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Source analysis of interictal spikes in polymicrogyria: Loss of relevant cortical fissures requires simultaneous EEG to avoid MEG misinterpretation

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Purpose: **Multiple source analysis of interictal EEG and MEG spikes was used to identify irritative zones in polymicrogyria (PMG). Spike onset times and source localization were compared between both modalities. PMG is characterized by a marked loss of deep cortical fissures. Hence, differences between EEG and MEG were expected since MEG signals are predominantly generated from tangentially orientated neurons in fissures.** ***Patients:*** **We studied 7 children and young adults (age 7.5 to 19 years) with localization-related epilepsy and unilateral polymicrogyria (PMG) as defined from anatomical MRI.** ***Methods:*** **122-channel whole-head MEG and 32-channel EEG were recorded simultaneously for 25 to 40 min. Using the BESA program, interictal spikes were identified visually and used as templates to search for similar spatio-temporal spike patterns throughout the recording. Detected similar spikes ($r > 0.85$) were averaged, high-pass filtered (5 Hz) to enhance spike onset, and subjected to multiple spatio-temporal source analysis. Source localization was visualized by superposition on T1-weighted MRI and compared to the lesion.** ***Results:*** **Nine spike types were identified in seven patients (2 types in 2 patients). Eight out of nine EEG sources and seven MEG sources modeling spike onset were localized within the visible lesion. EEG spike onset preceded MEG significantly in two spike types by 19 and 25 ms. This was related to radial onset activity in EEG while MEG localized propagated activity. In one case, the earliest MEG spike activity was localized to the normal hemisphere while the preceding radial EEG onset activity was localized within the lesion. Distances between EEG and MEG onset sources varied markedly between 9 and 51 mm in the eight spike types with concordant lateralization.** ***Conclusion:*** **Interictal irritative zones were localized within the lesion in PMG comparable to other malformations, e.g., FCD. Discrepancies in MEG and EEG were related to the lack of deep fissures in PMG. In two cases, MEG was blind to the onset of radial interictal spike activity and localized propagated spike activity. In two other cases, MEG localized to the more peripheral parts of the irritative zone. Simultaneous EEG recordings with MEG and multiple source analysis are required to avoid problems of MEG interpretation.**

Keywords: MEG; EEG; Polymicrogyria; Interictal spikes; Source analysis

Introduction

Cortical malformations are one of the most common causes of intractable partial epilepsy in childhood (Kuzniecky and Barkovich, 2001; Palmini et al., 1995; Sisodiya, 2000). As opposed to secondary lesions, cortical malformations are thought to have an intrinsic epileptogenic potential (Andermann, 2000; Palmini et al., 1995; Sisodiya, 2000). Evidence for intrinsic epileptogenicity of focal cortical dysplasia (FCD) arises from different findings: surgical outcome (Palmini et al., 1995; Wyllie, 1998), intracranial recordings (Boonyapisit et al., 2003; Francione et al., 2003; Morioka et al., 1999; Palmini et al., 1995; Sisodiya, 2000), epileptogenicity of resected human lesional tissue (Mattia et al., 1995), and MEG/EEG source analysis (Bast et al., 2004; Ishibashi et al., 2002; Morioka et al., 1999; Otsubo et al., 2001). In contrast to FCD, clinical and electrophysiological data in patients with polymicrogyria (PMG) are rare. Epidural recordings showed spike and seizure onset in the lips of schizencephalic cortex in one patient (Silbergeld and Miller, 1994). MEG recordings in 4 patients with bilateral perisylvian syndrome showed inconclusive results (Tanaka et al., 2000). Animal models of polymicrogyria suggested the perilesional cortex rather than the core of the lesion to be epileptogenic (Hagemann et al., 2000; Jacobs et al., 1999). This lack of clinical data is mainly caused by the fact that patients with polymicrogyria are less frequently candidates for epilepsy surgery and,

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hence, for invasive recordings. Lesions are usually extended and multilobar and a preserved physiological function in PMG is observed more frequently as compared to FCD (Janzsky et al., 2003). In a recent event-related MEG study in patients with bilateral perisylvian syndrome, Paetau et al. reported preserved motor cortex function within the lesion (Paetau et al., 2004). In addition to the high risk for surgery in many patients with PMG, epilepsy is less frequently resistant to antiepileptic drug treatment (Guerrini et al., 1996).

MEG source localization is an auxiliary non-invasive method in the process of presurgical evaluation for epilepsy surgery (Ebersole, 1997; Nakasato et al., 1994; Pataraia et al., 2004). It can be readily applied in children with intractable epilepsy (Bast et al., 2004; Minassian et al., 1999; Paetau et al., 1994). Non-invasive techniques like MEG and EEG source localization can also help to obtain in vivo information on the irritative zone of different types of cortical malformations. However, only neurons with tangential orientation, i.e., fissural neurons, contribute to the MEG signal in contrast to EEG which predominantly reflects activity from near-to-radially orientated neurons on the convexity.

PMG is a malformation in which neurons migrate to the cortex during development but do not form normal cortical layers or intracortical connections leading to many small microgyri separated by shallow sulci, a slightly thickened cortex, neuronal heterotopia, and often enlarged ventricles (Kuzniecky and Barkovich, 2001). Due to the resulting lack of deep cortical fissures, different sensitivities of EEG and MEG for interictal spike activities in the lesioned cortex are to be expected.

Therefore, we used combined EEG and MEG recordings to assess their sensitivity to interictal epileptiform activity in PMG and multiple source analysis to reveal differences between EEG and MEG.

Patients

We investigated seven patients, four males and three females, aged 7.5 to 19 years (mean 12.7 years). Clinical and MRI data are summarized in Table 1. Epilepsy with simple or complex partial seizures started at the age of 0.5 to 13 years (mean 6.3 years). One child additionally suffered from continuous spike wave status during sleep (CSWS, patient 7). Two patients had no previous antiepileptic medication while five patients had received up to four different antiepileptic drugs. Contralateral hemiparesis was observed in six patients and two patients were slightly mentally retarded. Anatomical T1-weighted MRI and cortical surface reconstruction are displayed in Fig. 1.

Methods

MRI acquisition

High-resolution structural 3D-MRI (T1, sagittal or transversal, 1 or 1.3 mm slice thickness) was performed in all patients for anatomical reference. The acquisition followed one of two different protocols. Protocol 1 (patients 2 and 5): Philips Gyroscan NT, 0.5 T, T1: 180 sagittal slices, 1 mm thickness. Additional FLAIR, T2-weighted and inversion recovery MRI. Protocol 2 (Patients 1, 3, 4, 6, 7): Picker Edge, 1.5 T, T1: 130 transversal slices, 1.3 mm thickness. T2-weighted and inversion recovery MRI.

MRI morphometry

The surfaces of the gray matter-CSF of the right and left hemispheres were rendered from the individual T1-wighted 3D-MRI images (Fig. 1) using the automatic segmentation tool of the

Table 1
Clinical data

Patient	Age (years)	Sex	Lesion		Clinical data		Epilepsy			
			Side	Localization	Hemiparesis	Mental retardation	Onset (years)	Seizure types	Semiology	AED trials
1	14	f	R	F, P, T, I	Y	Y	0.5	SP, CP, G	● Aura (unspecific) → clonic (left leg) → generalized tonic–clonic seizure	*PHB*
2	9	m	R	F, P, T, I	Y	N	8	CP, G	● Clonic (left leg) → automotor seizure ● Dialeptic seizure	*STM* CBZ
3	12	m	L	P	Y	N	10	SP	● Somatosensory aura (right foot)	none
4	19	m	R	F, P, T, I	Y	N	2.5	CP, G	● Clonic (left leg) → generalized tonic–clonic seizure ● Dialeptic seizure	*VPA* CBZ, DPH, STM
5	7.5	m	R	F, P, T, I	Y	N	3	CP, G	● Clonic (body left) → generalized tonic–clonic seizure	*PHB*
6	15	f	L	F	N	N	13	CP	● Hypermotor seizure	none
7	12.5	f	L	F, P, I	Y	Y	7	SP, CP	● Clonic seizure (right leg)	*CLB*, *STM* VPA, DEX

Side: L = left, R = right; Localization: F = frontal, T = temporal, P = parietal, I = insular; Seizure types: SP = simple partial, CP = complex partial, G = generalized; Semiology: arrows indicate the sequence of clinical symptoms in the seizure evolution; AED = antiepileptic drugs; cursive = current AED. PHB = phenobarbital, STM = sulthiam, CBZ = carbamazepine, VPA = valproate, DPH = phenytoin, CLB = clobazam, DEX = dexamethason.