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Magnetoencephalography localizing spike sources of atypical benign partial epilepsy

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Running title
MEG for ABPE

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Summary

Rationale: Atypical benign partial epilepsy (ABPE) is characterized by centro-temporal electroencephalography (EEG) spikes, continuous spike and waves during sleep (CSWS), and multiple seizure types including epileptic negative myoclonus (ENM), but not tonic seizures. This study evaluated the localization of magnetoencephalography (MEG) spike sources (MEGSSs) to investigate the clinical features and mechanism underlying ABPE.

Methods: We retrospectively analyzed seizure profiles, scalp video EEG (VEEG), and MEG in ABPE patients.

Results: Eighteen ABPE patients were identified (nine girls and nine boys). Seizure onset ranged from 1.3 to 8.8 years (median, 2.9 years). Initial seizures consisted of focal motor seizures (15 patients) and absences/atypical absences (3). Seventeen patients had multiple seizure types including drop attacks (16), focal motor seizures (16), ENM (14), absences/atypical absences (11), and focal myoclonic seizures (10). VEEG showed centro-temporal spikes and CSWS in all patients. Magnetic resonance imaging (MRI) was reported as normal in all patients. MEGSSs were localized over the following regions: both Rolandic-sylvian (8), peri-sylvian (5), peri-Rolandic (4), parieto-occipital (1), bilateral (10), and unilateral (8). All patients were on more than two antiepileptic medications. ENM and

absences/atypical absences were controlled in 14 patients treated with adjunctive

ethosuximide.

Conclusion: MEG localized the source of centro-temporal spikes and CSWS in the

Rolandic-sylvian regions. Centro-temporal spikes, Rolandic-sylvian spike sources, and

focal motor seizures are evidence that ABPE presents with Rolandic-sylvian onset seizures.

ABPE is therefore a unique, age-related, and localization-related epilepsy with a

Rolandic-sylvian epileptic focus plus possible thalamo-cortical epileptic networks in the

developing brain of children.

Introduction

Atypical benign partial epilepsy in childhood (ABPE) initially presents with the following signs and symptoms: (i) onset age of 2.5-6 years; (ii) multiple seizure types including focal motor, atypical absences, and myoclonic-atonic seizures; (iii) electroencephalography (EEG) showing central and mid-temporal spikes and diffuse slow spike-wave activities during drowsiness or sleep; and, (iv) normal development or mild mental retardation [1].

Despite multiple seizure types and slow spike and waves on EEG, ABPE is distinguished from Lennox-Gastaut syndrome by its characteristic spontaneous remission, lack of tonic seizures or developmental delay, and normal awake EEG background activity. Since hemi-convulsive seizures during sleep and contralateral/bilateral centro-temporal epileptiform discharges are present at the beginning, the electro-clinical findings of ABPE are indistinguishable from those of benign epilepsy with centro-temporal spikes (BECTS) [2-5]. BECTS is the most well-recognized, age-related idiopathic focal epilepsy with occasional epileptic seizures despite frequent centro-temporal spikes on EEG. In contrast, ABPE patients tend to develop atypical absences or myoclonic-atonic seizures during the course of their condition. Tovia et al. [6] showed that 0.5% of patients with BECTS were categorized as atypical variants, while Dooze et al. [7] found that 29% of the relatives of

ABPE patients had some abnormal activities on EEG. Finally, Gobbi et al. [8] reviewed several subtypes of idiopathic focal epilepsies to categorize ABPE as a “Rolandic Epilepsy-Related Disorder”; these age-related epilepsies including ABPE and BECTS were attributed to a maturational continuum with different manifestations.

Epileptic negative myoclonus (ENM) is one of the characteristic seizure patterns in ABPE. Oguni et al. [6] analyzed the ictal EEG findings of ENM and demonstrated generalized, bilateral synchronous discharges, while ictal magnetoencephalography (MEG) of an ABPE patient showed that the spike sources of ENM were localized at the peri-sylvian region [7].

MEG is a relatively new clinical technique that uses superconducting quantum interference devices (SQUIDs) to measure and localize sources of extracranial magnetic fields generated by intraneuronal electric currents. Current MEG machines have a whole-head array of more than 100 sensors contained within a helmet-shaped Dewar, which effectively covers most of the brain surface. MEG has been increasingly used for localization of the epileptic zone and functional mapping in epilepsy patients. MEG in BECTS patients showed spike sources with an anterior-posterior oriented perpendicular to the Rolandic fissure [8, 9]. No case series of ABPE have thus far used MEG to localize epileptic spike

sources.

We conducted a multi-center study to collect clinical, EEG, and MEG findings in ABPE patients, with MEG used to characterize the spike sources (MEGSSs) in ABPE. We hypothesize that the epileptic network in ABPE is localized in both the Rolandic-sylvian cortex and thalamo-cortical networks, based on their unique clinical and electrophysiological features.

Patients and Methods

We collaborated with four institutions on this study: the Department of Pediatrics, Hokkaido University School of Medicine (HU); Department of Pediatrics, Tohoku University School of Medicine (TU); Department of Pediatrics, National Center of Neurology and Psychiatry (NCNP), Japan; and the Division of Neurology, The Hospital for Sick Children (HSC), Toronto, Ontario, Canada.

Patients

We studied 18 patients with ABPE (9 females and 9 males). We diagnosed ABPE according to the triad of diagnostic criteria as follows: 1, focal motor seizures, absences/atypical absences, atonic seizures including ENM, myoclonic seizures and drop attacks described by parents; 2, EEG findings of central and middle temporal spikes and generalized slow spike-wave activity during drowsiness or sleep similar to continuous spike and slow waves during sleep (CSWS); 3, normal development or mild mental retardation during the clinical course.

EEG

Scalp video EEGs were recorded using the International 10-20 electrode placement system and electromyography (EMG) electrodes for bilateral deltoid muscles to capture ENM. Awake and sleep EEGs were recorded in all patients.

MEG and magnetic resonance imaging

Initial MEG studies were conducted at the onset of ENM. Seven patients had multiple MEG studies up to six times. Parents or guardians of all patients provided written informed consent for the MEG studies. MEG and EEG were done in a magnetically shielded room. MEG was recorded using a system with 306 SQUIDS (Vectorview; Elekta-Neuromag Ltd., Helsinki, Finland) at HU, NCNP, and TU, and with an Omega system (151 channels, VSM MedTech Ltd., Port Coquitlam, BC, Canada) at HSC. MEG data were recorded with a band pass filter of 0.03-133 Hz at HU, NCNP, and TU, and of 1-208 Hz at HSC. Sampling frequency was 400 Hz at HU, 600Hz at NCNP and TU and 625 Hz at HSC. EEGs were recorded using the International 10-20 system, with additional electrocardiogram (ECG) electrodes. MEG data were recorded for > 1 hour per patient, collecting data in 4-minute blocks at HU, NCNP and TU. At HSC, MEG was recorded in 15 two-minute blocks for a total of 30 minutes [10]. Patients were lying in the supine

position. Sedative agents were used for uncooperative patients. The relative position of the head and the MEG sensors were determined by attaching three small head-position indicator coils to the head. The positions of the coils were digitized and subsequently recorded by the MEG sensors for co-registration with 1.5 tesla (T)/3T magnetic resonance image (MRI) with high-resolution sequences.

MEG source analysis

MEG data were digitally filtered using a band filter of 3-30 Hz at HU, NCNP, and TU, or at 3-70 Hz at HSC for offline analysis. Segments containing abnormal paroxysms were selected manually. Individual spikes were analyzed to localize the spike source per spike using an equivalent current dipole (ECD) model or dynamic statistical parametric mapping (dSPM) [11, 12].

Results

Seizure profiles (Table 1)

Seizure onsets ranged from 1.3 to 8.8 years with a median age of 2.9 years. The seizures started as focal motor seizures in 15 patients (83%) and absences/atypical absences in 3 patients (17%).

All patients except one patient had multiple types of seizures in their seizure histories. Drop attacks, in which the precise seizure type remains unknown, were most common (16 patients, 89%). One patient (patient 17) presented with a history of only drop attack seizures. Focal motor seizures (16 patients, 89%), ENM (14 patients, 78%), absences/atypical absences (11 patients, 61%), myoclonic seizures (10 patients, 56%), and secondarily generalized tonic-clonic seizures (9 patients, 50%) were seen in more than half of the patients (Supplementary videos 1 and 2). Focal sensory seizures (6 patients, 33%) and epileptic spasms (2 patients, 11%) were also reported.

Past and Family history

There was no past history of epilepsy before the seizure onset in any of the 18 patients, while 3 (17%) had a positive family history of febrile seizures.

Cognitive functions

Cognitive function was evaluated in 15 patients. All 15 patients had the evaluations while they presented with ENM. A developmental quotient results ranged from 54 to 85 in 5 patients. The full-scale intelligence quotient test (Wechsler Intelligence Scale for Children) results ranged from 53 to 103 in 10 patients.

MRI

No patient showed an abnormality on MRI.

EEG (Figure 1)

EEG showed interictal centro-temporal spikes in all 18 patients. Continuous generalized and/or centro-temporal spike and waves during sleep were also noticed in all patients. When video EEG captured ENM, generalized high-amplitude spike or polyspikes and waves were associated with a brief attenuation of EMG activities corresponding to muscle atonia in 12 patients. (Supplementary video 1) Absences/atypical absences showed generalized and irregular spike and slow waves around 3 Hz on EEG in 16 patients (Supplementary video 2).

(Please insert Figure 1 here)

MEG (Figure 2, Table 2)

MEG localized MEGSSs over both Rolandic-sylvian fissures in 8 patients, the peri-sylvian region alone in 5 patients, and the peri-Rolandic region alone in 4 patients. One patient had MEGSSs in the left parieto-occipital region, even though EEG showed left centro-temporal spikes (patient 6). Most spike sources were oriented perpendicularly to either the Rolandic or sylvian fissure. The spike sources demonstrated identical orientations in 11 patients (61%). MEGSSs were located in bilateral hemispheres in 10 patients (56%) and in a unilateral hemisphere in 8 patients (44%). In all 10 patients with bilateral MEGSS, the MEGSS showed identical patterns and locations in the both hemispheres. ECD could not be estimated in one patient due to diffuse right hemispheric discharges without leading spikes. Therefore, we applied dSPM and localized the MEGSSs in the right sylvian fissure (patient 7). Seven patients underwent multiple MEG studies. Six patients with bilateral MEGSS became unilateral MEGSS. One patient showed consistent unilateral MEGSS. Six patients showed no MEGSS at the last MEG study when they were seizure free.

(Please insert Figure 2 here)

Treatments

All 18 patients were administered multiple antiepileptic medications ranging from 2 to 12 medications (mean 5.8) during their courses. Ethosuximide (ESM) succeeded in controlling various seizure types of ABPE, especially ENM and absences/atypical absences in 14 patients (78%); of these, all achieved seizure freedom after ESM was started, and 11 (89%) of the 14 were still on ESM at the last follow-up. Two of three patients in whom ESM was discontinued were no longer on any antiepileptic medication. CBZ was initially started in 16 patients (89%), but 14 (88%) experienced worsening of seizures after CBZ was initiated, and the treatment was discontinued. Two patients were seizure free on a combination of CBZ and ESM (Patient 6) or CBZ, ZNS, and CLB (Patient 8). Valproic acid (VPA) was tried in 16 (89%) patients, and 6 of these (38%) were still on VPA at the last follow-up. Other medications tried included zonisamide (10 patients, 56%), clobazam (10 patients, 56%), clonazepam (eight patients, 44%) acetazolamide (5 patients, 28%), phenytoin (5 patients, 28%), and diazepam (4 patients, 22%). The medications still being used at the last follow-up consisted of zonisamide in 3/10 patients (30%), clobazam in 4/10 patients (40%), clonazepam in 3/8 patients (38%), acetazolamide in 2/5 patients (40%), and diazepam in 2/4 patients (50%).

Two patients underwent epilepsy surgery. Patient 8 underwent cortical excision over the left supra-marginal gyrus at the age of 12 years. Surgical pathology revealed microdysgenesis with increased ganglion cells. She achieved 75-90% seizure reduction after the surgery, and was seizure free on three medications at 17.5 years old. Anterior two-thirds corpus callosotomy was performed at the age of 6 years for drop attacks in patient 9. The patient was seizure free on two medications at 10 years old.

Seizure outcome

The age at last follow-up of the 18 patients ranged from 5.4 to 17.5 years (median 11.8 years). All were seizure free, two patients (11%) without any medication. Five patients (28%) were only on one medication, including four patients with ESM. The remaining 11 patients had multiple medications; six were on 2 medications, four were on 3 medications, and one patient was on 4 medications. Among seven patients with multiple MEG studies, medication changes, cognitive results effected less prominent for MEGSS than seizure improvements.

Discussion

MEG localized a Rolandic-sylvian epileptic focus of ABPE

In ABPE, interictal MEG revealed localized clusters of spike sources around the Rolandic-sylvian fissures corresponding to both centro-temporal spikes and CSWS on EEG. The identically clustered Rolandic-sylvian MEGSSs of interictal epileptic discharges in patients with ABPE suggested that the epileptic focus was located around the Rolandic-sylvian regions involving the motor cortex in most cases. In our series, the peri-sylvian region MEGSSs were also recorded in 13 of 18 ABPE patients. In contrast, MEGSSs in BECTS were specifically localized along the Rolandic region with definite identical orientations vertical to the central sulcus [8, 9]. In the older children with BECTS, MEGSSs shifted to the lower part of the Rolandic region close to the operculum.

Kubota et al. [10] reported an ictal MEG study localizing the spike source of ENM with generalized EEG spikes at the sylvian fissure in one ABPE patient [7]. ENM was characterized by spike or polyspikes on EEG time-locked to attenuation of EMG activity, which corresponded to muscle atonia [6]. Series of ENM often caused atonic seizures. Both interictal and ictal MEGSSs indicate that a subset of the epileptogenic zones responsible for focal seizures and ENM in ABPE patients is localized around the Rolandic-sylvian regions. In contrast, MEGSSs in three patients with Lennox-Gastaut syndrome with ENM were

localized over inconsistent and various brain regions that did not include the Rolandic-sylvian regions [13].

Fifteen of eighteen patients in this series presented with focal motor seizures at the onset, and these persisted in addition to multiple other seizure types developing in 16 patients. ABPE might also be confused diagnostically with BECTS as ABPE appears superficially similar on scalp EEG and also presents with focal motor seizures. In ABPE patients, MEGSS extended to perisylvian region in addition to Rolandic region or localized even perisylvian region alone.

MEG localized spike dipoles in CSWS of ABPE

Sleep EEG often shows almost-continuous generalized or centro-temporal spike and waves during sleep in ABPE patients, resembling CSWS. Another differential diagnosis of ABPE is epileptic encephalopathy with CSWS (ECSWS), and there are no reports of source localizations using MEG in patients with ECSWS. The role of MEG remains to be explored in this entity. Kelemen et al. [17] reported three patients with CSWS secondary to destructive lesions in the thalamus [14], and CSWS development was often observed in patients with a thalamic lesion, indicative of thalamo-cortical dysfunction with an epileptic

network [15, 16]. ESM can be efficacious for seizures in ABPE patients, especially for ENM [6]. In 13 (72%) of the 18 ABPE patients studied herein, ESM completely suppressed their ENM. In other studies, systemic administration of ESM significantly reduced spike and wave discharges in genetic absence epilepsy models [17-19]. Continuous and generalized slow spike and waves during sleep in patients with ECSWS have been associated with secondary bilateral synchrony with leading foci [20, 21]. The CSWS in ABPE could also be due to secondary bilateral synchrony, but originating specifically from the Rolandic-sylvian regions. The effect of ESM on the clinical seizures and CSWS indicates that the epileptic substitute of thalamic and Rolandic-sylvian networks produce ABPE.

Patry et al. [25] reported six patients with ECSWS, and heterogeneous seizure types of ECSWS that comprise focal motor seizures, absences, and epileptic falls while awake [21] resemble those of ABPE. Consequently, it can be difficult to distinguish ABPE from ECSWS clinically not analyzing the localization of epileptic foci. Further investigation of MEG in ECSWS may therefore serve to differentiate epileptic sources in these patients and improve our understanding of the epileptic networks and mechanisms leading to the observed cognitive disabilities.

Conclusions

MEG localized spike dipoles of centro-temporal spikes and CSWS over the Rolandic-sylvian regions in ABPE, indicating that ABPE is the localization-related epilepsy with Rolandic-sylvian onset seizures. In addition, the effects of ESM on ENM and atypical absences suggest the involvement of thalamo-cortical circuitry in the epileptic network. ABPE is a unique age-related epilepsy involving the Rolandic-sylvian plus thalamo-cortical networks in the developing brain of children.

Disclosure of Conflicts of Interest

The authors have no financial or personal relations that could pose a conflict of interest.

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.

Figure legends

Figure 1

MEG and EEG in case 18

A: A-P bipolar EEG shows continuous spike and waves during sleep at the time of MEG study (low frequency filter, 3Hz; high frequency filter, 70Hz).

B: The same EEG of A is expanded to demonstrate left centro-temporal spikes preceding to the right central spikes after the red cursor.

C: 151 MEG channels are labeled by two colors (red for right hemisphere and blue for left hemisphere), and show the view of overlay (left), right channels (middle), and left channels (right). MEG shows more complex polyspikes than EEG on the overlay left channels. Note the MEG spikes (red cursor) leading to EEG spikes (behind the red cursor) on B.

D: MEG topography (left) and EEG topography (right). Note that magnetic and electric topographies are perpendicular to each other.

E: Axial MRI shows MEG spike source at the time of red cursor at the left Rolandic region (circle, position; tail, orientation, and moment).

F: Sagittal MRI shows the same MEG spike source of (E) at the left Rolandic region. The equivalent current dipole (spike source) is oriented horizontally, projecting negativity towards the frontal region and positivity towards the parietal region, corresponding to the EEG topography (D, right).

Figure 2

MRI with MEG spike sources in 18 cases

Red circles demonstrate the source of MEG spikes. Tails indicate orientations and moments of the MEG spike sources. Case 7 shows dynamic statistical parametric mapping. The color bar indicates the P value, ranging from gray, 1×10^{-1} to yellow, $1 \times 10^{-4.3}$.

Supplementary information

Video 1

Epileptic negative myoclonus of the arm and head drop in case 18

A-P bipolar EEG shows frequent bilateral/generalized high-amplitude spike/polyspikes and waves with left centro-temporal predominance. The high-amplitude polyspikes and wave at the middle of the EEG trace corresponds to a brief attenuation of the right deltoid EMG (R Deltoid EMG at the bottom) associated with epileptic negative myoclonus of the right hand and head drop on the video.

Video 2

Absence in case 18

A-P bipolar EEG shows paroxysmal generalized high-amplitude, 3-Hz spike and waves lasting 3.5 seconds that are associated with staring and blinking on the video. At the beginning, left centro-temporal spike and waves lead at T3-T5 and C3-P3. The right hemisphere is spared except for the homologous centro-temporal region at F8-T4 and F4-C4.

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Figure1
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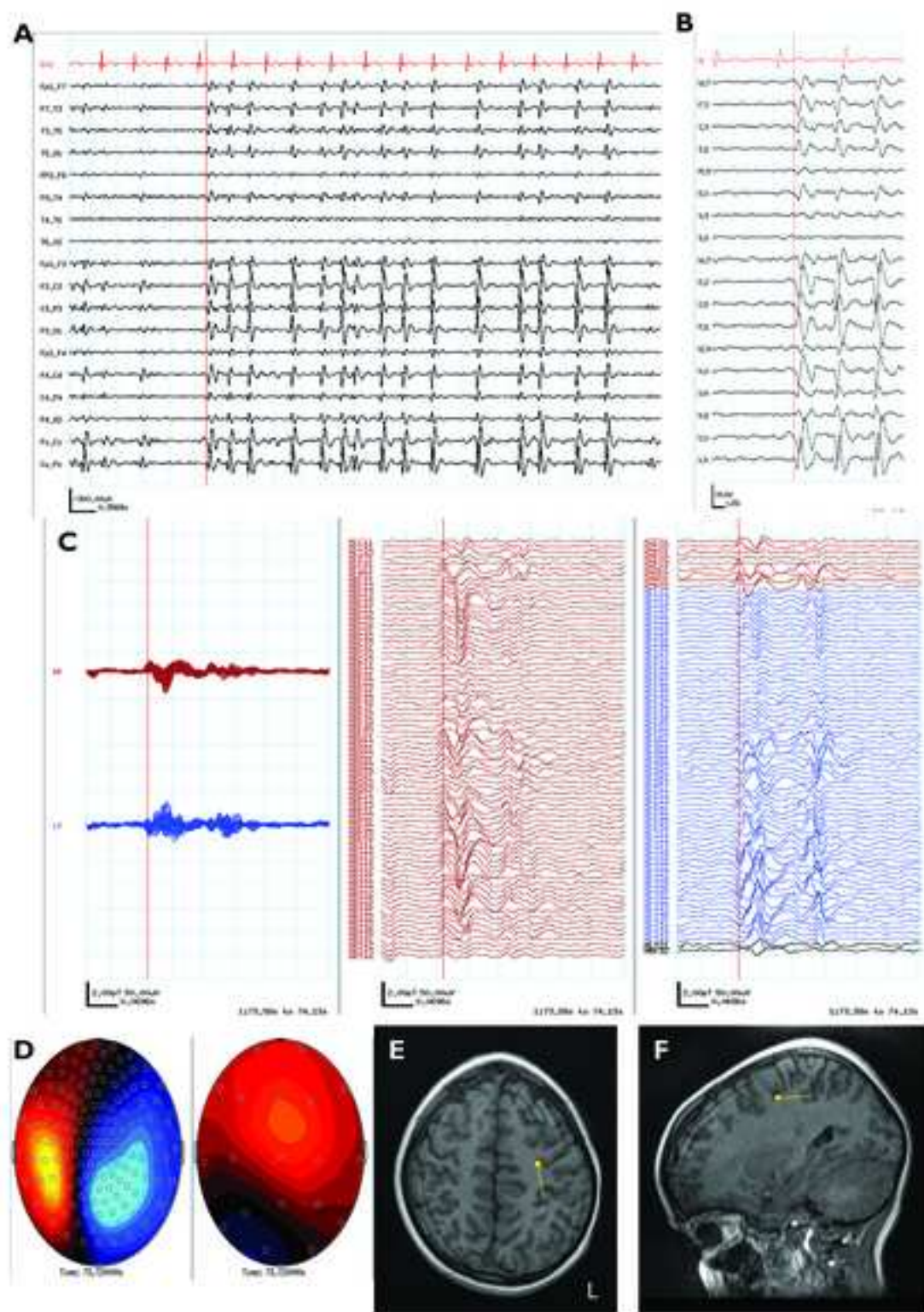


Figure2
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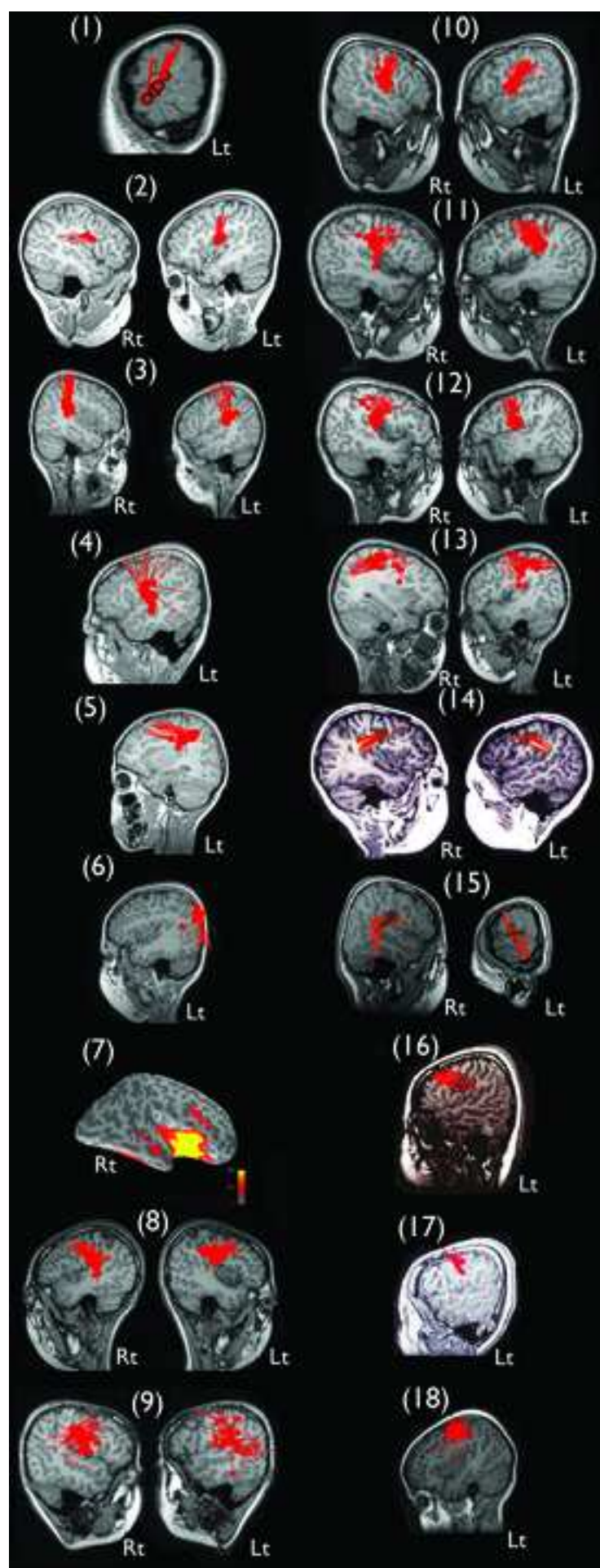


Table1

Seizure onset	1.3 - 8.8 years (median, 2.9 years)	
Initial seizures	Focal motor seizures	15 (83%)
	Absences/atypical absences	3 (17%)
Type of seizures in patient history	Drop attacks	16 (89%)
	Focal motor seizures	16 (89%)
	Epileptic negative myoclonus	14 (78%)
	Absences/atypical absences	11 (61%)
	Myoclonic seizures	10 (56%)
	Secondarily generalized tonic-clonic seizures	9 (50%)
	Focal sensory seizures	6 (33%)
	Epileptic spasms	2 (11%)

Table 1: Seizure profiles

Table2

Patients	Regions			Hemispheres	
	Rolandic	Sylvian	Other lobe	Bilateral	Unilateral
1		1			1
2	1	1		1	
3		1		1	
4		1			1
5	1				1
6			occipital		1
7		1			1
8	1	1		1	
9	1	1		1	
10		1		1	
11	1	1		1	
12	1	1		1	
13	1	1		1	
14	1			1	
15	1	1		1	
16	1				1
17	1				1
18	1	1			1
Total	12	13		10	8

Table 2: MEG spike source localization