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Magnetic Source Imaging for the Surgical Evaluation of EEG Secondary Bilateral Synchrony in Intractable Epilepsy

Edward F. Chang, MD¹, Srikantan S. Nagarajan, PhD², Mary Mantle, REEG/EP², Nicholas M. Barbaro, MD¹, and Heidi E. Kirsch, MS, MD^{2,3}

¹Department of Neurological Surgery, University of California, San Francisco

²Department of Radiology, University of California, San Francisco

³Department of Neurology, University of California, San Francisco

Abstract

Objective—Routine scalp EEG cannot always distinguish whether generalized epileptiform discharges are the result of primary bilateral synchrony or secondary bilateral synchrony (SBS) from a focal origin, in which the latter may be amenable to surgical resection. Whole-head magnetoencephalography (MEG) has superior spatial resolution compared to traditional EEG and can potentially elucidate seizure foci in challenging epilepsy patients undergoing evaluation for surgery.

Methods—Sixteen medically intractable epilepsy patients with suspected SBS were referred for magnetic source imaging (MSI). All patients had bilateral synchronous, widespread, and most often generalized spike-wave discharges on scalp EEG, plus some other clinical (e.g. seizure semiology) or MRI feature (e.g. focal lesion) suggesting focal onset and hence possible surgical candidacy. MSI is the combination of whole-head MEG and parametric reconstruction of corresponding electrical brain sources. MEG and simultaneous EEG were recorded with a 275-channel whole-head system. Parameters of a single equivalent current dipole were estimated from the MEG data, and the dipole location and orientation was superimposed on patients' MRIs.

Results—MSI revealed a focal dipole clusters in 12 of the total 16 patients (75%), of which a single dipole cluster was identified in seven patients (44%). Patient age, seizure type, seizure duration, VET and MRI results were analyzed to determine factors predictive of having focus clusters revealed on MSI. Of these factors, only focal MRI anatomic abnormalities were associated with focal MSI dipole clusters (Chi square test, $P=0.03$). Selective surgical resections (including the dipole cluster) in seven of eight patients (87%) resulted in seizure-free or rare seizure outcomes (Engels I and II).

Conclusions—These findings suggest an important role for MSI in the localization of focal onset in patients for whom there is a suspicion of SBS (based on clinical or MRI data). Identification of a focal seizure origin has significant implications for both resective and non-resective treatment of intractable epilepsy.

Keywords

magnetoencephalography; epilepsy; secondary bilateral synchrony; magnetic source imaging; epilepsy surgery

INTRODUCTION

Routine scalp EEG cannot always distinguish whether generalized epileptiform discharges are the result of primary bilateral synchrony (PBS) or secondary bilateral synchrony (SBS) from a focal origin. First described by Tükel and Jasper in 1952, SBS is defined as the rapid bilateral spread from a limited cortical area of electrical abnormality¹⁷. PBS, in contrast, is thought to have sources that are bilaterally symmetrical, with possible origination in subcortical structures projecting to multiple cortical areas, such as in genetic idiopathic generalized epilepsies^{1,2}. Misinterpretation of SBS as PBS has significant implications for patient management, as the former is often amenable to surgical remediation.

In SBS, cortico-cortical connections via the corpus callosum are thought to facilitate fast synchronization of epileptiform activity that arises from a focal source^{1,2,5}. It may be suggested by a consistent temporal relationship between a focal spike and an ensuing bilateral synchronous discharge, with a consistent time lag between the appearances of spike wave discharges in both hemispheres. In PBS, however, there is by definition no time lag between synchronization of activity in bilateral hemispheres^{1,2,17}. The region of maximum amplitude or of phase reversal may shift within an individual burst or indeed from burst to burst and unless a maximum is consistent, does not reliably differentiate PBS from SBS. Most reported cases of SBS arise from a focal source in the frontal lobe, followed by the temporal and parietal lobes². Frequently, medial frontal lobe sources such as a parasagittal meningioma can generate SBS, but cases have been also described in which the most likely sources were far from midline¹⁷.

Methods of differentiating SBS from PBS include the application of independent component analysis of EEG⁵, estimation of interhemispheric small time difference during spike wave bursts¹⁰, and the use of high temporal resolution EEG tomographic source reconstruction¹². Recently, whole-head magnetoencephalography (MEG) has been increasingly used to complement EEG in the evaluation of patients with epilepsy^{6,8,18}.

MEG has several theoretical advantages over conventional low-density scalp EEG, including increased spatial resolution and sensitivity. MEG is not limited by conductivity issues, as is EEG, and is thought to be more sensitive to tangential sulcal sources. A few case reports have recently described the utility of MEG and its superimposition on structural MRI, referred to as magnetic source imaging or MSI, in the workup of patients with SBS^{15,16}. Despite these advantages, the role of MEG in surgical evaluation of patients with partial epilepsies is unclear¹¹.

In this study, we aimed to describe our institution's experience with MSI in the evaluation of selected patients with suspected SBS.

METHODS

We retrospectively reviewed the records of sixteen patients with medically intractable epilepsy whom underwent MSI between 2001 and 2006. We selected patients whose clinical referral indicated that they had generalized or diffuse ictal and/or interictal discharges on routine scalp EEG but were thought to have focal-onset seizures on the basis of seizure semiology or on the basis of cerebral lesion(s) seen on neuroimaging (i.e. the referring physician intended to use MSI to help distinguish primary from secondary bilateral synchrony). We did not have additional information that would allow us to ascertain patient diagnosis. All patients had a history of uncontrolled seizures despite multiple trials of antiepileptic drugs (AEDs). Protocols for retrospective analysis of patient data were approved by the Institutional Review Board at UCSF.

Patient demographics (age, gender) and pertinent epilepsy-related history (years since seizures began, seizure type, seizure frequency) were obtained from medical chart/records. For patients that underwent resective surgery, postoperative seizure control was also recorded using the Engel criteria: seizure-free (class I), rare seizures (class II), meaningful improvement (class III), and no improvement (class IV).

Interictal M/EEG recordings were done using simultaneous 275-channel whole cortex MEG and 21-channel scalp EEG. The clinical MEG data was band-pass filtered between 1 to 70 or 3 to 70 Hz and analyzed by an experienced MEG technologist (MM) and a board-certified clinical neurophysiologist (HEK). Spikes were chosen for analysis based on duration (<80 ms), morphology, and lack of associated artifact (e.g., ECG, EMG, EOG). Although the MEG readers had access to the simultaneous EEG to help distinguish spikes from artifact, they also selected spikes that met criteria but appeared only on MEG, since frequently individual spikes did not appear on both modalities. Spike onsets were chosen and corresponding dipoles were fit by using the commercial software supplied by the manufacturer (whole-head: CTF Systems, VSM, Port Coquitlam, BC); dipoles with >97% correlation and >95% goodness-of-fit were selected and superimposed on patients' MRI scans (MSI) to produce magnetic source images (MSI). In several patients, automated interictal spike localization was done using an adaptive spatial filtering software application called Synthetic Aperture Magnetometry (SAM(g2))⁷.

RESULTS

Overall patient population

See Table 1 for patient demographics and seizure history. The median age was 19.4 years (range 3.5 to 45.1). The median duration from seizure onset was 12.4 years (range 1.8 to 35.1). Most patients had generalized tonic-clonic seizures (8/17) or complex partial seizures (7/17). One patient had simple partial seizures involving his left arm with secondary generalization.

All patients underwent inpatient video EEG telemetry, some preceding their MEG referral and some following MEG referral (Table 2). Most interictal recordings showed simultaneous bihemispheric spikes or generalized spike-wave discharges. In eight patients, interictal spikes were bifrontal with unclear lateralization. In another seven patients, interictal spiking patterns were bilateral with a suggestion of hemispheric predominance but judged by the referring physician(s) to be non-lateralizing overall. Ictal onsets were recorded in 14 patients. These were typically generalized, demonstrating either simultaneous bilateral (mostly bifrontal) initiation or extremely rapid lead in from one side. One patient (case 5) showed interictal high amplitude sharp waves and slowing over the left hemisphere but an ictal pattern that had a slight lead from the right hemisphere.

Parametric single dipole source modeling revealed discrete focal dipole clusters in 12 of the total 16 patients (75%) on MSI (Table 2). In seven patients, there was only single dipole cluster. Patient age, seizure type, seizure duration, VET and MRI results were analyzed to determine factors predictive of having discrete localized clusters revealed on MSI (Table 3). Of these factors, only focal MRI anatomic abnormalities were associated with a focal MSI dipole cluster (Chi square test, $P=0.03$).

Patients with focal anatomic abnormalities

Of the nine patients with focal MRI abnormalities, three had abnormal hippocampal morphology. Four patients had focal frontal cortical dysplasia. Two had focal post-traumatic encephalomalacia. MEG-derived equivalent current dipoles co-localized to the focal MRI abnormality in eight of nine patients (89%) (Cases 3, 5, 6, 7, 10, 11, 13, 14, and 15)(For

examples, see Figure 1-Case 13 and Figure 2-Case 15). One patient exhibited abnormal left hippocampal morphology on MRI, but both EEG and MEG showed generalized spike wave discharges that could not be modeled using a single equivalent dipole model (Case 1).

Seven patients underwent surgical resection including areas with co-localized abnormalities on MRI and MSI (Table 2). Engel class I outcome was achieved in five patients at last follow-up following surgery (71%). One patient had rare seizures (Engel II), and another had no improvement (Engel IV) at 2 years after surgery. One patient could not undergo resective surgery since the putative focus was in dominant hemisphere superior temporal gyrus and instead underwent vagal nerve stimulator placement (Case 5). At two year follow-up, this patient had no reduction in seizure frequency or severity.

Patients with no MRI-based anatomic abnormalities

Of seven patients with normal appearing MRIs, four had focal MSI dipole clusters and three had multi-focal scattered dipoles. One underwent a left temporal lobectomy including one of three clearly identified dipole clusters, and had Engel class II outcome at six- to 24- months (Figure 3 – Case 8). Another two had interictal activity in cortical areas that were deemed inoperable given localization to the dominant hemisphere superior temporal gyrus in one patient (Case 14), and to the right frontal insula in the other (Case 5- this patient underwent placement of a vagal nerve stimulator and did not have improvement). The other three patients had multi-focal scattered interictal spike dipoles and no localizing or lateralizing evidence to allow further presurgical workup (Figure 4-Case 4) (Cases 2 and 16).

DISCUSSION

In this study, we have described a cohort of patients with medically refractory epilepsy that were referred for MEG evaluation with suspicion of SBS. These patients had demonstrated clinical or MRI findings that were suggestive of focal or lateralized epileptiform sources, but their routine scalp EEGs had generalized or bilaterally synchronous discharges. We found that MEG was able to reveal a focal area of interictal spiking in a relatively high proportion (75%) of patients in this selected group with high pretest probability of focality. The presence of an anatomic abnormality on MRI was associated statistically with co-localized dipoles on MSI. MSI results supported the decision to pursue surgical resection in eight patients. Resections included the MSI dipole cluster in all cases, except for two cases. All of patients for whom a single cluster was identified had Engel class I or II outcomes at 12- and 24-months following surgery, confirming that they did have focal epilepsy whose source was identified on MSI.

In 1985, Blume and Pillay laid out strict EEG criteria for SBS in their study of 57 patients¹. The criteria required that spikes leading to SBS must last for two seconds, and that the morphology of focal triggering spikes must be different from that of the bisynchronous paroxysm, and similar to other focal spikes from the same region. In this classic scenario, where a focal spike train is followed by a broad synchronous burst, EEG and MEG should, in theory, both have similar abilities to identify the source, since they share similar temporal resolutions. However, this strict definition of SBS is not universally applicable, since absence of these features does not exclude SBS: a cortical focus may lie deep within a sulcus and initial discharges from it may be invisible to routine scalp EEG; or secondary generalization from a focus may be very rapid^{1,2,16}. Thus, typical cases encountered in practice do not include a localized spike or spikes preceding the generalized burst. In these cases, whole-head MEG using 100-300 sensors offers superior spatial resolution in dipole localization when compared to routine low-density scalp EEG. As pointed out by other authors, the single dipole ECD model that is used in routine MEG analysis (including here),

despite or perhaps because of its limiting assumptions, can in practice resolve the generalized burst to a single source^{9,11}.

Demonstration of an anatomic abnormality seen on MRI was the only factor associated with having a focal MSI dipole cluster. The additional confirmation from MSI when the EEG is equivocal is an important factor in the decision-making process to undergo surgery, and in some cases may help to tailor the resection in combination with electrocorticography⁴. Many other studies have highlighted the predictive value of MRI abnormality in the surgical outcome for epilepsy; however, it cannot be relied upon exclusively³.

In cases in which the MRI is normal, some recent reports have validated use of the MSI to guide surgery¹³. The success of this approach was dependent upon close concordance between EEG and MEG. In the relatively infrequent case of SBS, however, the low-density scalp EEG is often too ambiguous to guide surgical planning. However, more sophisticated EEG techniques, including higher-density recording with source localization, as well as simpler modeling algorithms such as sequential voltage mapping have also recently shown promise in source localization^{19,20}.

Overall, our data suggest that MEG is a useful tool to evaluate difficult cases of epilepsy in which the EEG suggests SBS. The yield of MSI appears to be highly dependent upon whether an anatomic abnormality is seen on MRI, but may also prove useful in some cases where MRI is normal. The sensitivity in this case is impossible to determine, however, as the presence of a lesion on MRI in the face of a generalized EEG pattern was an important determinant of patient referral for MSI.

There are several limitations to our study. Although other papers on MEG evaluation of SBS have been described for one or two patients, our cohort of 16 patients is still relatively limited. In addition, our ability to document and to ascertain the diagnoses of the patients included is limited as we only had the limited clinical information provided to us by the referring physician in many cases; this means that in our group, we can not rule out the possibility that some individuals had both primary generalized and partial epilepsy¹⁴. As source modeling algorithms improve to include multiple simultaneous or rapid sequential dipoles, MEG may offer a fuller explanation of the phenomenon of SBS. Surgical resection confirmed the source in some patients, but there was no independent information to achieve confirmation for those patients that did not undergo surgery.

CONCLUSION

Interictal MEG appears to be a useful noninvasive technique in the evaluation of patients with suspected SBS based on history, routine scalp EEG, and MRI evaluation. Patients with MRI abnormalities appear to be more likely to have a focal MSI dipole cluster adjacent to or co-localized with the abnormality, many of which may be amenable to surgical excision. MSI can help confirm that the sites of anatomic abnormality correlate to sites which generate seizures. Successful identification of epileptogenic foci may lead to surgical resection as a meaningful therapeutic option.

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Figure 1.

A 35 year-old man presented with long-standing generalized tonic clonic seizures (Table 2, Case 13). Routine EEG showed frequent bursts and runs of generalized spike and slow wave discharges on an otherwise normal background (A). His MRI revealed a subtle cortical dysplasia in the right frontal lobe. MEG with simultaneous EEG was performed and demonstrated frequent high amplitude spike and slow wave discharges that were maximal in the right frontal region (B, right hand panels); manual single equivalent current dipole (ECD) fitting was performed on these spikes and dipoles clustered in the right frontal regions (shown in yellow in left panel of B). Automated interictal spike localization using adaptive spatial filtering was done, which confirmed the results of manual ECD (shown in orange in left panel of B). He underwent a lesionectomy and was seizure-free after surgery.

Figure 2.

A 28 year-old man with history of generalized tonic clonic seizures since age 2 (Case 15). His MRI demonstrated abnormal left hippocampal morphology. Routine EEGs showed spike and spike and slow wave discharges that appeared generalized, though occasionally with a lead from the left hemisphere (A). MEG with simultaneous EEG was performed, and dipole fitting revealed a dipole cluster in his left medial temporal lobe on MSI. He underwent a left temporal lobectomy and is seizure free at 12 months.

Figure 3.

A 24 year-old man with history of generalized tonic clonic seizures since age 5 (Table 2, Case 8). He had multiple normal MRIs. Routine EEGs were said to show generalized spike and slow wave discharges with a bifrontal emphasis. MEG with simultaneous EEG was performed, showing discharges that appeared generalized, though some had a focal lead-in from F4 (top panel); there were also left temporal sharp waves that were better seen on MEG than on EEG (middle panel). Spikes and sharp waves were subjected to ECD fitting. MSI demonstrated four discrete dipole clusters: one in the right frontal lobe; another in the mid left frontal lobe; and one in the left temporal lobe. He underwent a partial left temporal lobectomy after subdural grid evaluation, with Engel class II outcomes at one year following surgery.

Figure 4.

A 15 year-old boy with an eight year history of complex partial seizures consisting of staring spells and unresponsiveness (Table 2, Case 4). MRI was normal and routine EEG was said to show generalized sharp and slow wave discharges with a frontal maximum. MEG with simultaneous EEG was performed and multi-focal spikes were identified, some of which were focal on both MEG and EEG, and some of which appeared to be generalized on EEG or were not well seen on EEG but had clear focality on MEG. MSI dipoles were scattered throughout the right superior frontal, left mid-frontal, bilateral perirolandic, and bilateral sylvian regions. He was therefore not a candidate for surgical resection.

Table one

Study cohort and seizure history

Case #	Age (yrs)	Duration (yrs)	Seizure Type	Seizure Frequency
1	22	2	GTC	1/week
2	4	3	infantile spasms	1/day
3	34	32	CP	15/month
4	15	8	CP	2/day
5	14	3	absence, CP	1-3/day
6	8	4	absence, GTC	2/day
7	25	9	CP	1/week
8	24	19	absence, GTC	1/3 months
9	17	16	CP	14/month
10	17	2	CP, GTC	3-5/day
11	3	3	SP	1/week
12	17	7	CP	1/day
13	45	35	GTC	3/month
14	43	35	GTC	1/day
15	28	26	GTC	1-2/month
16	29	17	GTC	1/week

GTC= generalized tonic clonic; CP= complex partial; SP= simple partial

Table 2
MRI, EEG, MSI, and Surgical Results for Patients with Secondary Bilateral Synchrony

Case#	MRI results	Video EEG Telemetry	MSI dipoles	Surgery	ENGEL-6MO	ENGEL-12MO	ENGEL-2YR
1	L hippocampal abnormal morphology	Interictal: Generalized SWD, slight skew towards L frontotemporal region. Ictal: onset non-localizing.	Multi-focal and scattered	Not indicated			
2	Normal	Interictal: Hypsarrhythmia. Ictal: Generalized.	L temporal, occipital; B/L parietal, frontal	Not indicated			
3	L hippocampal sclerosis and atrophy	Interictal: L temporal slowing, bilateral synchronous spikes, anterior emphasis. Ictal: Bilateral onset, occasional abnormal activity over L hemisphere with fast spread	L anterior temporal	L anterior temporal lobectomy	2	1	1
4	Normal	Interictal: Bifrontal SWD. Ictal: Bilateral onset	B/L multi-focal, perisylvian	Not indicated			
5	L insular dysgenesis	Interictal: High amplitude sharp waves and slowing over L hemisphere. Ictal: Onset in the R (contralateral) hemisphere.	L insula, R angular gyrus	VNS given inoperable location	4	4	4
6	R frontal cortical dysgenesis	Interictal: Bifrontal spikes (R>L). Ictal: Generalized onset	R frontal superior and medial gyri	R frontal lobectomy	3	2	2
7	R frontal encephalomalacia	Interictal: Generalized. Ictal: Bifrontal onset	R frontal	R frontal lobectomy	2	1	1
8	Normal	Interictal: Bifrontal SWD, bifrontal spiking. Ictal: None	L frontal and temporal, R frontal, L temporal	L temporal lobectomy	2	2	
9	Normal	Interictal: Diffuse multifocal spiking. Ictal: Generalized onset	R frontal	Not indicated			
10	R frontal dysgenesis	Interictal: Bifrontal SWD, bifrontal spiking. Ictal: Generalized onset	R posterior frontal	R frontal lobectomy	1	2	4
11	R parietal encephalomalacia	Interictal: Bifrontal spikes. Ictal: R frontal onset, rapid secondary generalization	R precentral gyrus, adjacent to encephalomalacia	R frontal lobectomy	1	1	1
12	Normal	Interictal: Bifrontal spikes skewed slightly to R. Ictal: Generalized high amplitude irregular slowing with high delta	R frontal middle and inferior gyrus, insula (precedes EEG)	Not indicated			
13	R frontal dysgenesis	Interictal: Diffuse spiking, slightly more on R. Ictal:	R frontal	R frontal lobectomy	1	1	1

Case#	MRI results	Video EEG Telemetry	MSI dipoles	Surgery		ENGEL-6MO	ENGEL-12MO	ENGEL-2YR
		Bilateral synchronous sharp wave, high amplitude						
14	Normal	Interictal; Bifrontal spikes. Ictal: Generalized	L superior and middle temporal gyrus	1	Inoperable location			
15	L abnormal hippocampus	Interictal: Bilateral diffuse spikes. Ictal: Irregular spike wave activity, B/L with L lead	L temporal	1	L temporal lobectomy	1	1	
16	Normal	Interictal: Generalized spikes, shifting emphasis. Ictal: None	R superior temporal, bilateral perirhlandic	8	Not indicated			

L= left, R=right, BL= bilateral, MRI= magnetic resonance imaging, MSI= magnetic source imaging, SWD = spike and slow wave discharges

Table 3

Analysis of Predictors for Localizing MSI Dipole Clusters

Potential Predictors	N (%)	P-value *
All	16 (100)	
Age (median=19.3 years)		0.47
Duration (median=8.5 years)		0.25
Frequency (median 1/day)		0.67
Seizure Type		0.82
GTC	8 (50)	
CP	7 (43.8)	
EEG localizing feature		
subtle laterality (L/R)	6 (37.5)	0.55
anterior/posterior emphasis	8 (50)	0.25
MRI focal abnormality	9 (68.8)	0.03

* unpaired t-test for age, duration, and frequency; chi test for seizure type, EEG features, and MRI abnormality