgical work-up including neuroimaging (MRI, fluorodeoxyglucose–positron emission tomography [FDG-PET]), neuropsychological evaluations, noninvasive long-term video-EEG and SEEG recordings (combined with subdural recordings in a single case), as well as the epilepsy surgery outcomes of four patients (two female; mean age 32 years) with refractory epilepsy related to regional infrasylvian PMG. The presurgical evaluation and consecutive surgical treatment were performed in the University Hospital of Nancy in two cases (Patients 1 and 2), at the University Hospital of Lyon (France) in one (Patient 3) and at the University Hospital of Freiburg (Germany) in another case (Patient 4).

Neuroimaging data

Preoperative neuroimaging was performed according to standard protocols in each center. Patients 1–3 were evaluated in the University Hospital of Nancy by means of a 1.5 T GE Signa scanner (GE Healthcare, Milwaukee, WI, U.S.A.) with an eight-element coil. The acquisition comprised an anatomic sequence using a three-dimensional (3D) spoiled gradient echo sequence, as described elsewhere (Maillard et al., 2009). Patient 4 was investigated in the University Hospital of Freiburg using a 1.5T Magnetom Vision scanner (Siemens, Erlangen, Germany) with a transmit/receive standard full head coil. The acquisition included a magnetization-prepared rapid-acquisition gradient echo (MP-RAGE) sequence. In addition, T2-weighted and fluid-attenuated inversion recovery (FLAIR) images were also acquired in both centers.

Brain FDG-PET was performed according to the European Association of Nuclear Medicine procedure guidelines (Bartenstein et al., 2002). Integrated PET and computed tomography (CT) images were recorded during the interictal state, using hybrid PET/CT systems: a Biograph camera in Nancy (Siemens, Knoxville, TN, U.S.A.) and a Siemens CTI ECAT EXACT tomograph in Freiburg (Siemens, Erlangen, Germany) as described previously (Juengling et al., 2002; Jennesson et al., 2010). No seizure was observed during the uptake period. FDG-PET images were reconstructed and visually analyzed by experienced nuclear medicine physicians.

Electrophysiologic data

All patients previously underwent long-term scalp EEG recordings in the context of presurgical evaluation. Due to the inconclusive findings of noninvasive investigations, intracranial EEG recordings with depth electrodes (Patients 1–3: Dixi Medical, Besançon, France; patient 4: Ad-Tech, Racine, WI, U.S.A.) and additional subdural electrodes (Patient 4: Ad-Tech) were performed to delineate the epileptogenic zone (Chauvel et al., 1987). Implantation sites and electrode trajectories were determined individually so as to adequately sample areas highlighted by noninvasive presurgical evaluation and at the same time circumvent vascular structures (Guenot et al., 2001; Fauser & Schulze-Bonhage, 2006; Maillard et al., 2009).

To visualize depth electrode positions a postoperative CT scan was merged with the preoperative MRI in Patients 1–3, while depth and subdural electrode positions in Patient 4 were determined from a 3D T1-weighted MRI dataset acquired after electrode implantation on the same scanner system as the preimplantation MRI. An average of four depth electrodes (range 1–6) and 30 contacts (range 23–42) targeted the PMG cortex in each patient, as presented in Figs. 1 and 2.

Scalp and intracranial video-EEG monitoring was performed 24 h/day for 5–10 days. The signal was recorded on a 128-channel amplifier (Patients 1–3: LTM 128 Headbox; Micromed, Mogliano Veneto, Italy; patient 4: Neurofile NT; It-med, Usingen, Germany) at a sampling rate of 1 kHz. Electrical stimulations delivered bipolar pulses via a 50-Hz train of 3–7 s or 1-Hz shocks. Impulsion was biphasic with 250–2,000 μs width; intensity was 0.2–3 mA (SEEG) to

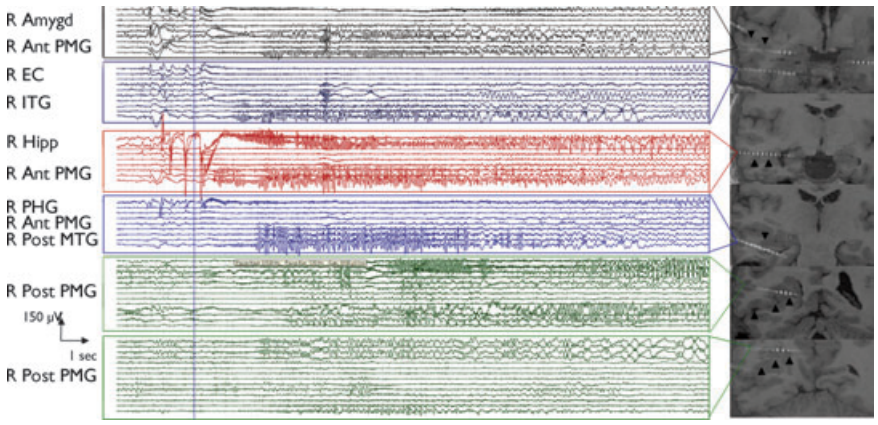

Figure 1.
Intracerebral recording with depth electrodes of a representative seizure (type1) in patient 1. The seizure onset (indicated by a vertical marker) is characterized by a fast low-voltage discharge initially involving the right amygdala, rhinal cortex, hippocampus, and parahippocampal gyrus secondarily spreading to the anterior and then to the posterior part of the PMG and of the middle and inferior temporal gyri. R, right; Amygd, amygdala; Ant, anterior; PMG, polymicrogyria; EC, entorhinal cortex; ITG, inferior temporal gyrus; Hipp, hippocampus; PHG, parahippocampal gyrus; MTG, middle temporal gyrus.

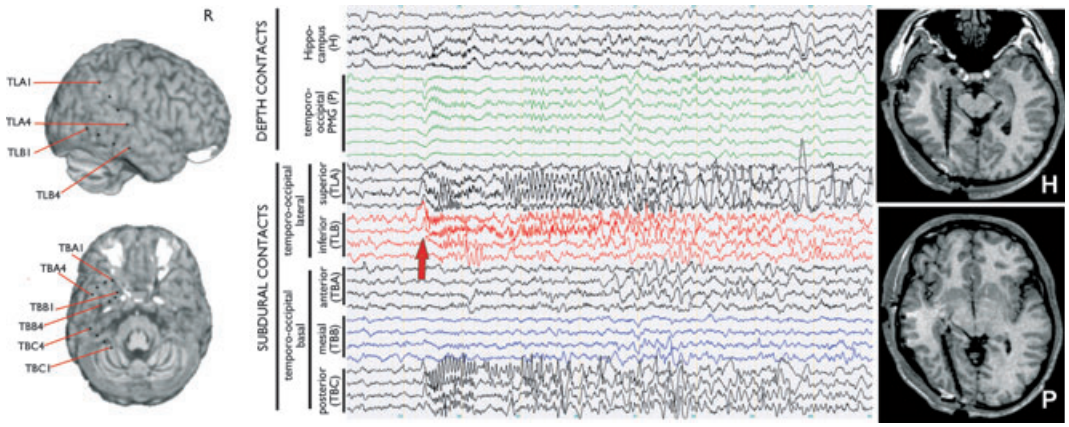

Figure 2.
Intracranial recording with depth electrodes (H, P: top to bottom represents anterior to posterior contacts) and subdural strips (TLA/B, TBA/B/C) of a representative seizure in patient 4. The arrow indicates the seizure onset constituting of a sharp wave with superimposed low-voltage fast activity (red arrow) recorded over the posterior part of the inferior temporal gyrus that rapidly spread to the posterior part of the superior temporal gyrus adjacent to the temporooccipital junction and the posterior mesial basal aspect of the PMG. The more ventral and posterior part of the PMG was spared by the initial low-voltage fast activity, whereas a distinct rhythmic activity transiently involved the posterior hippocampus and the anterior, mesial, and temporal part of the PMG.

15 mA (ECoG) (IRES 600: Micromed; OSIRIS Neurostimulator: inomed, Berlin, Germany). The patients were unaware of the timing of stimulation unless motor symptoms occurred.

Results

Medical history and seizure semiology

Patients did not have a history of childhood febrile seizures or developmental delay. Neuropsychological evaluation was unremarkable in all cases. Mean age at epilepsy onset was 12 years (range 6–18 years). The average frequency of partial seizures amounted to >4.5 per month. Partial seizures were initiated by a dreamy state in two of four, and visceral-sensory symptoms in three of four cases. Semiology comprised early oroalimentary automatisms in two of four, upper limb elementary automatisms in three of four (two early, one late), and loss of consciousness in four of four patients (three early, one late). Mean duration of

partial seizures was 103 s. Three of four patients had frequent (>2 yearly) secondary generalized tonic–clonic seizures (Table 1).

Neuroimaging findings

MRI revealed a PMG extending caudorostrally from the occipital to the anterior temporal region. In three of four cases the PMG localized within the right, nondominant hemisphere. The PMG involved the inferior and middle occipitotemporal gyri (Patients 1 and 2), the parahippocampal and fusiform gyri (Patient 3), and the fusiform and occipitotemporal gyri (Patient 4). It was associated with an ipsilateral deformation of the temporal horn and a closed-lip schizencephaly in three patients (Patients 1, 2, and 3). Ipsilateral hippocampal malrotation was established in three patients (Patients 1, 3, and 4), subcortical heterotopia (in the superior temporal gyrus) in one patient (Patient 1), and suspicion of focal cortical dysplasia in the lateral aspect of the temporooccipital junction in another (Patient 4). Neuroimaging revealed no abnormalities in the contralateral hemisphere (Table 2).

FDG-PET showed anteromesial temporal hypometabolism ipsilateral to but distinct from the PMG in three cases (Patients 1, 2, and 3). The metabolic pattern within the MR-visible PMG cortex varied from widespread hypometabolism including the PMG (Patient 4) to partial isometabolism of the PMG (Patients 1 and 2) (Table 2).

Electrophysiologic findings

Scalp EEG recordings

Interictal EEG focal discharges were rare, nonspecific, and projected on the temporobasal and anterior temporal electrodes ipsilateral to the PMG in all patients (spikes, sharp waves, and polyspikes). The first ictal EEG modification was a hemispheric (Patients 1 and 3) or focal (Patients 2 and 4) flattening. It was followed by 5–8/s rhythmic sharp waves anterior and basal temporal (Patients 1, 2, and 3) or basal temporooccipital (Patient 4) (Table S1).

Intracerebral EEG recordings

In only two of four patients (Patients 1 and 4) interictal repetitive focal discharges with a distinct morphology were recorded within the MRI-discernible PMG cortex (Fig. S1).

In *Patient 1* the epileptogenic zone was identified according to electroclinical data derived from the registration of five spontaneous seizures and six further seizures triggered by electrical stimulation (Table 3, Fig. 3). Two distinct seizure types were identified with the prevailing seizure type

Table 1. Medical history and seizure semiology as observed in presurgical work-up of the four patients with refractory epilepsy on the grounds of regional infrasylvian polymicrogyria with symptoms and signs given in order of appearance

Pt.	Age, gender, handedness	Age at epilepsy onset (y)	Initial ictal symptom	Early objective signs	Late objective signs	Mean seizure duration (s)	Total seizure frequency (sz/m)	SGTC seizure frequency (sz/y)
1	27, f, RH	18	Dreamy state Warm ascending sensation	Signalizes seizure onset Flush Loss of consciousness	R upper limb automatism L upper limb tonic posturing Tonic–clonic generalization	60	6–8	>2
2	36, f, RH	12	Epigastric *warm ascending* sensation "Breathless" sensation	Signalizes seizure onset R upper limb automatism Verbal automatism Oroalimentary automatism	Tonic–clonic generalization	83	3	<1
3	44, m, LH	6	Dreamy state	Oroalimentary automatism Verbal automatism Loss of consciousness L upper limb automatism Flush R upper limb tonic posturing	R facial cloni Tonic–clonic generalization	150	>4	>6
4	21, m, RH	13	Epigastric sensation Dizziness Visual elementary hallucination in L hemifield	Signalizes seizure onset Tachycardia, tachypnea R head/trunk deviation Loss of consciousness	L lower limb tonic posturing L facial cloni L head version Tonic–clonic generalization	120	>4	>4

Pt, patient; y, year; m, month; sz, seizure; f, female; m, male; RH, right handed; LH, left-handed; R, right; L, left; SGTC, secondary generalized tonic–clonic.

Table 2. Neuroimaging data including cranial MRI and FDG-PET

Pt.	Lat.	Brain MRI findings					Interictal FDG-PET findings
		PMG topography	Lateral ventricle	Adjacent neocortex	Ispilateral hippocampus	Contralateral hemisphere	
1	R	Lateral/basal temporooccipital junction, middle/inferotemporal gyrus, ventral extent to the temporal horn of the lateral ventricle	Deformation of the occipital and temporal horn of the lateral ventricle	Subcortical heterotopia of the superior temporal gyrus, type I schizencephaly	Malrotation	NA	Antero mesial/temporopolar hypometabolism; isometabolism in the posterior temporobasal part of the PMG
2	R	Posterior inferior/middle temporal gyrus, inferior/ middle occipital gyrus	Deformation of the temporal horn	Type I schizencephaly	NA	NA	Anterior mesial/temporopolar hypometabolism; isometabolic PMG
3	L	Fusiform gyrus, parahippocampal gyrus, caudal extent to temporooccipital junction	Deformation of the temporal horn	Type I schizencephaly	Malrotation and sclerosis	NA	Widespread mesiolateral temporal and mesial occipital hypometabolism
4	R	Fusiform gyrus, inferior temporal gyrus, caudal extent along the collateral to the calcarine fissure	NA	FCD IIa[a] in the temporooccipital junction	Malrotation	NA	Widespread temporo-occipital hypometabolism including the PMG

Pt, patient; Lat, lateralization; NA, no abnormalities.
[a]MRI findings raised suspicion of dysplasia in the lateral aspect of the temporooccipital junction, which was confirmed by histologic examination of the resected tissue.

(type 1: 10 of 11 seizures) corresponding to an initial anterior mesial temporal low-voltage fast activity secondarily spreading to the anterior and then to the posterior PMG and to the inferior and middle temporal gyri. This case has been previously analyzed in the context of a validation of electrical source imaging by intracerebral investigations (Maillard et al., 2009; Koessler et al., 2010). This first seizure type was reproduced by shock and train electrical stimulation of the amygdala, hippocampus and entorhinal cortex (Fig. 1). The second seizure type (lateral, basal, and posterior) was observed just once and was not reproducible by electrical stimulation. Seizure onset was characterized by an initial low-voltage fast activity sparing the mesial temporal structures and involving the anterior and middle regions of the PMG as well as the superior, middle, and inferior temporal gyri and the anterior bank of the posterior SZ with secondary spread to the mesial temporal structures. In summary, there were two epileptogenic networks: the prevailing network initially involved the anterior mesial temporal structures and spread secondarily to the anterior PMG; the second network initially involved the anterior part of the PMG and spread secondarily to the anterior mesial temporal structures.

In *Patient 2* identification of the epileptogenic zone was based on the electroclinical data derived from three reproducible seizures triggered by low-intensity electrical stimulation (50 Hz, 1 mA) of the right amygdala (Table 3, Fig. 3). It reproduced the usual simple partial seizures with the same time course of ictal signs as spontaneous seizures captured during the long-term video-EEG recording. They were characterized by a warm epigastric ascending sensation, a sensation of being ''breathless,'' allowing the patient to warn, followed by chewing automatisms without loss of contact. The SEEG seizure pattern was characterized by low-voltage fast activity beginning during the stimulation that involved the amygdala, anterior hippocampus, entorhinal and perirhinal cortex, progressively slowing while remaining localized to the aforementioned contacts for an average duration of 105 s. Electrical stimulations of the PMG did not elicit any seizure or initial sensation characteristic of seizure. Therefore, the epileptogenic network was shown to be limited to the anterior mesial temporal structures and to spare the PMG.

In *Patient 3* the delineation of the epileptogenic zone was based on the electroclinical data from the two spontaneous seizures that were recorded (Table 3, Fig. 3). Ictal SEEG revealed initial polyspikes in the left entorhinal cortex, the entirety of the left temporal pole, the amygdala that subsequently spread to the superior and middle temporal gyri, and to the anterior part of the PMG. The hippocampus and the posterior part of the PMG were spared by the discharge. Electrical train stimulation (50 Hz, 1 mA) of the temporal pole, entorhinal cortex, and amygdala elicited the initial sensation characteristic for seizure onset that was associated with a local postdischarge. Stimulation of the PMG cortex

Table 3. Interictal and ictal intracranial EEG findings of invasive presurgical investigation with depth electrodes in all patients (SEEG) and additional subdural electrodes in Patient 4

Pt.	Interictal SEEG within the PMG	Ictal SEEG within the PMG	Interictal SEEG outside the PMG	Ictal SEEG outside the PMG
1	SW in anterior/mesial PMG	Type 1 (10/11): secondary SW involvement Type 2 (1/11): widespread LVFA	PS in anterior H, ER	Type 1 (10/11): LVFA in anterior H, A, ER, PHG Type 2 (1/11): secondary SW spread to H, ER
2	DS in anterior PMG; no SW	No involvement	Repetitive SW in anterior H, A, ER	LVFA in A, anterior H, ER, PR
3	Normal background	Secondary spread to the anterior PMG	PS in anterior H; LVFA in ER	PS temporopolar, ER, A; secondary spread to STG, MTG
4	SW in mesial/posterior temporal and basal occipital PMG (s)	SW/LVFA in the lateral posterior temporal PMG (s); secondary spread to the occipital basal PMG (s); RA in mesial/anterior PMG	SW in posterior H; repetitive SW in temporo-occipital junction (s)	RA in posterior H; secondary spread to STG

Pt, patient; SEEG, Stereoelectroencephalography; PMG, polymicrogyria; SW, sharp wave; PS, polyspikes; DS, delta slow; LVFA, low-voltage fast activity; H, hippocampus; ER, entorhinal cortex; PR, perirhinal cortex; A, amygdala; RA, rhythmic activity; PHG, parahippocampal gyrus; MTG, middle temporal gyrus; STG, superior temporal gyrus.

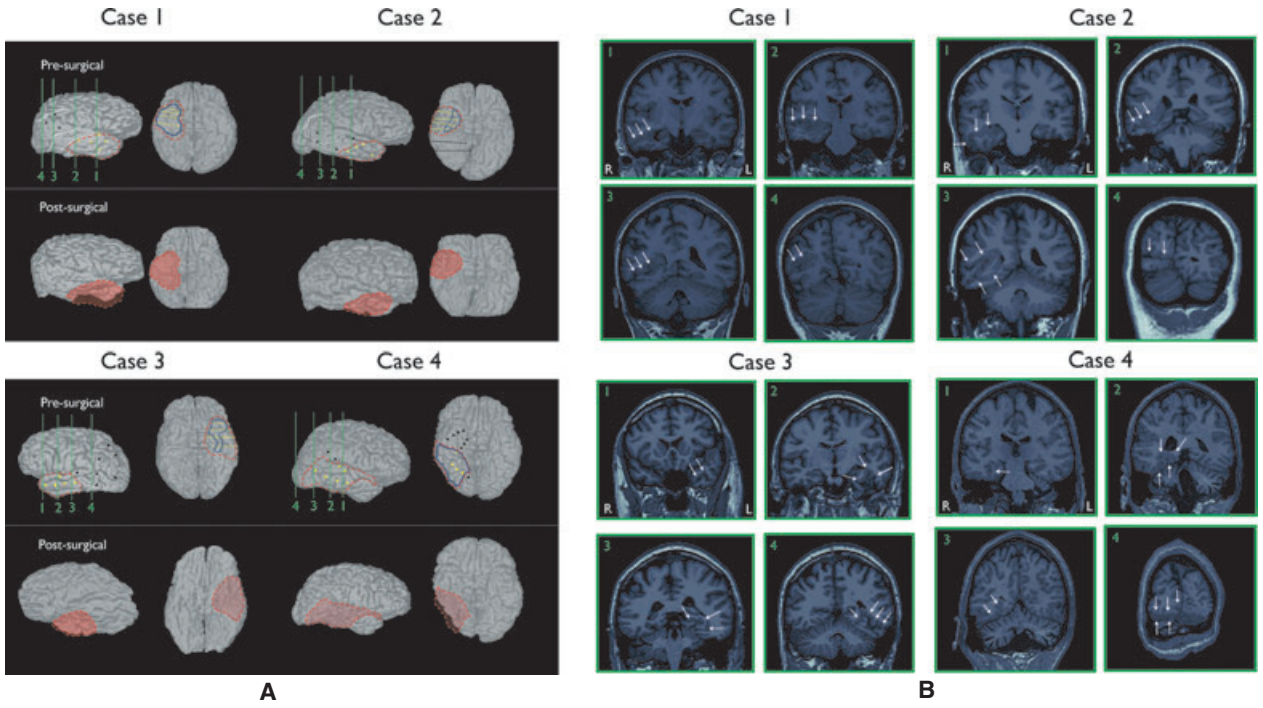

Figure 3.
(**A**) Comparative presentation derived from the presurgical and postsurgical 3D-MRI displaying the malformation (white lines delineate the cleft in cases of associated schizencephaly), the implantation scheme, the epileptogenic zone (continuous blue line), and the resection zone (dotted red line) in all four patients. On the lateral view, the entry points of each electrode are presented. On the inferior view, only the trajectories of the electrodes exploring the basal and medial aspects are presented by transparence. Yellow points/lines indicate electrodes involved by the initial ictal discharge. Vertical green lines indicate the anteroposterior locations of the corresponding brain MRI slices in **B**: slices 1 and 4 correspond to the most anterior and the most posterior limits of the malformation, respectively. (**B**) Preoperative brain MRI of all four cases: the white arrows indicate the abnormal sulci.

failed to elicit a full seizure or the initial seizure sensation. In summary, the epileptogenic network initially involved the MTS and spread secondarily to the PMG.

In *Patient 4*, identification of the epileptogenic zone derived from the registration of five spontaneous seizures (Table 3, Fig. 3), beginning with the usual epigastric

sensation and dizziness and followed by tachycardia and tachypnea, tonic posturing of the left lower limb, facial clonі, and head version preceding secondary generalization in three cases. The intracranial EEG seizure pattern was characterized by a sharp wave with superimposed low-voltage fast activity recorded over the posterior part of the inferior temporal gyrus that spread rapidly to the posterior part of the superior temporal gyrus adjacent to the temporooccipital junction and the posterior mesial basal aspect of the PMG (Fig. 2). The more occipital basal part of the PMG was spared by the initial low-voltage fast activity, whereas a distinct rhythmic activity transiently involved the posterior hippocampus and the anterior, mesial temporal part of the PMG. Furthermore, four subclinical seizures were recorded with a seizure pattern consisting of a low-amplitude fast activity in the temporobasal part of the PMG localized within the fusiform gyrus followed by repetitive polyspikes in the anterior hippocampal contacts and showing a rapid propagation to the anterior mesial temporal part of the PMG and the mesial hippocampal contacts. In each of nine events recorded, there was a seizure onset in distinct contacts sampling the PMG within the inferior temporal and fusiform gyri with a rapid spread to the superior temporal gyrus and transient involvement of the hippocampus and mesial basal temporal PMG, sparing the occipital part of the PMG. To summarize, the epileptogenic network initially involved part of the PMG and secondarily spread to the MTS.

In conclusion, part of the PMG was initially involved in the epileptogenic zone in two of four patients (Patient 1/seizure type 2, Patient 4) and secondarily involved in the propagation network in two patients (Patient 1/seizure type 1, Patient 3). It is noteworthy that involvement was restricted to a part of the PMG and that in Patient 1 two epileptogenic networks were determined, with the initial involvement of the PMG restricted to the less active network. In contrast, the mesial temporal structures—including the amygdala, the anterior hippocampus, the rhinal cortex, and the temporal pole—were initially involved in the epileptogenic network in three patients (Patients 1, 2, and 3) and secondarily involved in one (Patient 4). Furthermore, it should be noted that the electrical stimulation of the PMG did not elicit a seizure or the initial sensation characteristic of a seizure in any patient.

Resective surgery and seizure outcome

Resection involved parts of the PMG cortex in three of four (Patients 1, 3, and 4) and anteromesial temporal lobe structures in three of four cases (Patients 1, 2, and 3) (Fig. 3). Histopathologic investigation in Patients 1, 3, and 4 confirmed the presence of polymicrogyric cortex within resection borders, whereas resected lateral temporal cortex was found to harbor a focal cortical dysplasia (FCD) type IIa in Patient 4.

On follow-up a favorable outcome was established in all patients. Patients 1, 2, and 4 were seizure free under monotherapy at last follow-up, corresponding to an Engel class Ia outcome 3, 2, and 6 years after surgery, respectively. Patients 3 and 4 were diagnosed with contralateral homonymous hemianopia. Patient 3 was seizure free in the first 3 years following resective surgery (Engel Ia), but presented with an isolated aura and a complex partial seizure during the following 2 years (Engel class II).

Discussion

In this study we analyzed intracerebral EEG recordings and outcomes of subsequent resections in order to explore the correlations between the epileptogenic zone and the MRI-detectable lesion in four cases of refractory epilepsy related to regional infrasylvian PMG. PMG is thought to be highly epileptogenic, with the majority of patients eventually developing seizures (Leventer et al., 2010). However, in our series intrinsic epileptogenicity was confirmed in only two of four patients that presented both interictal epileptic discharges and low-voltage fast activity at ictal onset in designated areas within the PMG cortex. The interictal repetitive focal discharges observed in these two patients clearly differ from the continuous rhythmic epileptic discharges encountered in FCD (Chassoux et al., 2000; Fauser & Schulze-Bonhage, 2006). Furthermore, electrical stimulation targeting confirmed epileptogenic areas of the PMG failed to elicit seizures in all patients, whereas in previous studies, spontaneous seizures were reproduced by electrical stimulation in only 2 of 4 PMG (Chassoux et al., 2008) and in 20 of 28 FCD cases (Chassoux et al., 2000). This highlights the different electrophysiologic and epileptogenic properties of PMG compared to FCD, especially the greater difficulty in eliciting seizures by electrical stimulation of confirmed epileptogenic part of the PMG.

Our observations underscore the heterogeneous epileptogenicity of PMG and corroborate the findings of recent studies using novel modalities such as EEG–functional (ffMRI) (Kobayashi et al., 2005), electrical source imaging (ESI) (Maillard et al., 2009), magnetic source imaging (MSI) (Burneo et al., 2004), or combined magnetic and electric source imaging (MSI/ESI) in simultaneous EEG/magnetoencephalography (MEG) recordings (Bast et al., 2005). As a matter of fact, PET findings in our study were also consistent with the electroclinical delineation of the epileptogenic zone showing hypometabolism in remote cortical areas involved at seizure onset in all four cases and in part of the polymicrogyria that was involved by the initial discharge or secondary spread in three of four cases. Our study further shows that PMG plays a variable role in the anatomofunctional organization of seizures and can be completely spared or secondarily involved or initially but partially involved in the epileptogenic network. It emphasizes that in cases of extensive or bilateral PMG, a limited and tailored resection may lead to a significant improvement or recovery. These observations are consistent with the heterogeneous histopathologic cortical organization of the PMG

including less excitable neural tissue such as a cell sparse zone (Takano, 2011) and with experimental models of PMG suggesting a widespread functional disruption that extends beyond the visible abnormality (Redecker et al., 2000).

Despite the methodical limitations regarding spatial resolution, the lack of intrinsic epileptogenicity in parts of the PMG cortex should not be ascribed to a sampling bias inherent in the implementation of depth electrodes in the light of an extensive sampling of the PMG in all patients. Intracranial recordings with depth electrodes indisputably constitute the best available method to analyze the full depth and extent of the epileptogenic network involving mesial temporal structures and validate the hypothesis arising from noninvasive anatomical electroclinical investigations. Depth electrodes alone or in combination with subdurals targeted the dysplastic PMG cortex, mesial temporal structures, and further points of interest within the presumed epileptogenic network ranging from a full coverage of the PMG, amygdala, hippocampus, and temporal lobe to an extensive sampling including the insula, posterior cingulate, and temporooccipital junction. The additional implementation of subdural coverage in patient 4 added substantially to the sampling of the PMG as well as of the adjacent cortex that was histologically shown to harbor an FCD type IIa. The introduction of multiple depth and subdural electrode contacts facilitated the exploration of key points within the network of ipsilateral malformations involving the PMG, SZ, FCD, and mesial temporal structures.

This study is in line with the limited data available from an earlier intracranial EEG study (Chassoux et al., 2008) supporting the notion of a large epileptogenic network involving cortical areas outside the PMG. Taken together, these two studies highlight the diversity of epileptogenic networks associated with PMG that commonly extend beyond the margins of the visible malformation. In our study, however, these remote epileptogenic cortical areas could be morphologically intact on MRI (case 2) or harbor hippocampal malrotation in two of three cases with initial ictal medial temporal lobe structures involvement (cases 1 and 3) or FCD (case 4).

Our study further highlights that these complex epileptogenic networks may either include or spare parts of the MR-detectable PMG and its margins. These findings conform to recent functional and electroclinical studies of intractable epilepsy in cortical malformations including nodular heterotopia (Tassi et al., 2005; Valton et al., 2008), tuberous sclerosis (Jacobs et al., 2008), FCD, and neurodevelopmental tumors (Aubert et al., 2009; Fauser et al., 2009). These studies have shown that the epileptogenic network may extend to remote cortical areas and in some cases spare MRI visible tuber or nodular heterotopia (Jacobs et al., 2008; Tassi et al., 2005. Taking into account the extent of the actual epileptogenic zone rather than the extent of morphologic abnormality is crucial for surgical success, that is, seizure control in intractable epilepsy, as shown in our study.

The intricate and aberrant electrophysiologic relationships of dysplastic cortex to widespread cortical networks (Duchowny, 2009) may explain the rather poor results of resective surgery in PMG, with reportedly only 50% of patients reaching seizure freedom, regardless of lobar localization (Chang et al., 2011). In our series, three of four patients achieved an Engel class I and one of four an Engel class II outcome, with favorable surgical results consistent with the findings of electrophysiologic investigations. The limited number of observations may prohibit extrapolations regarding post-surgical outcomes in regional infrasylvian PMG, but undoubtedly adds valuable observations to the sparse body of data regarding epilepsy surgery in PMG (Chassoux et al., 2008; Maillard et al., 2009). Furthermore, our results show that favorable outcomes may be achieved by limited resections in extensive PMG, provided the electroclinically confirmed epileptogenic zone is removed in its entirety. Our results emphasize the relevance of the definition of the epileptogenic zone as provided by intracranial recordings against the MRI-delineation of a presumed epileptogenic lesion. This constitutes a substantial difference of the rarely encountered PMG from the more frequently diagnosed FCD, where completeness of resection is the prerequisite for seizure freedom (Chassoux et al., 2000; Fauser et al., 2004; Chang et al., 2011).

Conclusion

In this study of intralesional recordings in patients with intractable epilepsy due to unilateral, regional, infrasylvian PMG, we confirm intrinsic and heterogenous epileptogenicity in the PMG cortex with the malformation only occasionally and partially involved in the epileptogenic zone. In this special group of patients with temporal lobe PMG, the presence of a widespread MRI malformation associated with intractable epilepsy does not necessarily call for an extensive resection with possible functional losses, since the epileptogenic zone may be only partly overlapping with PMG cortex.

Disclosure

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

References

Aubert S, Wendling F, Regis J, McGonigal A, Figarella-Branger D, Peragut JC, Girard N, Chauvel P, Bartolomei F. (2009) Local and remote epileptogenicity in focal cortical dysplasias and neurodevelopmental tumours. *Brain* 132:3072–3086.

Barkovich AJ, Hevner R, Guerrini R. (1999) Syndromes of bilateral symmetrical polymicrogyria. *AJNR Am J Neuroradiol* 20:1814–1821.

Barkovich AJ, Kuzniecky RI, Jackson GD, Guerrini R, Dobyns WB. (2005) A developmental and genetic classification for malformations of cortical development. *Neurology* 65:1873–1887.

Bartenstein P, Asenbaum S, Catafau A, Halldin C, Pilowski L, Pupi A, Tatsch K; European Association of Nuclear Medicine. (2002) European

Association of Nuclear Medicine procedure guidelines for brain imaging using [(18)F]FDG. *Eur J Nucl Med Mol Imaging* 29:BP43–BP48.

Bast T, Ramantani G, Boppel T, Metzke T, Ozkan O, Stippich C, Seitz A, Rupp A, Rating D, Scherg M. (2005) Source analysis of interictal spikes in polymicrogyria: loss of relevant cortical fissures requires simultaneous EEG to avoid MEG misinterpretation. *Neuroimage* 25: 1232–1241.

Burneo JG, Bebin M, Kuzniecky RI, Knowlton RC. (2004) Electroclinical and magnetoencephalographic studies in epilepsy patients with polymicrogyria. *Epilepsy Res* 62:125–133.

Chang EF, Wang DD, Barkovich AJ, Tihan T, Auguste KI, Sullivan JE, Garcia PA, Barbaro NM. (2011) Predictors of seizure freedom after surgery for malformations of cortical development. *Ann Neurol* 70: 151–162.

Chassoux F, Devaux B, Landré E, Turak B, Nataf F, Varlet P, Chodkiewicz JP, Daumas-Duport C. (2000) Stereoelectroencephalography in focal cortical dysplasia: a 3D approach to delineating the dysplastic cortex. *Brain* 123:1733–1751.

Chassoux F, Landre E, Rodrigo S, Beuvon F, Turak B, Semah F, Devaux B. (2008) Intralesional recordings and epileptogenic zone in focal polymicrogyria. *Epilepsia* 49:51–64.

Chauvel P, Buser P, Badier JM, Liegeois-Chauvel C, Marquis P, Bancaud J. (1987) [The ''epileptogenic zone'' in humans: representation of intercritical events by spatio-temporal maps]. *Rev Neurol (Paris)* 143: 443–450.

Duchowny M. (2009) Clinical, functional, and neurophysiologic assessment of dysplastic cortical networks: implications for cortical functioning and surgical management. *Epilepsia* 50(Suppl. 9):19–27.

Fauser S, Schulze-Bonhage A. (2006) Epileptogenicity of cortical dysplasia in temporal lobe dual pathology: an electrophysiological study with invasive recordings. *Brain* 129:82–95.

Fauser S, Schulze-Bonhage A, Honegger J, Carmona H, Huppertz HJ, Pantazis G, Rona S, Bast T, Strobl K, Steinhoff BJ, Korinthenberg R, Rating D, Volk B, Zentner J. (2004) Focal cortical dysplasias: surgical outcome in 67 patients in relation to histological subtypes and dual pathology. *Brain* 127:2406–2418.

Fauser S, Sisodiya SM, Martinian L, Thom M, Gumbinger C, Huppertz HJ, Hader C, Strobl K, Steinhoff BJ, Prinz M, Zentner J, Schulze-Bonhage A. (2009) Multi-focal occurrence of cortical dysplasia in epilepsy patients. *Brain* 132:2079–2090.

Ferrer I. (1984) A golgi analysis of unlayered polymicrogyria. *Acta Neuropathol* 65:69–76.

Guenot M, Isnard J, Ryvlin P, Fischer C, Ostrowsky K, Mauguiere F, Sindou M. (2001) Neurophysiological monitoring for epilepsy surgery: the Talairach SEEG method. StereoElectroEncephaloGraphy. Indications, results, complications and therapeutic applications in a series of 100 consecutive cases. *Stereotact Funct Neurosurg* 77:29–32.

Guerrini R, Barba C. (2010) Malformations of cortical development and aberrant cortical networks: epileptogenesis and functional organization. *J Clin Neurophysiol* 27:372–379.

Guerrini R, Filippi T. (2005) Neuronal migration disorders, genetics, and epileptogenesis. *J Child Neurol* 20:287–299.

Guerrini R, Dubeau F, Dulac O, Barkovich AJ, Kuzniecky R, Fett C, Jones-Gotman M, Canapicchi R, Cross H, Fish D, Bonanni P, Jambaqué I, Andermann F. (1997) Bilateral parasagittal parietooccipital polymicrogyria and epilepsy. *Ann Neurol* 41:65–73.

Jacobs J, Rohr A, Moeller F, Boor R, Kobayashi E, LeVan Meng P, Stephani U, Gotman J, Siniatchkin M. (2008) Evaluation of epileptogenic networks in children with tuberous sclerosis complex using EEG-fMRI. *Epilepsia* 49:816–825.

Jennesson M, Milh M, Villeneuve N, Guedj E, Marie PY, Vignal JP, Raffo E, Vespignani H, Mancini J, Maillard L. (2010) Posterior glucose hypometabolism in Lafora disease: early and late FDG-PET assessment. *Epilepsia* 51:708–711.

Juengling FD, Kassubek J, Martens-Le Bouar H, Reinhardt MJ, Krause T, Nitzsche EU, Moser E, Korinthenberg R. (2002) Cerebral regional hypometabolism caused by propofol-induced sedation in children with severe myoclonic epilepsy: a study using fluorodeoxyglucose positron emission tomography and statistical parametric mapping. *Neurosci Lett* 335:79–82.

Kobayashi E, Bagshaw AP, Jansen A, Andermann F, Andermann E, Gotman J, Dubeau F. (2005) Intrinsic epileptogenicity in polymicrogyric cortex suggested by EEG-fMRI BOLD responses. *Neurology* 64: 1263–1266.

Koessler L, Benar C, Maillard L, Badier JM, Vignal JP, Bartolomei F, Chauvel P, Gavaret M. (2010) Source localization of ictal epileptic activity investigated by high resolution EEG and validated by SEEG. *Neuroimage* 51:642–653.

Kuzniecky R, Andermann F, Guerrini R. (1994) The epileptic spectrum in the congenital bilateral Perisylvian syndrome. CBPS Multicenter Collaborative Study. *Neurology* 44:379–385.

Lehéricy S, Dormont D, Sémah F, Clémenceau S, Granat O, Marsault C, Baulac M. (1995) Developmental abnormalities of the medial temporal lobe in patients with temporal lobe epilepsy. *AJNR Am J Neuroradiol* 16:617–626.

Leventer RJ, Jansen A, Pilz DT, Stoodley N, Marini C, Dubeau F, Malone J, Mitchell LA, Mandelstam S, Scheffer IE, Berkovic SF, Andermann F, Andermann E, Guerrini R, Dobyns WB. (2010) Clinical and imaging heterogeneity of polymicrogyria: a study of 328 patients. *Brain* 133:1415–1427.

Maillard L, Koessler L, Colnat-Coulbois S, Vignal JP, Louis-Dorr V, Marie PY, Vespignani H. (2009) Combined SEEG and source localisation study of temporal lobe schizencephaly and polymicrogyria. *Clin Neurophysiol* 120:1628–1636.

Redecker C, Luhmann HJ, Hagemann G, Fritschy JM, Witte OW. (2000) Differential downregulation of GABAA receptor subunits in widespread brain regions in the freeze-lesion model of focal cortical malformations. *J Neurosci* 20:5045–5053.

Sisodiya SM. (2000) Surgery for malformations of cortical development causing epilepsy. *Brain* 123:1075–1091.

Takano T. (2011) Seizure susceptibility in polymicrogyria: clinical and experimental approaches. *Epilepsy Res* 96:1–10.

Tassi L, Colombo N, Cossu M, Mai R, Francione S, Lo Russo G, Galli C, Bramerio M, Battaglia G, Garbelli R, Meroni A, Spreafico R. (2005) Electroclinical, MRI and neuropathological study of 10 patients with nodular heterotopia, with surgical outcomes. *Brain* 128:321–337.

Valton L, Guye M, McGonigal A, Marquis P, Wendling F, Régis J, Chauvel P, Bartolomei F. (2008) Functional interactions in brain networks underlying epileptic seizures in bilateral diffuse periventricular heterotopia. *Clin Neurophysiol* 119:212–223.

Supporting Information

Additional supporting information may be found in the online version of this article:

Figure S1. Interictal repetitive focal discharges with a distinct morphology recorded within the MRI-discernible PMG cortex in patient 1 presented in both scalp and depth EEG recordings.

Table S1. Interictal and ictal scalp EEG findings of non-invasive presurgical investigation.

Please note: Wiley-Blackwell is not responsible for the content or functionality of any supporting information supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.