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Magnetoencephalography in Fronto-Parietal Opercular Epilepsy

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Abstract

Objective—To clarify the clinical and neurophysiological profiles of fronto-parietal opercular epilepsy in which epileptic spikes are detected with magnetoencephalography (MEG) but not with scalp electroencephalography (EEG).

Methods—Four patients presented with epileptic spikes localized to the fronto-parietal opercular cortex, which were only appreciated following MEG recordings.

Results—In all cases, seizure semiology suggested early activation of the operculum and lower peri-rolandic cortex consistent with the somatotopic organization of this region, i.e. tingling sensation involving the throat and hemi-face or contralateral upper limb, and spasms of the neck and throat. MEG spikes were localized in the fronto-parietal operculum. Three of the four patients underwent invasive electrocorticography and/or stereo-EEG recordings, and spikes were confirmed to arise from the estimated area of MEG dipole localization. Two patients remained seizure-free for over 1 year after resection of the epileptogenic region; the other patient declined resective surgery due to proximity to the language cortex.

Conclusion—This study demonstrates the usefulness of MEG in localizing spikes arising from within the fronto-parietal opercular regions, and implies that MEG may provide localizing information in patients with symptoms suggestive of opercular epilepsy, even if scalp EEG recordings fail to disclose any epileptogenic activities.

Introduction

Neurophysiological evaluation of epileptic brain activities (epileptic spikes) is indispensable for the diagnosis of epilepsy. Magnetoencephalography (MEG) is an important method for the noninvasive localization of epileptic spikes, particularly given its higher spatial resolution compared to surface electroencephalography (EEG). EEG and MEG measure different profiles of the same phenomenon, that is the electrical profile and the corresponding magnetic profile of the activity in a large population of neurons. It is generally believed that the two modalities are complementary, and so combined usage may

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Conflict of Interest

No financial interest is involved in the publication of this manuscript.

provide additional information because some spikes are only detected by one or the other modality (Iwasaki et al., 2005).

MEG is specifically sensitive to tangential current sources, whereas EEG has better sensitivity to radial currents. This difference partly explains the differential spike detectability of the two modalities. MEG might be more sensitive to neuronal activity in the superior temporal plane compared to EEG based on the anatomical geography (Iwasaki et al., 2003). The operculum, the regions of the fronto-parietal and temporal lobes facing the sylvian fissure, form a large cortical area perpendicular to the scalp surface, and this area is potentially important for the generation of spikes that can be easily detected by MEG (Knowlton, 2008). However, few studies have examined the electromagnetic and clinical characteristics of patients with epilepsy originating in this area in more detail.

We present our characterization of 4 patients with epileptic spikes originating from within fronto-parietal opercular cortex, which were clearly detected by MEG but not by repeated scalp EEG.

Methods

Subjects

A total of 300 patients underwent MEG recording for presurgical evaluation in our laboratory from 2008 to 2011. Twelve of these 300 patients were suspected to have epilepsy arising from the opercular region. Both EEG and MEG detected spikes in 7 patients, whereas EEG detected no spikes in the other 5 patients. Further MEG successfully detected spikes localized within the fronto-parietal operculum in 4 of these 5 patients (Fig. 1), which had not been detected by the previous multiple scalp EEG studies. Neither EEG nor MEG detected any spikes in the remaining patient. Figure 1 schematically illustrates the fronto-parietal opercular region. The fronto-parietal operculum is confined by the anterior and posterior ascending rami of the sylvian fissure, and consists of the posterior part of the inferior frontal gyrus, the lower ends of the precentral and postcentral gyri, and the lower end of the anterior part of the inferior parietal lobule (Crossman, 2008).

Data acquisition

Scalp EEG was recorded in accordance with the international 10–20 system with additional anterior temporal electrodes. MEG and simultaneous scalp EEG recorded for 60-min periods during awake and sleep conditions using 1000 Hz sampling rate, with a whole-head system consisting of 204 planar gradiometers (VectorView; Neuromag, Helsinki, Finland). The acquired data were low-pass filtered at 50 Hz. High-pass filtering was used at 4–6 Hz to extract the spike component from the slower background activity. Single dipole modeling was applied for the MEG spikes within a spherical head model using the source modeling software supplied by the vendor (Neuromag, Helsinki, Finland). Equivalent current dipoles for the spikes, or spike dipoles, with a goodness of fit of over 85% were regarded as reliable (Salayev et al., 2006). Stereo-EEG recordings were obtained with depth electrodes consisting of 8–12 cylindrical 2.5-mm long platinum contacts with a diameter of 1.1 mm at 5-mm separations (Integra Epilepsy™; Integra, Plainsboro, NJ, USA). Stereo-EEG data were also sampled at 1000 Hz and band-pass filtered between 0.5 and 70 Hz. The angle of the spike dipole to the vertical line was measured in each patient as shown in Fig. 1 and Table 1.

Case 1—A 30-year-old left-handed male began having seizures from age 12 years. The patient had no identifiable risk factors for epilepsy. The initial manifestation of his seizures was a tingling sensation in the throat and occasionally the left face, followed by twitching of

the left side of the face. He would then experience difficulty breathing accompanied by drooling and garbled speech. Left face clonic activity was observed during longer seizures. Consciousness was completely preserved during these events. Seizures typically lasted for 30 seconds and occurred up to 10 times per day, despite trials of numerous antiepileptic medications. Multiple scalp-EEG including prolonged video-EEG recordings during the awake and sleep states failed to reveal any clear interictal epileptiform abnormalities. Ictal EEG patterns were non-localizable. Interictal fluorodeoxyglucose positron emission tomography (FDG-PET) showed subtle hypometabolism in the right fronto-temporal operculum. Ictal single photon emission computed tomography (SPECT) failed to uncover any specific area of hyperperfusion, possibly due to the brevity of the patient's seizures. High-resolution magnetic resonance (MR) imaging reviewed by a dedicated neuro-radiologist identified no abnormalities. Following detailed discussion in a multidisciplinary patient management conference, invasive evaluation with stereotactically placed depth EEG (SEEG) electrodes was recommended targeting the perisylvian, opercular, and lower perirolandic cortices on the right. Simultaneous SEEG and MEG recordings were performed in a magnetically shielded room as part of an ongoing clinical investigation in our MEG laboratory (Wang et al., in press). Frequent epileptic spikes were detected by MEG, but could not be identified by concurrent scalp EEG. However, stereo-EEG recordings showed that these spikes involved the depth electrode placed within the right fronto-parietal operculum. The corresponding MEG spike dipoles were found to form a tight cluster with vertical orientation located within the right fronto-parietal operculum in the same region implicated by simultaneous SEEG recording (Fig. 2). Ictal EEG discharges also involved these same SEEG electrodes. Partial resection of the right fronto-parietal operculum including the area of interictal spikes resulted in the patient becoming seizure-free (2-year follow up). Histological examination revealed type IIB (balloon-cell) focal cortical dysplasia.

Case 2—A 54-year-old right-handed male began having seizures at the age of 43 years. He had been diagnosed with tuberous sclerosis complex a few years prior to seizure onset. His perinatal and development history was unremarkable, and his cognitive abilities were within the average range, but in retrospect he did have a strong family history of epilepsy on the paternal side of his family. Seizures were characterized by tingling sensation involving the left arm and occasionally shoulder, followed by stiffness of the left, and then the right arm. Impairment of consciousness was noted with longer seizures. However, he had no history of secondary generalized tonic-clonic seizures. Typical duration of seizures was 30 seconds to 2 minutes, and frequency was once every 2–3 days, despite trials of several antiepileptic medications as well as vagus nerve stimulation. Multiple scalp-EEG including prolonged video-EEG recordings during the awake and sleep states failed to reveal any clear interictal epileptiform abnormalities. Ictal EEG patterns were either non-localizable or showed early regional changes involving the right centro-parietal electrodes. FDG-PET did not reveal any particular areas of hypometabolism. MR imaging showed multiple cortical tubers in both hemispheres. Simultaneous whole-head MEG and scalp EEG recordings detected frequent MEG spikes but no clearly correlated scalp EEG spikes. Individual MEG spike dipoles had uniform anterior orientation and were estimated to form a tight cluster within the right fronto-parietal opercular region (Fig. 3a). After detailed discussion in a multidisciplinary patient management conference, invasive evaluation with combination of electrocorticography and depth electrodes was recommended, targeting the affected areas, such as the fronto-parietal convex and peri-opercular insular region on the right. Invasive monitoring showed that these spikes involved the right fronto-parietal to frontal operculum, and the findings were consistent with the ictus. Right frontal lobectomy, which included the right fronto-parietal operculum including the origin of the interictal spikes, resulted in the patient becoming seizure-free for over 1 year.

Case 3—A 23-year-old right-handed female began having seizures at the age of 19 years. The patient had no identifiable risk factors for epilepsy. Her seizures were preceded by an aura of right arm tingling followed by aphasia. She was unable to speak or comprehend what others were saying prior to losing awareness. She would occasionally suffer focal clonic seizures involving the right arm and face, followed by secondary generalized tonic-clonic seizures during longer seizures. Seizures typically lasted from 10 seconds to 2 minutes, with a frequency of 7–10 times per month, despite trials of several antiepileptic medications. Multiple scalp-EEG including prolonged video-EEG recordings during the awake and sleep states failed to reveal any clear interictal epileptiform abnormalities. Ictal EEG patterns were either non-localizable or lateralized to the left hemisphere. Interictal FDG-PET showed mild hypometabolism involving the left fronto-temporo-parietal operculum. Ictal SPECT did not reveal any particular area of hyperperfusion. MR imaging showed a stable 7-mm diameter lesion within the right cerebellar peduncle, possibly a low grade glioma, but no other abnormalities. Simultaneous MEG and scalp EEG recordings again revealed frequent MEG spikes but no clear correlated EEG spikes. MEG spike dipoles were similarly estimated within the left fronto-parietal opercular region (Fig. 3b). The patient was referred for stereo-EEG evaluation, which confirmed that these spikes involved the depth electrode placed within the right fronto-parietal operculum in proximity to the posterior ascending ramus. Ictal EEG discharges originated from this region. The stereo-EEG results agreed with the MEG spike dipole localization, but the patient declined resective surgery because she was considered to be at high risk for postoperative language impairment.

Case 4—A 34-year-old right-handed male began having seizures at the age of 10 years. His perinatal and development history were unremarkable. He had no other risk factors except for a history of an isolated simple febrile seizure at age 2.5 years. Habitual seizures started with abrupt spasm involving the neck and throat muscles, followed by salivation and sometimes vomiting, during which consciousness was preserved. He had no history of secondary generalized tonic-clonic seizures. Seizures occurred almost every day, with variable frequency of once to 25 times per day, despite trials of several antiepileptic medications. Multiple scalp-EEG including prolonged video-EEG recordings during the awake and sleep states failed to reveal any clear interictal epileptiform abnormalities. Ictal EEG patterns were non-localizable. Interictal FDG-PET showed subtle focal hypometabolism involving the right frontal operculum. Postictal SPECT showed hypoperfusion involving the right periopercular region. High-resolution MR imaging showed no abnormalities except for a Chiari type 1 malformation. Simultaneous MEG and scalp EEG recordings revealed clear frequent MEG spikes but no clear correlated EEG spikes. Individual MEG spike dipoles were estimated within the right fronto-parietal opercular region, and appeared to form a tight cluster with uniform upward orientation suggesting a generator within the upper bank of the sylvian fissure (Salayev et al., 2006) (Fig. 3c). The therapeutic strategy team agreed that the seizures originated from the right fronto-parietal operculum. Further invasive evaluation has been proposed to the patient to clarify the detail of the epileptic region.

Results

Table 1 summarizes the clinical characteristics of all cases. Initial seizure symptoms were as follows: tingling sensation involving the throat and hemi-face (Case 1) or contralateral upper limb (Cases 2 and 3), and spasms of the neck and throat (Case 4). In all cases, the MEG spike dipoles were estimated to be tightly clustered within the right (Cases 1, 2, and 4) or left (Case 3) fronto-parietal operculum, and were topographically consistent with the somatotopy of the initial seizure manifestations in each patient, although variability in the spike dipole orientation to the vertical line was seen (mean 31.6°, range 11.8–71.8°); as shown in Table 1. Three of the four patients underwent invasive electrocorticography and/or

stereo-EEG recordings, and the EEG peaks were confirmed to arise from the region of the estimated MEG dipoles. Two of these three patients became seizure-free for at least 1 year after resection of the epileptogenic region. The other patient declined resective surgery due to proximity to the language cortex.

Discussion

This study illustrates the accuracy of MEG for the localization of opercular epilepsy and for the detection of epileptogenic spikes arising within the fronto-parietal operculum in a subset of patients in whom EEG had failed to show clear spikes (Iwasaki et al., 2003).

Our study found that multiple scalp EEGs detected interictal spikes in only 7 of 12 patients with fronto-parietal operculum epilepsy. In contrast, MEG detected spikes in 4 of the 5 patients without EEG spikes, and the epileptogenic origin was confirmed in 3 of these 4 patients, and supported by seizure freedom in two patients. These observations show that clinicians should always be mindful of the limitations of scalp EEG. In particular, the absence of spikes by EEG does not necessarily imply that epileptogenic spikes are not being generated. Sometimes re-review of EEG recordings will identify the correlates of MEG spikes as sharp transients with low amplitude, but such activities are easily missed in a clinical setting, especially if subtle or do not have clear epileptiform features based on conventional clinical EEG interpretation. Therefore, repeated failure of scalp EEG to detect definite spikes does not eliminate the possibility of an active opercular epileptic focus. We also need to consider that MEG is also totally reliable based on the fact that neither MEG nor EEG detected spikes in one of our 12 patients. This patient was diagnosed with musicogenic epilepsy characterized by the total absence of interictal spikes detected by chronic intracranial recording. This study includes too few patients to clarify the rate of patients with operculum spikes not detected by MEG, and the only negative case has special characteristics. More experience is needed, but we suggest that MEG is helpful for confirming or establishing the diagnosis of opercular epilepsy based on interictal recordings.

The seizure semiology in our 4 cases identified by MEG suggests activation of the opercular and lower peri-rolandic cortices in accordance with Penfield's homunculus (Penfield and Rasmussen, 1950). Localization of the MEG dipoles in all cases was concordant with such seizure semiology. The accuracy of the MEG results was validated by the findings of invasive evaluation in two patients (one with simultaneous stereo-EEG and MEG recordings and subsequent successful epilepsy surgery). Notably, the somatotopic representation of the lower peri-rolandic and opercular areas has not been fully clarified (Schott, 1993). A previous study evaluating the relationship between MEG spike dipole localization and seizure semiology in benign focal epilepsy of childhood with centrotemporal spikes (BECTS) indicated possible complex and variable somatotopic representation within the lower rolandic area (Kakisaka et al., 2009, 2011) as previously speculated (Penfield and Rasmussen, 1950). Spike dipoles of BECTS were estimated around the lower area of the central sulcus and showed little variance, whereas the corresponding initial seizure manifestations were more variable (Kakisaka et al., 2011). This variability in clinical symptoms might be explained by a complex and variable somatotopy and/or diverse propagation patterns of ictal discharges within this region. Generally, the primary motor cortex covering orofacial area or lower rolandic area is regarded to have a lower seizure threshold compared with the higher rolandic area (Kotagal and Luders, 2008).

The present study supports the conventional speculation that MEG has high sensitivity to spikes originating from the cortex along the sylvian fissure, and also emphasizes the utility of MEG in patients in whom the seizure symptoms that suggest early opercular activation but scalp EEG fails to detect epileptic spikes. The geometry of the fissural cortices

(including the two banks of the sylvian fissure) is best suited to MEG analysis, since the currents/dipoles generated are tangentially oriented (Iwasaki et al., 2003; Knowlton, 2008). A comprehensive study of 8 patients with opercular-insular epilepsy documented with intracerebral (SEEG) recordings demonstrated the sporadic and often non-localizing nature of interictal scalp EEG abnormalities (Proserpio et al., 2011). The limited value of interictal scalp EEG was attributed to the anatomy of the opercular-insular cortex generating the epileptic discharges in these patients. In a recent series of 3 challenging patients with MR imaging-occult focal epilepsy, MEG had “additive” value in uncovering the peri-insular focus and directing surgical decision-making (Heers et al., 2011). As in our series, all three patients underwent localizing MEG study, although no interictal spikes were seen on prolonged scalp EEG recordings in two (Heers et al., 2011). The results are consistent with our findings of the difficulty in detection of opercular-insular spikes with EEG, although the correlates of MEG spikes may be appreciable as sharp transients with low amplitude as described above. The peculiar profile of this type of spikes can be explained by the potential distribution model of the cerebral cortex (Gloor, 1985). In this model, the electrode would detect spikes more effectively if placed near the spike source in the radial direction, but would detect few or no spikes if placed in the tangential direction, regardless of the distance from the source. Therefore, the orientation of spike dipole could also affect spike detection with EEG. However, this study cannot clarify the relationship because of the small number of subjects. More experience with cases is necessary to settle this question.

We believe that the present five cases represent a group of patients with focal epilepsy that share common electroclinical characteristics: Seizure semiology explained by activation of the opercular or lower peri-rolandic cortex, with sensorimotor seizures involving mainly the throat, face, or contralateral arm along with autonomic and vegetative manifestations suggestive of early insular activation; and potential benefit from MEG for the detection of epileptic spikes in the absence of positive detection by interictal scalp EEG. This constellation of electroclinical features has not been clearly recognized or mentioned in current classifications of seizures (Williamson and Engel, 2008). Our series did not include patients with epilepsy arising from the temporal operculum, who commonly manifest with auditory aura and other symptoms suggestive of perisylvian cortex activation. Such patients with temporal opercular epilepsy may also benefit from the higher sensitivity of MEG to tangential sources as suggested by previous reports (Iwasaki et al., 2003), and by our current understanding of the geometry of this region (Knowlton, 2008).

In conclusion, we emphasize the importance of MEG for the evaluation of patients with suspected epileptogenic zone within the opercular cortex, particularly if scalp EEG provides no diagnostic indications.

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Fig. 1.

Sagittal (left) and coronal (right) schema of the fronto-parietal operculum, located between the anterior ascending and posterior ascending rami of the sylvian fissure, and consisting of the posterior part of the inferior frontal gyrus, the lower ends of the precentral and postcentral gyri, and the lower end of the anterior part of the inferior parietal lobule. Angle between the spike dipole and vertical line is calculated as shown in the coronal schema.

Fig. 2.

Case 1. Representative spikes recorded with stereotactically placed depth EEG (SEEG) electrodes and MEG (upper). Contour map (solid line indicates magnetic field efflux, and broken line indicates magnetic field influx from the brain surface) estimated based on the peak of the MEG spike highlighted in this image (middle left). Corresponding MEG spike dipoles superimposed on the patient's sagittal MR image (circle indicates estimated location and bar indicates orientation of each individual dipole; lower left). Location of SEEG electrode contact inserted within the right opercular region (middle right), and postoperative sagittal MR image illustrating the area of resection within the right fronto-parietal operculum overlapping with the estimated location of the MEG spike focus (lower right).

Note that the patient has been seizure-free for 2 years following surgical resection of the epileptogenic cortex based on simultaneous interictal MEG/SEEG as well as ictal SEEG recordings.

Fig. 3. Cases 2–4 (a–c, respectively). Waveforms of simultaneous scalp EEG and MEG (top), corresponding contour maps (middle), and spike dipoles estimated based on the peak of the MEG spike and, if any, postoperative MR image (Case 2) or location of the contact of sEEG electrodes with which spikes were detected (Case 3) (bottom). Arrows on contour maps indicate the estimated dipole at the peak of each spike. Solid line indicates magnetic field efflux, and broken line indicates magnetic field influx from the brain surface. Circle indicates estimated location and bar indicates orientation of each individual dipole. MEG reveals clear spikes in contrast with simultaneous scalp EEG that shows no obvious epileptiform abnormalities. Spike dipoles are confidently estimated in each case to form a

tight cluster within the fronto-parietal opercular region. Localization of MEG spike dipoles was concordant to invasive findings in Cases 2 and 3.

Table 1

Clinical profiles of the 4 cases

Case	Sex	Age	Age of seizure onset	Etiology	Family history (Epilepsy)	MRI	Previous interictal EEG	Clinical seizure (Initial symptom)	EEG seizure onset	MEG dipole location	Degree (θ fig) of MEG dipole to vertical line	Resection
1	M	30	12	CD type IIB	none	normal	No spikes	tingling sensation of throat	non-localized	R FP operculum	22.9	Yes (seizure free >2y)
2	M	54	43	TS	yes	multiple tubers	No spikes	tingling sensation of L arm & shoulder	R CP or non-localized	R FP operculum	71.8	yes (seizure free >1y)
3	F	24	19	unknown	none	R cerebellar lesion	No spikes	tingling sensation of R arm	L or non-localized	L FP operculum	11.8	No
4	M	34	10	unknown	none	Chiari 1 malformation	No spikes	spasm of neck-throat muscle	R or L or non-localized	R FP operculum	20.0	Pending further evaluation

Abbreviation: CD, cortical dysplasia; CP, centro-parietal; FP, fronto-parietal; L, left; R, right; TS, tuberous sclerosis