Can Magnetoencephalography Aid Epilepsy Surgery?

Robert C. Knowlton, MD, MSPH

Director, UAB-HSF MEG Laboratory, Director, UAB Seizure Monitoring Unit, Department of Neurology, University of Alabama at Birmingham Epilepsy Center, Birmingham, Alabama

Magnetoencephalography (MEG) has a long history of development for the application of epilepsy. Technical and clinical validation of spike source estimation has been demonstrated in most partial epilepsies. The question that needs to be clarified concerns clinical value: Do identification and localization of epileptiform discharges play an important role in the determination of epilepsy localization for surgery? EEG is the mainstay in the investigation of seizure disorders and will remain so because it alone possesses the attribute of long-term recordings that can capture seizures. In contrast, MEG has the unique capability of nearly instantaneous high-resolution recording, with detection sensitivity and spike localization precision beyond that of EEG. Do these distinctions matter from a clinical standpoint?

The magnetoencephalogram (MEG) is a remarkable technological accomplishment. In a superconducting environment with induction coils submerged in liquid helium at near absolute zero temperature, whole-head arrays of detectors record the incredibly small magnetic fields (10^{-12} T) generated by intraneuronal currents of the human brain in vivo. Although analogous to the EEG in that both measure and record signal reflecting neuronal activity, fundamental differences exist (1). Today's MEG systems allow rapid high-resolution (100–300 channels) recordings of cortical function and dysfunction that are neither attenuated nor distorted by the skull or other variable intervening tissue layers between the scalp and brain. These technical attributes created the tendency, at least historically, to use MEG rather than EEG for source analysis. High-resolution

EEG recording combined with real-head modeling (i.e., using the subject's own anatomy from their MRI or CT) may overcome some of the source localization challenges of EEG; however to date, this approach still has not been used or validated to any appreciable extent in the clinical arena.

MEG, in contrast, has been studied and used extensively for clinical application since the inception of multidetector array systems became available in the early 1990s. In fact, in the United States, MEG-based source localization, called magnetic source imaging (MSI) when combined with structural imaging, received Food and Drug Administration approval for clinical use in 1997 and was given Current Procedural Terminology (CPT) codes for epilepsy localization and presurgical brain mapping in 2003. Yet, in spite of nearly two decades of MEG clinical investigation, controversy and questions remain as to what contribution MEG adds to EEG and the role that it plays among other established epilepsy localization tests, particularly multimodality imaging and intracranial EEG (ICEEG). MEG presurgical brain mapping is well established for primary sensory and motor modalities; more complex cognitive mapping is probably best served by MEG or its combination with ƒMRI, thus providing high spatial and temporal resolution to resolve networked areas of brain processing that are likely to overlap. Although brain mapping is often an integral component of the presurgical evaluation, this review is limited to MEG and epilepsy localization.

Accuracy and Sensitivity

Before discussing MEG source localization for epilepsy, it is of value to address the question of whether MEG can accurately localize interictal epileptiform discharges (spikes and sharp waves). Although seizures can be captured, recorded, and even localized by MEG (2–4), it is rare that an ictal event occurs during the scan. Thus, the information provided by MEG spike source localization, even if technically accurate, may not reflect the actual localization of the patient's epilepsy. The history and seizure semiology help in discerning which spikes are most related to the patient's habitual seizures. Also, spikes seen at the scalp by either EEG or MEG should not be confused with those recorded at the cortex, for which terms, such as "irritative zones," are used. Spikes recordable at the scalp are a strongly selected subset of robust, large amplitude discharges that contrast greatly with the far more numerous and scattered spikes recorded on ECoG (5,6). In neocortical epilepsies (lateral temporal and extratemporal) frequent unifocal spikes that tightly cluster on source localization have a strong correlation

with seizure onset recorded with ICEEG (7,8). Ultimately, the potential value of spike localization has to be determined on a case-by-case basis.

Once the value of spike localization is accepted, then the next most important questions are whether MEG has the sensitivity to detect spikes of interest and if there is any clinically significant difference between MEG and EEG in sensitivity to detection. Multiple, some interrelated variables are involved in the criteria that have to be met for a spike to be recordable at the scalp, including extent of depolarized cortex (simultaneous or sufficiently overlapping by cortico−cortical propagation), depth from surface, amplitude, dipolar orientation, and conductivity of intervening tissues. To what degree and which of these variables affect EEG versus MEG may result in a detection sensitivity difference. Depth is a heavily weighted variable, and in this case, EEG might have a slight advantage because MEG detectors are not as close to the scalp as pasted electrodes. This advantage might be more than offset, however, by the attenuation from conductivity differences caused by the skull, which are not applicable to MEG.

The extent of involved cortex required to detect a spike signal at the scalp has been increasingly studied and may indeed be different for MEG than EEG. From temporal lobe studies of simultaneous ICEEG, it is estimated that at least 6–8 cm^2 of basal lateral cortex is necessary for MEG detection of spikes (9–11). For spikes in the lateral convexity (longitudinal frontal sulcus), only 3–4 cm^2 is necessary with MEG recording (11). For EEG, a 6 cm^2 area has been used widely, since the 1965 study by Cooper et al. (12); however, this estimate was based on an in vitro experiment that did not include background noise. A much more recent in vivo study with subdural grids over the anterior lateral temporal cortex showed very few spikes involving less than 10 cm^2 were recognizable on the scalp EEG and that most typical anterior temporal lobe spikes reflected 20–30 cm^2 of cortical source area (6). Together, these findings suggest that MEG may have a better sensitivity than EEG. Unfortunately, no simultaneous scalp EEG, MEG, ICEEG studies involving direct comparison have been reported.

Several studies have compared detection of spikes in routine exams with scalp EEG and MEG. Most are series of temporal lobe epilepsy patients and only one used high-density EEG recording (13–16). From these reports, no clear differences are seen; most spikes are detected by both modalities, and only small percentages are detected by only one. One exception is posterior lateral temporal sources, for which MEG had higher yields (15). This increase in sensitivity also may herald the same outcome for extratemporal convexity regions. Sources that involve sulcal banks produce more tangentially oriented dipoles (e.g., the longitudinal frontal sulci, the intraparietal sulcus, and both banks of the sylvian fissure), which are particularly well detected with MEG.

The orientation of the source dipole is also an important factor—a limitation that will apply more to MEG, which cannot record perfectly radial sources (e.g., those confined to the crown of gyrus, which albeit, is a highly unlikely physiological circumstance). In one sense this putative limitation of MEG can be an attribute for localization by giving rise to a more geometrically simple and spatially limited source to model. EEG has an increase in contribution from volume currents that are further spatially and temporally blurred by the skull.

The question of whether MEG is more sensitive than EEG remains unanswered, but the likelihood that it is for many neocortical sources has provoked much enthusiasm for its use in epilepsy surgery evaluation. If MEG does detect more spikes than EEG in neocortical epilepsy, a new challenge arises—how to reliably identify true epileptiform discharges on MEG alone. Confounding, sharp transients that are of no epileptiform significance have not been well defined for MEG, although they have been for EEG. Also, MEG spikes coincident with EEG discharges have different morphological characteristics (17,18). Most of the differences consist of spatial and temporal blunting (duration and sharpness) of the EEG, presumed to reflect volume current propagation through surrounding tissues of varying conductivity. This effect is amplified in disturbed brain and skull regions, such as cystic lesions and prior craniotomies, which are common scenarios in epilepsy surgery. Differences in morphological characteristics have a more important role in regard to dipole modeling accuracy than sensitivity but add to problems associated with increasingly widespread use of MEG. More training in MEG interpretation for clinical neurophysiology is critically needed.

Accuracy

Regardless of whether MEG is more sensitive than EEG, another potential advantage for MEG is greater source localization accuracy—an issue assumed to be a forte of MEG. Key advantages of MEG are: (1) absence of magnetic field distortion and attenuation by highly variable conductivities between brain and sensor (which apply to EEG) and (2) the ease of very high-density sampling. Yet, for both MEG and EEG, solving the inverse problem, that is, determining where a source would have to be located to generate the fields actually observed at the scalp, remains challenging; numerous assumptions have to be taken into account. If areas of interest are highly unifocal (i.e., not overlapping either spatially or temporally with other sources), then the single equivalent current dipole (ECD) model may be appropriate to obtain reasonably valid source estimates. Indeed, with MEG mapping of focal evoked fields (e.g., somatosensory or auditory), a high degree of accuracy on the order of millimeters has been demonstrated in normal and abnormal brains, including in patients with tumors and other destructive

lesions (19–21). However, epilepsy spikes can be much more complicated, and as discussed, involve a relatively large amount of cortex, even if they are considered single and focal.

Extended source models, based on current distribution of a fixed set of dipoles using minimum norm estimation, are theoretically better than ECD modeling for the sources of most spikes (22). Moreover, many spike discharges visualized at the scalp are complex and likely comprise overlapping sources. For these cases, the ECD model cannot be expected to provide a satisfactory answer, however, multidipole spatiotemporal modeling may be considered (23). Ideally, an a priori knowledge of plausible physiological sources (e.g., secondary bilateral synchrony of overlapping mesial frontal lobe sources) would be available for the model. Importantly, although limited by strict assumptions regarding the epileptiform discharge source, to date, only the ECD model has been investigated to any extent for clinical validation.

Validation

Numerous direct and indirect approaches have tried to determine accuracy of MEG for epilepsy source localization. The direct methods use either implanted dipoles or simultaneous ICEEG–MEG recordings. Indirect methods include measures of colocalization with epileptogenic tissue, either visualized on imaging or delineated with ICEEG and then, ideally, confirmed by surgical resection and histopathology. Recordings from implanted dipoles (created by a pair of special electrodes included at ICEEG electrode implantation) provide precise knowledge of location, with validation rigor similar to phantom studies, but with in vivo characterization of effects from intervening tissue and skull of the human head. In initial studies, estimates of error include means that range from a few millimeters (24) to nearly two centimeters (25), with error greatly dependent on both signal-to-noise and depth. However, all such studies were performed with only single or 7-channel instruments that required repositioning several times to fully sample the observed field patterns. Additionally, radiographs were used to determine the locations of the implanted dipoles. Both of these aspects of earlier recordings contributed to errors in measurements.

Simultaneous ICEEG and large array MEG studies offer the best opportunity to validate spontaneous epileptiform discharge source localization. The few studies performed have all confirmed that MEG spike source localization is roughly concordant with ECoG mapping of spikes (9–11). Only one study incorporated an extratemporal lobe spike source (11). None included quantitative error estimates. Some caution regarding precision is warranted because complete characterization of sources is not always possible with the limited placement of intracranial electrodes required for clinical use. Also, surgical dressings and

electrode connectors increase the distance between brain and detectors and further decrease signal-to-noise.

The bulk of clinical validation attempts have involved correlation of spike dipole source localization with ultimate surgical localization. In lesion cases, studies have consistently shown MEG to be concordant with ICEEG findings, including various tumors and intrinsically epileptogenic developmental lesions (26–28). In addition to validation, such cases demonstrate the ability of MEG spike localization to delineate the topographical relation of epileptogenic tissue to the lesion, as visualized on imaging (29). Even colocalization with cryptogenic lesions (not seen on MRI) has provided clinical validity (27).

Clinical Value

In contrast to assessing validity, it has been a challenge to determine the clinical value of MEG for epilepsy surgery evaluation. An obvious approach is to study MEG prediction using gold standards for epilepsy localization. One gold standard might be ICEEG localization of seizures—an ultimate arbiter in surgical decision making that is not influenced by the many uncontrolled variables in surgical outcome. If MEG spike localization was found to correlate with ICEEG seizure localization, then the usefulness of MEG for surgical evaluation could be more widely accepted. The potential roles of a relatively high sensitivity, noninvasive test would be numerous: from a screening tool with high specificity for surgical candidates deemed most appropriate, to adding localizing information not available from established tests, to improving ICEEG placement, or to replacing more expensive tests (possibly, including ICEEG in a subset of cases). Studies specifically addressing prediction of ICEEG establish that highly localized MEG studies are concordant with seizure onsets recorded with subdural grid recordings (7,8,30–32).

Other studies, with relatively large series of broadly selected surgical candidates, have attempted to address additional issues of clinical value. However, unlike studies of standard diagnostic tests, studies investigating the impact of a test in the context of epilepsy surgery are fraught with difficulties. For example, protocols for surgery evaluation are highly nonstandardized across centers and are tailored frequently on a case-by-case basis, even within centers. Additionally, sensitivity and specificity often cannot be reliably obtained—decisions to proceed with further evaluation are often subjective. ICEEG may yield an incorrect finding, leading to no surgery or the wrong surgery, and not infrequently, surgical outcomes are affected by other factors independent of test localization accuracy (e.g., limited resection). In spite of these major issues, investigators have diligently tried to address them in design and analysis.

Accordingly, Stefan and colleagues (33) examined MEG performed on a broadly collected group of 455 patients with

intractable epilepsy, of which 50% were considered treatable with surgery. The investigators measured MEG agreement with the most highly suspected localization of the patient's epilepsy, based on all tests available and the consensus of multiple investigators. In addition, each localization outcome was measured using a 5-point rating scale (i.e., disagreement, no contribution, agreement, additional information, and novel influence on surgery decision). Similarly, two large studies examined the relative accuracy and contribution of MEG to the most established noninvasive tests of localization, which are ictal and interictal scalp EEG with video (VEEG) and MRI (34,35). Concordance measures were based on degree of resection overlap with and without analysis that included surgical outcome. Unique to this work was the fact that MEG was considered experimental and therefore, was not used in deciding how to define the region to be resected. These and other studies have consistently shown an overall sensitivity between 70 and 80 percent for a positive MEG study, with spikes captured and satisfactory ECD source localization achieved. No significant difference in sensitivity stands out between temporal and extratemporal lobe epilepsy, although some disparity in findings is noted, including factors related to varying whole-head instrument coverage of the inferior temporal region (14). The various measures of diagnostic localization accuracy were greater for MEG than that for VEEG (35). This finding is not surprising, especially in extratemporal lobe epilepsy for which ictal scalp EEG recordings are frequently nonlocalizing as a result of artifact and rapid propagation. The outcome is best not interpreted to indicate that VEEG is not necessary; rather, it strongly suggests that MEG can positively contribute to localization. Indeed, a common conclusion from each of the studies was that MEG added value in approximately 35 to 40 percent of patients with inconclusively localizing VEEG. Moreover, many patients with normal or nonlocalizing MRI also may be similarly aided.

Conclusions

Nearly all MEG–EEG comparison studies independently recognize that the modalities are complementary, whether used to better characterize sources for optimal modeling (36) or in a clinical role, to combine rapidly acquired accurate spike source localization with ictal neurophysiology from long-term EEG recording and implicit localization from neuroimaging. Limited availability of MEG for clinical application is rapidly diminishing. It soon should be feasible to answer more difficult questions about the role of MEG in seizure localization (particularly those with the largest impact on both efficacy and cost of epilepsy surgery), such as whether MEG can: (1) improve early patient selection, (2) increase accuracy of ICEEG sampling, or (3) reduce the proportion of patients who require invasive studies. The technology of MEG is not isolated in these tasks of epilepsy surgery clinical research, as EEG spike source localization with real-head modeling and fMRI–EEG-based spike localization also offer similar potential. However, currently, MEG has a large head start in clinical validation. So, to answer the question proposed in the title, evidence does exist to support the current use of MEG spike source localization in any patient for whom the question of seizure localization remains after VEEG recording of habitual seizures and for whom strong clinical suspicion continues for unifocal epilepsy that may be treated surgically.

References

1. Cuffin BN, Cohen D. Comparison of the magnetoencephalogram and electroencephalogram. *Electroencephalogr Clin Neurophysiol* 1979;47:132–146.
2. Assaf BA, Karkar KM, Laxer KD, Garcia PA, Austin EJ, Barbaro NM, Aminoff MJ. Ictal magnetoencephalography in temporal and extratemporal lobe epilepsy. *Epilepsia* 2003;44:1320–1327.
3. Eliashiv DS, Elsas SM, Squires K, Fried I, Engel J Jr. Ictal magnetic source imaging as a localizing tool in partial epilepsy. *Neurology* 2002;59:1600–1610.
4. Tilz C, Hummel C, Kettenmann B, Stefan H. Ictal onset localization of epileptic seizures by magnetoencephalography. *Acta Neurol Scand* 2002;106:190–195.
5. Ray A, Tao JX, Hawes-Ebersole SM, Ebersole JS. Localizing value of scalp EEG spikes: a simultaneous scalp and intracranial study. *Clin Neurophysiol* 2007;118:69–79.
6. Tao JX, Ray A, Hawes-Ebersole S, Ebersole JS. Intracranial EEG substrates of scalp EEG interictal spikes. *Epilepsia* 2005;46:669–676.
7. Knowlton RC, Elgavish R, Howell J, Blount J, Burneo JG, Faught E, Kankirawatana P, Riley K, Morawetz R, Worthington J, Kuzniecky RI. Magnetic source imaging versus intracranial electroencephalogram in epilepsy surgery: a prospective study. *Ann Neurol* 2006;59:835–842.
8. Oishi M, Kameyama S, Masuda H, Tohyama J, Kanazawa O, Sasagawa M, Otsubo H. Single and multiple clusters of magnetoencephalographic dipoles in neocortical epilepsy: significance in characterizing the epileptogenic zone. *Epilepsia* 2006;47:355–364.
9. Baumgartner C, Pataraia E, Lindinger G, Deecke L. Neuromagnetic recordings in temporal lobe epilepsy. *J Clin Neurophysiol* 2000;17:177–189.
10. Mikuni N, Nagamine T, Ikeda A, Terada K, Taki W, Kimura J, Kikuchi H, Shibasaki H. Simultaneous recording of epileptiform discharges by MEG and subdural electrodes in temporal lobe epilepsy. *Neuroimage* 1997;5(4 Pt 1):298–306.
11. Oishi M, Otsubo H, Kameyama S, Morota N, Masuda H, Kitayama M, Tanaka R. Epileptic spikes: magnetoencephalography versus simultaneous electrocorticography. *Epilepsia* 2002;43:1390–1395.
12. Cooper R, Winter AL, Crow HJ, Walter WG. Comparison of subcortical, cortical and scalp activity using chronically indwelling electrodes in man. *Electroencephalogr Clin Neurophysiol* 1965;18:217–228.

13. Iwasaki M, Pestana E, Burgess RC, Luders HO, Shamoto H, Nakasato N. Detection of epileptiform activity by human interpreters: blinded comparison between electroencephalography and magnetoencephalography. *Epilepsia* 2005;46:59–68.

14. Leijten FS, Huiskamp GJ, Hilgersom I, Van Huffelen AC. High-resolution source imaging in mesiotemporal lobe epilepsy: a comparison between MEG and simultaneous EEG. *J Clin Neurophysiol* 2003;20:227–238.

15. Lin YY, Shih YH, Hsieh JC, Yu HY, Yiu CH, Wong TT, Yeh TC, Kwan SY, Ho LT, Yen DJ, Wu ZA, Chang MS. Magnetoencephalographic yield of interictal spikes in temporal lobe epilepsy. Comparison with scalp EEG recordings. *Neuroimage* 2003;19:1115–1126.

16. Zijlmans M, Huiskamp GM, Leijten FS, Van Der Meij WM, Wieneke G, Van Huffelen AC. Modality-specific spike identification in simultaneous magnetoencephalography/electroencephalography: a methodological approach. *J Clin Neurophysiol* 2002;19:183–191.

17. de Jongh A, de Munck JC, Goncalves SI, Ossenblok P. Differences in MEG/EEG epileptic spike yields explained by regional differences in signal-to-noise ratios. *J Clin Neurophysiol* 2005;22:153–158.

18. Fernandes JM, da Silva AM, Huiskamp G, Velis DN, Manshanden I, de Munck JC, da Silva FL, Cunha JP. What does an epileptiform spike look like in MEG? Comparison between coincident EEG and MEG spikes. *J Clin Neurophysiol* 2005;22:68–73.

19. Gallen C, Sobel D, Lewine J, Sanders J, Hart B, Davis L, Orrison W. Neuromagnetic mapping of brain function. *Radiology* 1993;187:863–867.

20. Sobel D, Gallen C, Schwartz B, Waltz T, Copeland B, Yamada S, Hirschkoff E, Bloom F. Locating the central sulcus: comparison of MR anatomic and magneto encephalographic functional methods. *Am J Neuroradiol* 1993;14:915–925.

21. Sutherling W. Localization precision of whole cortex neuromagnetometer system for human epilepsy studies. *Epilepsia* 2001;42(Suppl 7).

22. Fuchs M, Wagner M, Kohler T, Wischmann HA. Linear and nonlinear current density reconstructions. *J Clin Neurophysiol* 1999;16:267–295.

23. Stephen JM, Aine CJ, Ranken D, Hudson D, Shih JJ. Multi-dipole analysis of simulated epileptic spikes with real background activity. *J Clin Neurophysiol* 2003;20:1–16.

24. Rose DF, Sato S, Ducla-Soares E, Kufta CV. Magnetoencephalographic localization of subdural dipoles in a patient with temporal lobe epilepsy. *Epilepsia* 1991;32:635–641.

25. Balish M, Sato S, Connaughton P, Kufta C. Localization of implanted dipoles by magnetoencephalography. *Neurology* 1991;41:1072–1076.

26. Bast T, Oezkan O, Rona S, Stippich C, Seitz A, Rupp A, Fauser S, Zentner J, Rating D, Scherg M. EEG and MEG source analysis of single and averaged interictal spikes reveals intrinsic epileptogenicity in focal cortical dysplasia. *Epilepsia* 2004;45:621–631.

27. Knowlton RC, Laxer KD, Aminoff MJ, Roberts TP, Wong ST, Rowley HA. Magnetoencephalography in partial epilepsy: clinical yield and localization accuracy. *Ann Neurol* 1997;42:622–631.

28. Morioka T, Nishio S, Ishibashi H, Muraishi M, Hisada K, Shigeto H, Yamamoto T, Fukui M. Intrinsic epileptogenicity of focal cortical dysplasia as revealed by magnetoencephalography and electrocorticography. *Epilepsy Res* 1999;33:177–187.

29. Hader WJ, Mackay M, Otsubo H, Chitoku S, Weiss S, Becker L, Snead OC 3rd, Rutka JT. Cortical dysplastic lesions in children with intractable epilepsy: role of complete resection. *J Neurosurg* 2004;100(2 Suppl Pediatrics):110–117.

30. Mamelak AN, Lopez N, Akhtari M, Sutherling WW. Magnetoencephalography-directed surgery in patients with neocortical epilepsy. *J Neurosurg* 2002;97:865–873.

31. Minassian BA, Otsubo H, Weiss S, Elliott I, Rutka JT, Snead OC 3rd. Magnetoencephalographic localization in pediatric epilepsy surgery: comparison with invasive intracranial electroencephalography. *Ann Neurol* 1999;46:627–633.

32. Sutherling WW, Crandall PH, Cahan LD, Barth DS. The magnetic field of epileptic spikes agrees with intracranial localizations in complex partial epilepsy. *Neurology* 1988;38:778–786.

33. Stefan H, Hummel C, Scheler G, Genow A, Druschky K, Tilz C, Kaltenhauser M, Hopfengartner R, Buchfelder M, Romstock J. Magnetic brain source imaging of focal epileptic activity: a synopsis of 455 cases. *Brain* 2003;126(Pt 11):2396–2405.

34. Pataraia E, Simos PG, Castillo EM, Billingsley RL, Sarkari S, Wheless JW, Maggio V, Maggio W, Baumgartner JE, Swank PR, Breier JI, Papanicolaou AC. Does magnetoencephalography add to scalp video-EEG as a diagnostic tool in epilepsy surgery? *Neurology* 2004;62:943–948.

35. Wheless JW, Willmore LJ, Breier JI, Kataki M, Smith JR, King DW, Meador KJ, Park YD, Loring DW, Clifton GL, Baumgartner J, Thomas AB, Constantinou JE, Papanicolaou AC. A comparison of magnetoencephalography, MRI, and V-EEG in patients evaluated for epilepsy surgery. *Epilepsia* 1999;40:931–941.

36. Fuchs M, Wagner M, Wischmann HA, Kohler T, Theissen A, Drenckhahn R, Buchner H. Improving source reconstructions by combining bioelectric and biomagnetic data. *Electroencephalogr Clin Neurophysiol* 1998;107:93–111.