Case Report

Magnetoencephalography-identified preictal spiking correlates to preictal spiking on stereotactic EEG

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Abstract

Magnetoencephalography (MEG) is a noninvasive diagnostic modality that directly measures neuronal signaling by recording the magnetic field created from dendritic, intracellular, electrical currents of the neuron at the surface of the head. In clinical practice, MEG is used in the epilepsy presurgical evaluation and most commonly is an “interictal” study that can provide source localization of spike-wave discharges.

However, seizures may be recorded during MEG (“ictal MEG”) and mapping of these discharges may provide more accurate localization of the seizure onset zone. In addition, spike-negative EEG with unique MEG spike-waves may be present in up to 1/3 of MEG studies and unique MEG seizures (EEG-negative seizures) have been reported. This case report describes a patient with unique MEG seizures that exhibited MEG pre-ictal spiking in a tight cluster consistent with the independent interictal epileptiform activity. Stereotactic EEG demonstrated pre-ictal spiking concordant with the MEG pre-ictal spiking.

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Introduction

Magnetoencephalography (MEG) is a noninvasive diagnostic modality that directly measures neuronal signaling by recording the magnetic field created from dendritic, intracellular, electrical currents of the neuron at the surface of the head. In clinical practice, MEG is used in the epilepsy presurgical evaluation and most commonly is an “interictal” study that can provide source localization of spike-wave discharges. However, seizures may be recorded during MEG (“ictal MEG”) and mapping of these discharges may provide more accurate localization of the seizure onset zone (SOZ). In addition, spike-negative EEG with unique MEG spike-waves may be present in up to 1/3 of MEG studies and unique MEG seizures (EEG-negative seizures) have been reported.

This case report describes a patient with MEG-predominant seizures (seizures better identified on MEG compared to simultaneous EEG recording) that began with preictal spiking. A subsequent stereotactic EEG (sEEG) evaluation revealed preictal spiking concordant with the MEG findings. These results led to responsive neural stimulator (RNS) implantation within this region and the patient has experienced an approximate 90% reduction in the frequency of his disabling seizures. Ictal MEG and preictal spiking can assist in the sEEG implantation strategy and may improve surgical outcome.

Case report

A 31-year-old right-handed male with a history of drug-resistant focal epilepsy presented for a repeat epilepsy presurgical evaluation after previous unsuccessful neuromodulation epilepsy surgery, as detailed below.

He was the product of an uncomplicated pregnancy and delivery. There was no history of febrile seizures, family history of epilepsy, or history of stroke, central nervous system infection, or brain tumor. At the ages of 10 and 13 years old, he experienced head trauma, each resulting in a loss of consciousness.

Approximately 1 year after his head injury at the age of 13 years old, he began to experience focal aware seizures characterized by a “fuzzy” paresthesia throughout his upper thighs. Seizures continued until the age of 16 years old when he experienced his first focal to bilateral tonic-clonic seizure. After this seizure he began to
experience multiple seizure types. However, by the time of his epilepsy presurgical and surgical evaluations, beginning in 2005, his predominant seizure types were the Type A and Type B seizures (outlined in Table 1).

From 2005-2008, he underwent an epilepsy presurgical evaluation, and during this evaluation a MEG was obtained (the results of this study are outlined in Table 2). Although the MEG revealed sources within the left sylvian region, scalp EEG and brain MRI were suggestive of an epileptic network within the left frontal lobe. His case was presented at a patient management conference, and in light of his noninvasive diagnostic studies, he underwent intracranial EEG (iceEG) monitoring with bilateral frontal lobe subdural grids as well as subdural grids and strips within the left temporal and parietal regions. Invasive EEG monitoring did not reveal discrete ictal onsets, but ictal evolution was present within the left frontal lobe. These results were reviewed in a patient management conference, and the findings were suggestive of a widespread epileptic network involving the left frontal lobe. As part of the Neuropace pivotal trial, he underwent responsive neural stimulator (RNS) implantation within the left frontal lobe. Following RNS implantation, there was no reduction in his seizure frequency, and he experienced adverse reactions related to cortical stimulation. As such, the device was explanted, and his seizures persisted despite multiple trials of antiseizure medication.

Then, in 2016, a repeat epilepsy presurgical evaluation was initiated. At the time of this epilepsy presurgical evaluation, in 2016 and 2017, he could have up to 10–15 Type A seizures per day and 1 Type C seizure per week. His antiseizure medication regimen consisted of pregabalin, lacosamide, and clobazam polytherapy. In the past, he had failed trials of phenytoin, carbamazepine, gabapentin, lamotrigine, levetiracetam, topiramate, oxcarbazepine, and retigabine (as an investigational drug).

During inpatient video-scalp EEG monitoring, innumerable focal ictal onsets were recorded arising from the left frontal head region. A brain MRI demonstrated mild hippocampal asymmetry as well as left frontal lobe encephalomalacia (related to his previous head trauma). Prior bilateral frontal and left parietal craniotomies were also present (from previous iceEG, detailed above). Single photon emission computed tomography coregistered with MRI (SISCOM) processing of ictal and interictal single photon emission computed tomography scans identified multiple foci of relative ictal hyperperfusion, most prominently within the left, greater than right, paramedian fronto-parietal cortex directly adjacent to the left frontal lobe encephalomalacia. A functional MRI (fMRI) revealed successful localization of the primary motor cortex, primary auditory cortex, and frontal eye fields. Distribution of language related activation suggested left hemispheric dominance.

After these studies were completed, a third MEG was obtained in 2017. Sixty minutes of data were acquired in epochs up to 15 min in length using the following parameters: DC coupled instead of a high-pass filter, a low-pass filter of 100 Hz, and a sampling rate of 508.61 Hz. Waveforms were visually inspected with a bandpass of 1–100 Hz with a notch filter. MEG and EEG were reviewed using BESA and STA/R software. Selected spikes in the MEG were mapped using the equivalent current dipole (ECD) model. A single dipole was selected to represent each sharp wave. In the STA/R system, the dipole selection criteria included a coefficient of 0.9 or better, RMS of 400 fT or more, dipole moment generally of less than 400 nAm, and a confidence volume less than 1 cm³. In general, the ECD was selected from the onset of the spike up to the point of maximum amplitude of the spike. The ECD calculation was performed using 35–45 magnetometer channels, which were chosen to best represent the contour plot of the center of the magnetic field.

During this study, a total of 9 habitual seizures were recorded. Ictal electrographic data was lateralized to the left hemisphere within the left frontal and left fronto-central regions. On MEG, pre-ictal spiking (PIS) was present and lateralized to the left hemisphere with the discharges consistently mapped using ECD to the left posterior sylvian fissure, left posterior superior temporal gyrus, and left parietal operculum with the majority of PIS ECD on MEG mapping to the left parietal operculum. Interictal epileptiform activity was present in both the EEG and MEG, but it was more frequent, with more robust spike-wave discharges on MEG. The interictal epileptiform activity on MEG also mapped in a tight cluster within the left posterior sylvian fissure, left posterior superior temporal gyrus, and left parietal operculum (Figs. 1–4).

In total, he has undergone 3 MEG studies. The 2008 study was done during his initial presurgical evaluation, while the second MEG was completed in 2011, after RNS explantation. The third MEG study was completed during his epilepsy presurgical evaluation in 2016–2017.

On review of the 3 MEG studies, the 2008 and 2017 studies identified interictal epileptiform activity within the sylvian fissure, while the 2011 reported interictal epileptiform activity within the

| Table 1: Seizure Semiology. |
|-----------------------------|
| **Seizure Type** | **Semiology** | **Frequency** | **Miscellaneous** |
| Type A  | FAS | Begins with “fuzzy” paresthesias throughout bilateral upper thighs that slowly that progresses down his leg and when they reach his knees, the paresthesias become painful (burning and tingling dysesthesia). During this time, he experiences fear. | 10–15 per day |
| Type B  | FIAMS | Begins with Type A seizure then rapidly progresses to rigidity and retropulsion such that he will fall in an unprotected fashion. | 1 per week |
| Type C  | FAS | Alternating fear (impending sense of death) and diffuse, nondescript pain throughout his body lasting from 30 s to 60 min. | Rare; difficult to recall last seizure |
| Type D  | FAS | Begins with an intense fear of impending death with a nondescript ascending sensation in his right lower extremity. | Rare; difficult to recall last seizure |
| Type E  | FIAMS | Seizures are characterized by impaired awareness with bilateral shoulder jerking and his right upper extremity abducted and flexed while his lower extremities are splayed in tonic fashion. | Rare; difficult to recall last seizure |
| Type F  | FIAS | Unresponsive staring. | Rare; difficult to recall last seizure |
| Type G  | FBTCS | Limited | Free for approximately 18 years |

Abbreviations: FAS – focal aware seizure, FIAMS – focal impaired awareness motor seizure, FIAS – focal impaired awareness seizure, FBTCS – focal to bilateral tonic-clonic seizure.
left middle frontal gyrus. Although seizures were present on all 3 MEG studies, ictal data could not be successfully modeled in the 2008 and 2011 studies. As such, ictal data were only analyzed in the 2017 study. A summarized comparison of these 3 studies is detailed below, in Table 2. On the basis of the 2017 MEG results as well as his other noninvasive diagnostic studies, sEEG implantation was pursued. sEEG-targeted regions included the left parietal operculum (MEG-identified region of interest [ROI]), left posterior insular cortex (SISCOM-identified ROI), left parietal convexity (fMRI-identified right thigh sensory ROI), left perilesional frontal lobe (adjacent to MRI-identified lesion), and left posterior frontal lobe (SISCOM-identified ROI).

During 8 days of video-sEEG monitoring, there were 25 discrete (habitual Type A, B, C, E, and F seizures) seizures arising near-simultaneously (within milliseconds) in the left parietal operculum and left posterior insular derivations. Following a typical seizure, the patient had a flurry of brief focal aware seizures with motor features (FAS + motor) exhibiting onsets in left lateral frontal and temporal gyri.

### Table 2

Simultaneous EEG and MEG studies.

| Year | EEG spike-waves (Y/N) | MEG spike-waves (Y/N) | EEG and/or MEG seizures (Y/N) | MSI (using ECD) |
|------|-----------------------|-----------------------|------------------------------|---------------|
| 2008 | Y – L F (F3 maximum)  | Y – L F               | Y – 1 seizure more prominent on EEG (ML and PS regions); no obvious MEG activity on MEG | Y – L DSR (interictal discharges only) |
| 2011 | Y – L FT (F3, FP1, Fz, F7) | Y – L F               | Y – 1 seizure arising from central head regions on EEG; no obvious activity on MEG | Y – L MFG (interictal discharges only) |
| 2017 | Y – L FCP, P5W        | Y – L FT              | Y – 9 unique MEG seizures with predominant PIS on MEG | Y – L pSF, L pSTG, and L pO (both interictal and ictal discharges) |

Abbreviations: Y – yes/present, N – no/not present, L – left, F – frontal, ML – midline, PS – parasagittal, DSR – deep sylvian region, FT – fronto-temporal, MFG – middle frontal gyrus, FCP – fronto-centro-parietal, PIS – pre-ictal spiking, pSF – posterior sylvian fissure, pSTG – posterior superior temporal gyrus, pO – parietal operculum.

**Fig. 1.** Interictal epileptiform activity on MEG. A – Scalp-EEG with subtle sharp wave discharges (negative at P7 and positive at F3); B – MEG spike-wave discharge over the left frontal and temporal sensors with counter map; C – ECD of MEG spike-wave discharge mapping to the left posterior sylvian region within the left parietal operculum. Note, 4 second page speed on EEG and MEG. Interictal epileptiform activity was defined by isolated sharp and spike-wave discharges that were not distinctly associated with repetition or rhythmicity. These discharges were not accompanied by evolving epileptiform activity.
posterior frontal derivations (more robustly in the medial posterior frontal contacts). Extraoperative brain mapping was completed with Nihon Kohden MS-120-EEG cortical stimulator. Stimulation parameters included a frequency of 50 Hz, pulse width of 3 μsec, and a train duration 3–5 msec. Stimulation was started at 1 mA with incremental increases until clinical symptoms, seizures, or after discharges were produced, or a stimulation intensity of 7 MA was reached. Cortical stimulation reproduced the patient’s habitual seizure semiology with stimulation of posterior insular contacts (contacts PI1-2 and PI4-5 at 50 Hz, 2 mA) and parietal opercular contacts (contacts PO6-7 at 50 Hz, 3 mA).

In December 2018, he underwent implantation of a responsive neurostimulator with active leads targeting the left parietal operculum and left centromedian nucleus of the thalamus. Inactive leads were placed in left posterior insular and left posteromesial frontal lobe.

Responsive neurostimulator (RNS) detection was fine-tuned, and eventually cathodal stimulation was initiated on all four centromedian contacts (details of the RNS adjustments and seizure frequency are detailed below, in Fig. 5). Optimization of RNS therapy, has resulted in a greater than 90% reduction in the frequency of his most frequent and disabling seizures (Type A and B seizures).

Discussion

In this case, a male with drug-resistant focal epilepsy underwent multiple epilepsy presurgical evaluations, invasive EEG monitoring with subdural grid implantation, RNS implantation in the left frontal lobe, and then explanation of RNS. A repeat (third total) MEG was obtained during another epilepsy presurgical evaluation in 2017 and this study demonstrated MEG-predominant seizures that exhibited MEG preictal spiking in a tight cluster concordant with the cluster of independent interictal epileptiform activity. Stereotactic EEG revealed pre-ictal spiking concordant with the MEG pre-ictal spiking. He had repeat RNS implantation within the left parietal operculum and left centromedian nucleus of the thalamus. He has experienced a meaningful, approximately 90%, reduction in the frequency of his disabling seizures.

The utility of MEG in the epilepsy presurgical evaluation, particularly through source localization with the ECD, has been well-documented [1–13]. In fact, several case reports and case series have articulated MEG sensitivity in identifying sources within the sylvian region, including the operculum and insula [14,15]. However, the majority of MEG studies are “interictal” studies. Seizures only occur during approximately 12% of MEG cases [16]. In this case, interictal epileptiform and seizures were present. Analysis
of these independent discharges were concordant and revealed sources within the posterior sylvian region.

In a large case series from Alkawadri et al., 44/377 patients undergoing a MEG at the Cleveland Clinic experienced at least 1 seizure during the MEG [16]. Equivalent current dipole analysis was possible in 29 patients and sublobar concordance between ictal and interictal ECD was present in 18/21 patients [16]. Overall, ictal MEG ECD correlated with the lobe of onset identified with icEEG in 7/8 cases [16].

Similar findings were also reported by Fujiwara et al [17] and Medvedovsky et al [18]. In one study, there was concordance with ictal and interictal MEG source localization in the same lobe in 5/8 cases [17]. However, ictal MEG source localization was closer to the SOZ defined by invasive EEG monitoring [17]. Medvedovsky et al. reported ictal-onset MEG and interictal MEG sources were nearly equal, but ictal-MEG was more sensitive to the SOZ identified by intracranial EEG monitoring [18].

MEG-unique ictal spike-waves have also been described [16,19]. In the case series from the Cleveland Clinic Epilepsy Center, 7% of ictal MEG studies were EEG-negative seizures [16]. In a separate case report by Kakisaka et al., MEG-unique spike-waves preceded the MEG-EEG ictal patterns [19].

Preictal spiking is a common seizure onset pattern that has been described with icEEG monitoring in various focal epilepsies [20–22]. The presence of preictal spiking on MEG is less well-described but has been reported as an ictal pattern. For example, the most common MEG rhythms at ictal onset in the case series from the Cleveland Clinic Epilepsy Center was repetitive spiking (11/44 cases, 25%). However, this pattern was not specifically correlated to the ictal patterns on sEEG [16]. To our knowledge, this is the first report that correlates MEG-unique preictal spiking with preictal spiking on sEEG and RNS detection.

It has been hypothesized preictal spiking is the result of neuronal hypersynchronization within an epileptic network [20–22]. If the initiating hypersynchronous neuronal activity originates in a sulcus or fissure, creating a tangential source, MEG would be more sensitive than scalp EEG in detecting this activity [23–25]. In 2 separate case reports, Kakisaka et al. described MEG-unique (scalp-EEG negative) ictal spike-waves and hypothesized the early prominence of MEG-unique ictal spike waves was related to the seizures’ directional profile, that is, an early, more prominent, tangential source [19,26].

Additionally, MEG’s sensitivity to sources within the sylvian fissure, e.g., insula and operculum, has been described in a cases series from Mohamed et al. [14,15]. In one case series, MEG spike-waves located within the anterior operculoinsular region, posterior operculoinsular region, and diffuse perisylvian region were present in 13/14 patients [15]. In the case presented here, the presence of

Fig. 3. sEEG preictal spike-waves with evolving to an electrographic seizure A – Coregistration of the left parietal operculum sEEG electrode to the patient’s brain MRI; B – Early preictal spiking (orange arrows) within the left parietal operculum; C and D – Increase frequency of preictal spiking with parietal operculum and adjacent contacts (PO – parietal operculum, PI – posterior insula, LES – lower extremity sensory); E – Transition of preictal spiking to an electrographic seizure (large red arrow).
Fig. 4. Summary of MEG and sEEG findings
A – Interictal discharge on MEG with ECD
B – One MEG predominant spike-wave discharge (scalp-EEG sharp wave, negative at P9, P7, and F3) preictal spike-wave discharge; C – ECD mapping of interictal discharges (red triangles) and preictal spiking (green triangles) forming a tight cluster within the left posterior sylvian region; D – Coregistration of the left parietal operculum sEEG electrode to the patient’s brain MRI; E – Transition of preictal spiking on sEEG to an electrographic seizure (large red arrow).

Fig. 5. Responsive Neural Stimulator (RNS) settings and seizure outcomes
Initiation of thalamic stimulation (0.5 μC/cm², 125 Hz, 5 s); Initiation of two therapy stimulation with cortical bipolar (+→−→−) stimulation (0.5 μC/cm², 200 Hz, 100 ms) followed immediately by thalamic stimulation (0.5 μC/cm², 125 Hz, 5 s); Reduction in cortical and thalamic charge density due to paresthesias; Two therapy stimulation with cortical bipolar (+→−→−) stimulation (1.0 μC/cm², 200 Hz, 100 ms) followed immediately by low frequency thalamic stimulation (1.0 μC/cm², 5 Hz, 5 s); Two therapy, lead-to-lead, low frequency stimulation with cortical leads anodal (+) and thalamic leads cathodal (−) for 5 s (1.0 μC/cm², 7.1 Hz) followed immediately by lead-to-lead stimulation with cortical leads cathodal (−) and thalamic leads anodal (+) for 5 s (1.0 μC/cm², 7.1 Hz).
neuronal hypersynchronization within the parietal operculum may have created a tangential field that was detected on MEG as preictal spiking before propagation to adjacent structures.

It is not uncommon for MEG to change the iEEG implantation strategy [6,11,27]. Although in this case two previous MEG studies in 2008 and 2011 recorded seizures, no definitive MEG spike-waves were identified by the MEG readers at that time. Following his MEG in 2017, which identified MEG-unique preictal spiking, the iEEG implantation was refined to sEEG with coverage specifically in the left parietal operculum. The patient’s previous iEEG monitoring consisted of SDGs within the left frontal lobe and the ability of sEEG to detect seizures within deep cortical structures may explain the differences in outcomes between his initial RNS implantation with the subsequent RNS implantation in 2017. Therefore, it could be reasonable to pursue sEEG implantation, in place of subdural implantation, when MEG-unique spike-waves map to a sulcus or within a fissure. Correlating ictal onsets between unique MEG spike-waves and sEEG may also improve potential RNS targets as well as surgical outcomes. In this case, the MEG results assisted in sEEG implantation that subsequently delineated an RNS target and resulted in a marked reduction (approximately 90%) in the frequency of his disabling seizures.

Conclusions

This case demonstrates a correlation between MEG-predominant preictal spiking and preictal spiking on sEEG. These studies provided robust data for RNS implantation, which resulted in a pronounced reduction in disabling seizures. Although ictal MEG may be uncommon, the presence of ictal patterns, such as preictal spiking, on MEG may allow for more accurate sEEG implantation and improved surgical outcomes. The utility of MEG in defining interictal and ictal localization in patients with focal seizures emphasizes its need for considering regular use in the epilepsy presurgical evaluation.

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