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EEG, MEG, and source localization: their value in epilepsy

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Abstract
Purpose of review: source localization of cerebral activity using EEG or MEG can reveal non-invasively the generators of the abnormal signals recorded in epilepsy, such as interictal epileptic discharges and seizures. Here, we review recent progress showcasing the usefulness of these techniques in treating patients with drug-resistant epilepsy.
Recent findings: The source localization of interictal epileptic discharges by high-density EEG and MEG has now been proved in large patient cohorts to be accurate and clinically relevant, with positive and negative predictive values rivaling those of structural MRI. Localizing seizure onsets is an emerging technique that seems to perform similarly well to the localization of interictal spikes, although there remain questions regarding the processing of signals for reliable results. The localization of somatosensory cortex using EEG/MEG is well established. The localization of language cortex is less reliable, although progress has been made regarding hemispheric lateralization. Source localization is also able to reveal how epilepsy alters the dynamics of neuronal activity in the large-scale networks that underlie cerebral function.
Summary: given the high performance of EEG/MEG source localization, these tools should find a place similar to that of established techniques like MRI in the assessment of patients for epilepsy surgery.

Keywords: epilepsy, electroencephalography, magnetoencephalography, source imaging, seizure onset zone, high-frequency oscillations

Introduction

EEG or MEG source localization refers to the estimation of the intracranial generators of an electric or magnetic field recorded at the surface of the head. In theory, an infinite number of combinations of intracranial generators can yield the same surface field; thus, the so-called inverse problem is ill-posed. However, it is possible to impose biologically realistic constraints onto the mathematically possible solutions and thus reduce their number; for instance, only generators in the gray matter may be considered, or the number of active generators may be restricted to one or a handful [1,2]. The distinctive EEG/MEG signatures of epilepsy, whether interictal epileptic discharges (IEDs) or seizures themselves, lend themselves well to source localization. Technical progress in both hardware and software, with the development of high-channel count EEG or MEG acquisition systems one the one hand, and of sophisticated programs to analyze these data on the other, have made EEG/MEG source localization available to greater numbers of epilepsy centers worldwide. Here, we review the literature on the topic, focusing on recent developments such as source localization of ictal events, simultaneous surface and intracranial recordings, and the role of EEG/MEG source localization in functional brain mapping.

EEG/MEG source localization of interictal epileptic discharges

Because IEDs are much more frequent than seizures and have no overt behavioral correlate, they are easily recorded with MEG as well as EEG. Thus, most epilepsy centers focus on the source localization of IEDs. In the majority of patients, the source of IEDs effectively colocalizes with the seizure onset zone, as was shown in a study of patients who underwent IED source localization with high-density EEG (hdEEG) and then later had their seizure onset zone delineated with intracranial EEG (iEEG) [3,4]. In recent years, large single-center studies have consistently established the value of IED source localization in the assessment of patients for epilepsy surgery. In one of the largest patient cohorts in this field, the performance of hdEEG source localization of IEDs was compared to that of structural MRI with respect to the clinical gold standard of post-operative freedom from seizures [5,6]. Specifically, including the maximum of the inverse solution in the resection volume was strongly associated with a much greater rate of seizure freedom (odds ratio 13.1 [6]). The performance of hdEEG was as good as that of MRI, if not better (the odds ratio for MRI was 10.9), reflecting the fact that MRI can fail to be beneficial due to normal or non-focal findings. Importantly, hdEEG performed well in patients whose MRI shows no lesion [7] and in patients with large brain lesions or prior cerebral resections [8]. Another recent hdEEG study, which focused on temporal lobe epilepsy, also found a higher probability of seizure freedom if the sources of surface-recorded IEDs were included in the resected brain volume [9]. Source localization of IEDs by MEG was also associated with seizure freedom in another large, single-center cohort [10], with an odds ratio of 5.1. Thus, hdEEG/MEG source localization of IEDs is a powerful tool to approximate the location of the epileptogenic zone, the extent of brain tissue whose removal will lead to seizure freedom [11].

Simultaneous surface and intracranial recordings

Whether EEG and MEG are sensitive to deep cerebral sources, such as the medial temporal or basal frontal lobes, has been debated. Simultaneous intracranial EEG (iEEG) and surface recordings can help resolve this debate. In a study that focused on medial temporal lobe epilepsy using simultaneous hdEEG and iEEG, 45% of the intracranially detectable IEDs were also visible at the surface. Of note, down-sampling the surface EEG to a low-density, 19-channel montage reduced that proportion to 22% [12]. Another study, which focused on frontal lobe epilepsy using simultaneous low-density EEG and iEEG, found that only 14% of intracranial frontal sources were readily visible at the surface [13]. The obvious drawback of that study is that the low number of surface EEG electrodes might have precluded the detection of a significant number of IEDs. MEG is thought to be sensitive mostly to superficial sources. Indeed, a recent study that used gradient magnetic-field topography to analyze IEDs simultaneously with iEEG obtained accurate localization (at the gyral level) of IEDs generated on the lateral surface of the cerebral hemisphere, whereas IEDs originating from deeper regions were missed [14].

How many sensors are needed?

An important question in source localization is the number and localization of the sensors. Prior research had established that the accuracy of IED localization improved with higher-channel count EEG recordings: the largest increment in accuracy occurred when the number of electrodes increased from 31 to 63, with a smaller but measurable gain upon increasing to a 123-electrode system [15]. This question was examined again in a recent study that manipulated the coverage of the head surface in addition to electrode number: the authors found that montages that sampled the inferior temporal areas, with electrodes around and below the ears and on the cheeks and neck, performed better than montages with identical electrode numbers that only covered the scalp above the hairline [16]. The lack of inferior temporal coverage in standard EEG montages has in fact been recognized, leading to the guideline that routine EEG recordings should incorporate at least 25 electrodes, including inferior temporal electrodes, as opposed to the 19 electrodes of the international 10-20 system [17]. Because they lie directly over muscle, cheek and neck electrodes are more sensitive to artefacts, which could compromise the identification of low-amplitude IEDs in waking EEG recordings. This disadvantage can be compensated by recording the EEG during sleep, where muscle artefacts are not an issue. Current hdEEG systems provide prolonged recordings over an entire day and night. Automated IED detection (see below) can help the clinician deal with the large datasets collected over long time periods.

Which part of the IED should be localized?

Another important point pertains to which time point of the IED to apply source localization to. Given that the IED has a certain duration, source localization can be applied to its onset, its peak, or any point in between. It was previously established that significant propagation of cerebral activity can occur during an IED [18]. This point was reassessed in a large cohort of 50 patients, of whom 8 had extratemporal lobe epilepsy. The reference standard was the final decision on the area to be resected, and EEG was obtained with 25 electrodes. The study showed that significant propagation of cerebral activity occurred in about half of IEDs [19]. In 60% of those cases, source localization remained confined to the same sublobar region despite the propagation. In the patients in whom significant propagation occurred, the authors suggested considering the source localizations at both the onset and the peak of the IED as being potentially informative. Our own practice is to systematically perform hdEEG source localization at the 50% rising phase of the IED, which has been shown to be highly reliable when compared to the gold standard of post-operative outcome, and in our opinion provides a very good trade-off between a sufficient signal-to-noise ratio and the potential risk of propagation [3,5,6].

Because EEG/MEG recordings inherently have a low signal-to-noise ratio (SNR), estimating the source of IEDs is generally performed on multiple exemplars. This leads to a choice between averaging together the EEG traces of individual IEDs and then estimating the source of the averaged IED (averaging at the sensor level), or estimating the source of individual IEDs and then averaging these sources together (averaging at the source level) [20]. The earlier approach increases the signal-to-noise ratio of IED onsets, but there is a risk of averaging together IEDs that in fact were generated by distinct sources, thus blurring the accuracy of source localization. Averaging at the source level has the advantage of being able to provide a measure of variance (and thus confidence estimates) on the source localization, but the source estimation of single IED onsets can be thrown wildly off course by their low SNR [21]. We rely on the selection of IED exemplars with similar morphology by expert neurophysiologists and perform source localization of averaged IEDs to maximize the SNR at the 50% rising phase of the IED [6].

Automated IED detection and source localization

One criticism leveled at EEG/MEG source localization is that it is perceived as a labor-intensive technique, requiring advanced training and several hours of specialist time per patient [22,23]. In that respect, commercially available automated IED detection software, whose performance approximates that of human expert neurophysiologists, may represent a significant gain of time for the clinician [24]. An interesting development arose from a study that applied an almost fully automated analysis protocol to long-term monitoring, low-density EEG recordings [25]. In that study, the aforementioned software was used to detect IEDs, which were then clustered according to their surface voltage topography and subjected to source localization. The overall accuracy of that approach was comparable to that of the other noninvasive techniques such as interictal positron emission tomography (PET) and ictal single-photon emission computed tomography (SPECT). That study is noteworthy because it suggests that low-density EEG-based IED source localization could be added to the armamentarium of the workup for epilepsy surgery with minimal effort on the medical team’s part. Applying a similar automated analysis pipeline to hdEEG recordings, especially using EEG systems that allow recording for many hours including sleep, could improve the accuracy of hdEEG IED source localization thanks to the improved signal-to-noise ratio resulting from considering a greater number of IEDs.

The clinical usefulness of EEG/MEG source localization

How can EEG/MEG source localization of IEDs, a technique whose spatial resolution and accuracy are in the centimeter range, be of any use to patients considering epilepsy surgery? We believe that EEG/MEG source localization can make the largest contribution in complex clinical situations, i.e. in patients in whom the results of routine scalp EEG and structural MRI were not sufficiently conclusive to offer epilepsy surgery. When MRI and EEG/MEG source localization are compared in that patient population in terms of their association with postoperative seizure freedom, overall MRI does not in fact outperform EEG/MEG [5,6]. In fact, each one of the various noninvasive modalities at the disposal of the clinician (MRI, EEG/MEG source localization, PET, SPECT) can contribute independent information on the location of the putative epileptogenic zone [6,26], but except for MRI, none does so with millimeter resolution. Nuclear imaging techniques are not at disposition in all centers, but EEG with high electrode counts can be obtained in all patients. A solid hypothesis of the presumed region or regions identified by EEG/MEG source analysis helps to plan the placement of intracranial electrodes for better spatial resolution. The challenge of epilepsy surgery planning is to weigh the results of each technique appropriately, especially when their findings do not concur.

Ictal EEG/MEG recordings: source localization of the seizure onset zone

Despite the success of EEG/MEG source localization of IEDs, there are instances where the technique will fail to help a given patient. First, some patients have too few IEDs, and a short recording session might fail to record any. This is more of an issue for MEG, where a typical recording session rarely lasts longer than a couple of hours, than for hdEEG, which can now be recorded for up to 24 hours, including during sleep [27]. Second, in some patients, IEDs can be generated by more than one brain area, only one of which corresponds to the seizure onset zone [3]. Thus, focusing only on the most frequent IED might fail to localize the seizure onset zone in cases where that zone is not the most active IED generator. In such cases in particular, source localization of actual seizures might be very beneficial.

Recordings and source localization of seizures pose unique challenges for MEG. First, because MEG recordings rarely last above a couple of hours, capturing a seizure during a MEG recording is relatively improbable, except in patients who suffer several seizures per day. This is not an issue with EEG. Second, because the MEG sensors are fixed to the machine (and not attached to the patient, as is the case for EEG), MEG recordings of seizures can be severely perturbed by seizure-related movements of the head. Nevertheless, seizures do sometimes occur during MEG recordings, and these data may provide precious insight into the localization of the seizure onset zone [28].

Table 1 summarizes recent studies on the source localization of seizure onsets. Taken collectively, these studies suggest that seizure onset source localization can be achieved with similar accuracy to the localization of IEDs. Furthermore, the association between the inclusion of the seizure onset in the surgical resection and seizure freedom appears comparable to that observed with IED source localization in the larger cohorts mentioned above [6,10]. Just as is the case with IEDs, the accuracy of seizure onset source localization depends on the number of sensors, with the largest drop in performance occurring below 64 EEG electrodes in one study [30].

A variety of technical approaches are available to localize the source of seizure onsets. A 64-electrode EEG study including 38 seizures from 22 patients found high agreement, reaching almost 90%, between several different methods [32]. A further promising development in seizure onset localization is the inclusion of directed connectivity analysis: thus, not only the most active source is taken into consideration when localizing the onset of a seizure, but also how strongly each source broadcasts its activity to other brain regions (the so-called outgoing connections). Such an approach was shown to be more accurate than merely considering the most active source, with accuracies improving from 42% to 94% with low-density EEG recordings [29], and from 40% to 100% in a smaller cohort of patients investigated with hdEEG [30].

In the near future, it is to be hoped that simultaneous intracranial and scalp recordings will allow comparing source localization of ictal onsets using hdEEG (or MEG) with iEEG. Such a dataset would prove precious to determine which technical approach to estimating the solution to the inverse problem is the most accurate in that setting. Furthermore, larger cohort studies of ictal source localization will be necessary to reveal its accuracy (and positive predictive value) with respect to the gold standard of post-operative seizure control.

Localization of eloquent cortex using EEG/MEG source localization

Using EEG or MEG to study the neural correlates of sensation and cognition in healthy people has a long history. These paradigms and techniques have also been applied to epilepsy surgery candidates in order to map out functionally eloquent cortex. For instance, hdEEG-recorded somatosensory-evoked potentials (SEPs) were previously shown to be as accurate as functional MRI (fMRI) to localize the somatic sensory representation of the hand [36]. The results of the two techniques were within 3 and 8 mm of each other, except in the medial-lateral direction. This is due to the fundamental differences of the signal sampled by hdEEG and fMRI: whereas SEPs directly reflect neuronal activity generated in the depth of the central sulcus, fMRI measures blood flow changes, and consequently localize the site where sensory information is integrated later in time (i.e. the lateral surface of the post-central gyrus).

The question was recently revisited in a MEG test-retest study of healthy volunteers, which found that the localization of the hand somatosensory representation varied up to 8 mm from one recording session to the next in a given participant [37], giving an upper bound to the accuracy that one can expect from the technique. Another study compared hdEEG and MEG source localization to that of fMRI in healthy subjects, using very similar numbers of sensors for the two techniques [38]. hdEEG tended to perform slightly better than MEG to localize motor cortex during a tapping task, when taking fMRI as the gold standard. Importantly, the good performance of hdEEG depended on using each participant’s brain and head anatomy to build the source reconstruction, as previously shown for the localization of interictal epileptic discharges [5].

Lateralization and localization of language cortex

The localization of language-relevant cortex has also been examined. In an MEG study of 32 patients performing a covert picture naming task, activations were reliably observed in the inferior frontal gyrus (corresponding to the anatomical Broca's area) in all patients, and in the posterior superior temporal gyrus (corresponding to the anatomical Wernicke's area) in most [39]. The authors of that study designed a region-of-interest based analysis of activation in the left and right inferior frontal gyri to determine hemispheric lateralization of language. The main weakness of that study is that the MEG data were not compared to any other test of language lateralization (such as fMRI or intracarotid amobarbital injection).

Another MEG study of 11 patients used two different tasks: a covert semantic category verbal fluency task and an auditory verbal memory task [40]. MEG source localization of cerebral activity during the verbal memory task found activations in the left and right lateral temporal cortices (including Wernicke's area on the left side). In the verbal fluency task, activations were also mostly seen in the temporal lobes bilaterally. A lateralization index was also defined, not in the source space, but by pooling the amplitude of signals at many MEG sensors together on each side of the head; that lateralization index was found to agree in 86% of cases with other assessments of language lateralization (fMRI in 7 patients, intracarotid amobarbital injection in 3, electrical stimulation mapping in 1). The results of that study suggest that hemispheric lateralization might be reliably achieved with EEG/MEG recordings, although validation in larger cohorts is necessary before any firm conclusion can be drawn.

In a recent hdEEG study [41], event-related potentials were recorded in 36 patients who performed 3 tasks: a verbal working memory task, a phonological task, and a semantic decision task (all the word stimuli were presented visually). Using fMRI as a gold standard, the authors found that the semantic decision task (determining whether a stimulus was a word of a pseudo-word) yielded the best concordance, reaching 87% for Broca's area and 77% for Wernicke's area. However, it should be underlined that fMRI is an imperfect gold standard, because language lateralization in fMRI can change as a consequence of seizures occurring prior to the fMRI scanning session [42]. Prolonged hdEEG for seizure monitoring with timely language event-related potential sessions could circumvent this problem.

Combining EEG/MEG source localization with other modalities

Simultaneous EEG and fMRI studies combine the high temporal resolution of the EEG signals with the spatial precision of fMRI [43]. In a pediatric EEG-fMRI study, 64-electrode EEG was recorded inside the MRI scanner in 53 children with epilepsy (age range, 7-18 years) for 20 minutes [44]. IED localization was performed using both EEG source localization and fMRI analysis time-locked to the occurrence of the IED on the EEG. In a subset of 29 patients who had a well-defined epileptogenic zone, EEG-fMRI accurately localized the epileptogenic zone in

11 out of 26 cases (in the other 3 patients, the method failed to yield a result), whereas EEG source localization was correct in 17 out of 22. When both methods converged, the result was accurate in 11 of 12 cases. Results concordant with successful epilepsy surgery were found in 8 of 20 patients using EEG-fMRI, in 13 of 16 patients based on EEG source localization, and in 9 of 9 using the combination of both techniques. This study establishes the feasibility of EEG-fMRI recordings in children and suggests that this combined modality may contribute clinically relevant information to the localization of the putative epileptogenic zone.

A more technical report suggested an approach to combining simultaneous EEG and MEG recordings to improve the overall localization accuracy. In that report, combined EEG-MEG recordings (54 EEG electrodes, 275 MEG sensors) were compared to either modality taken in isolation to localize IEDs in two patients [45]. While preliminary, the results suggest that combined EEG-MEG recordings are better able to account for the precise localization and, more interestingly, the extent of the IED generators than either technique alone. In fact, source localization, like all other imaging techniques, has so far been unable to identify the true extent of the epileptogenic zone. Future studies are necessary to determine if this enigma can be solved.

Imaging networks in epilepsy using EEG/MEG source localization

Epilepsy is increasingly construed as a disease of neuronal networks involving multiple brain regions spanning wide expanses of the brain [46,47]. In an attempt to describe these networks, hdEEG source localization was applied to IEDs in 16 temporal lobe epilepsy patients, and an analysis of directed connectivity (using Granger-causal modeling) was then performed in the source space [48]. The anterior temporal lobe was found to be a major driver of activity, as expected. Intriguingly, the network recruited by IEDs differed significantly between right and left temporal lobe epilepsy patients: in left-sided patients, the network was mostly confined to the ipsilateral temporal and frontal lobes, whereas in right-sided patients, it involved contralateral temporal and frontal regions. This observation correlated with the observation that most left temporal lobe epilepsy patients showed deficits in verbal memory, whereas right-sided patients had memory difficulties in both visual-spatial and verbal modalities [48]. These concordant neurophysiological and neuropsychological findings indicate that left and right temporal lobe epilepsies are not a mirror image of each other; furthermore, they hint at the existence of a complex relationship between the physiology of hemispheric specialization and the detrimental influence of pathological activity in epileptic networks.

That complex relationship was also probed in resting-state hdEEG recordings outside of IEDs. It was found that the connectivity pattern within the default mode network of temporal lobe epilepsy patients differed from that of healthy controls [49]. Specifically, those regions that were part of the epileptic networks had lower connectivity within the default mode network, and the main driver of activity in that network was the hippocampus in patients, versus the posterior cingulate cortex in controls. In addition, patients with depression had lower outflow from the anterior cingulate gyrus, a finding which suggests that the technique might also be relevant for characterizing psychiatric diseases or comorbidities. These findings point towards the possibility that connectivity analysis of resting-state neurophysiological recordings might be used to identify biomarkers of temporal lobe epilepsy, even in the absence of overt epileptic activity such as IEDs [43].

The current role of EEG/MEG-based connectivity analysis in epilepsy is, for the most part, investigational. Future work will need to establish how to best quantify the strength of connectivity as well as the direction of information flow in neuronal networks. Pending these methodological clarifications, connectivity analysis is likely to inform aspects of epileptic networks that have direct clinical relevance, like the delineation of the putative epileptogenic zone [50], the mechanisms underlying the initiation, propagation and termination of seizures, as well as how epileptic activity can alter the normal function of other networks [51,52].

Conclusion

hdEEG and MEG are safe and non-invasive tools that can localize the putative epileptogenic zone with high reliability. Validation has now been obtained in several hundred patients. Sensitivity and specificity measures compare favorably to other established techniques, like PET, SPECT and even MRI, given that not all lesions are visible to MRI or that the findings of MRI can be non-conclusive. Both hdEEG and MEG are easily applicable in subjects in whom collaboration is limited and therefore can be extended to pediatric populations without the necessity of sedation and immobility during image acquisition. hdEEG is probably more easily integrated into the clinical routine, given that it does not need special shielding and has lower running costs, albeit this may change with new generation MEG machines. Other applications of both techniques include the localization of eloquent cortex, which has been well studied so far only for the somatosensory cortex. However, promising findings were also obtained for hemispheric language lateralization for both hdEEG and MEG, while localization still awaits rigorous studies in patients undergoing per-operative or pre-operative direct cortical stimulation. Further studies will determine the place of hdEEG or MEG as tools to localize eloquent cortex in the preparation of neurosurgical interventions outside the context of epilepsy surgery. In summary, electromagnetic tools with sufficiently high number of sensors/electrodes have shown their utility in a number of clinical settings. In the next 10 to 20 years, their use will most likely consolidate as part of the assessment for epilepsy surgery, as well as propagate to other indications, for instance to psychiatric diseases.

Key points

- The high accuracy and predictive positive value of high-density EEG or MEG source localization of interictal epileptic discharges to determine the putative epileptogenic zone have recently been validated in large cohort studies, and it is recommended to add this technique to the imaging armamentarium.
- Source localization of ictal onsets seems to be as accurate as that of interictal epileptic discharges to localize the putative epileptogenic zone.
- The lateralization and localization of eloquent cortex (sensory and motor areas and language) can technically be performed with EEG/MEG, but further studies in large

cohorts with systematic comparison to other techniques are necessary in order to assess their clinical relevance.

- EEG/MEG source localization and connectivity analysis can reveal the dynamics of activity within epilepsy networks as well as alterations in the function of resting-state networks, with the potential for developing future biomarkers of epilepsy even in the absence of interictal epileptic discharges.

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Figures and Tables

Table 1. Recent ictal source localization studies

Reference	Number of patients and seizures	Method and number of sensors	Duration of recording	Concordance with reference standard (a)	Concordance with iEEG (a)	Concordance with successful surgery (b)
Nemtsas et al. [27]	14 patients	EEG: 204 electrodes in 13 patients, 128 electrodes in 1	18-21 hours	Ictal: 7/9 with MRI Interictal: 6/9 with MRI	3/4	5/6
Staljanssens et al. [29]	27 patients, 111 seizures	EEG: 27-32 electrodes	1-8 days	NA	NA	18/27
Staljanssens et al. [30]	5 patients	EEG: 204 electrodes	24 hours	NA	NA	4/5
Ramanujam et al. [31]	32 patients	MEG: 306 channels	1.5-2 hours	Ictal: 11/19 with MRI Interictal: 11/21 with MRI	NA	5/5 (2 operations were hemispherotomy)
Beniczky et al. [32]	22 patients, 38 seizures	EEG: 64 electrodes	Presumably several days	16/22 with epilepsy surgery team	12/17	12/14
Habib et al. [33]	8 patients	EEG: 21 electrodes	Presumably several days	Ictal: 6/8 with SPECT Interictal: 5/8 with SPECT	NA	NA
Badier et al. [34]	6 patients	MEG: 248 channels	15 minutes	NA	4/6	NA
Jeong et al. [35]	13 patients	MEG: 306 channels	60 minutes	8/13 with resected brain volume (c)	NA	7/9

NA, data not available. ILAE: International League Against Epilepsy.

(a) Concordance at the sublobar level.
(b) Concordance with the resected brain volume in patients who were subsequently seizure-free (Engel or ILAE class I).
(c) Regardless of seizure outcome.