Electric source imaging for presurgical epilepsy evaluation: current status and future prospects

Megevand, Pierre Bastien; Seeck, Margitta

How to cite

MEGEVAND, Pierre Bastien, SEECK, Margitta. Electric source imaging for presurgical epilepsy evaluation: current status and future prospects. In: Expert Review of Medical Devices, 2020, vol. 17, n° 5, p. 405–412. doi: 10.1080/17434440.2020.1748008

This publication URL: https://archive-ouverte.unige.ch/unige:142454

Publication DOI: 10.1080/17434440.2020.1748008

Electric source imaging for presurgical epilepsy evaluation: current status and future prospects

Pierre Mégevand and Margitta Seeck

Dr. Pierre Mégevand, MD, PhD
Epilepsy unit, Neurology division, Clinical neuroscience department, Geneva University Hospitals
Rue Gabrielle-Perret-Gentil 4, 1205 Genève, Switzerland
and
Basic neuroscience department, Faculty of medicine, University of Geneva
Chemin des Mines 9, 1202 Genève, Switzerland

Prof. Margitta Seeck, MD
Corresponding author
Epilepsy unit, Neurology division, Clinical neuroscience department, Geneva University Hospitals
Rue Gabrielle-Perret-Gentil 4, 1205 Genève, Switzerland
Tel. +41 22 372 84 76
E-mail Margitta.Seeck@hcuge.ch

Abstract

Introduction: electric source imaging (ESI) refers to the estimation of the cerebral sources of electric signals recorded at the head surface using electroencephalography (EEG). Thanks to the availability of EEG systems with high numbers of electrodes and to progress in software to analyze the signals they collect, ESI can be applied to epilepsy-related pathological EEG signals like interictal spikes and seizures.
Areas covered: in this narrative review, we discuss selected original research articles on the use of ESI in epilepsy patients considered for surgery. Epilepsy-related activity can be localized accurately using ESI, as established by comparison to the gold standards of intracranial EEG and seizure control following epilepsy surgery. The information brought by ESI complements successfully that of other techniques like magnetic resonance imaging and positron-emission tomography, and is clinically relevant to patient management.
Expert commentary: EEG is a readily available technique to measure brain activity in real time. Given its accuracy and usefulness, ESI should become part of the routine practice of clinical neurophysiology laboratories and epilepsy centers in the presurgical management of epilepsy patients.

Keywords

Electric source imaging; electroencephalography; high-density EEG; source localization; inverse solution; epilepsy; interictal epileptiform discharges; epileptic seizures; epilepsy surgery

"This is an Accepted Manuscript of an article published by Taylor & Francis in EXPERT REVIEW OF MEDICAL DEVICES on April 04, 2020, available at: http://www.tandfonline.com/10.1080/17434440.2020.1748008."

1. Introduction

With dozens of millions of people affected worldwide, epilepsy is one of the most common and disabling neurological disorders [1]. Epilepsy consists in an enduring predisposition to suffer from epileptic seizures, which are defined as the transient occurrence of signs or symptoms due to abnormal excessive or synchronous neuronal activity in the brain [2]. Thus, the documentation of abnormal cerebral neuronal activity by electroencephalography (EEG) plays a key role in the diagnosis and management of epilepsy. Drug-resistant epilepsy, where antiepileptic medications fail to control seizures, affects about a third of patients with epilepsy [3]. In these patients, epilepsy surgery, i.e. the removal or disconnection of the brain region responsible for generating seizures (the epileptogenic zone), represents an important therapeutic option, as it can lead to freedom from seizures or significantly reduce seizure frequency and severity [4,5].

Attempting to locate and delineate the epileptogenic zone requires a thorough multidisciplinary investigation, known as presurgical epilepsy evaluation [6]. Electric source imaging (ESI), the estimation of the cerebral source of an electric potential field recorded at the surface of the head, plays an important role in this evaluation [7]. In principle, electromagnetic source imaging can be applied to any electric or magnetic potential field recorded at the head surface [8]. Here, we focus on ESI of epilepsy-related EEG signals, interictal epileptiform discharges (also called interictal spikes, see Table 1) and seizure activity. We particularly insist on high-density EEG (hdEEG), where high electrode counts (60 electrodes and above) are used to map the scalp electric potential field.

Not all patients with drug-resistant epilepsy are candidates for epilepsy surgery [9]; however, even those who are not can benefit from a thorough multidisciplinary evaluation in a comprehensive epilepsy center [10]. Indeed, expert management of antiepileptic drugs, palliative surgical procedures, invasive neuromodulation, and other non-pharmacological approaches can all significantly reduce the burden of disease even in patients who are not amenable to curative resective surgery [11–13].

1.1 Selection of articles to review

In this narrative review, we discuss selected articles that deal with clinically relevant issues in ESI for epilepsy surgery. The choice of topics and articles that we cover inherently contains a measure of subjectivity, which we hope is partially offset by our expertise as active researchers in the field for the past 25 years. For a more thorough review of the existing literature on the accuracy of ESI and magnetoencephalography in the presurgical epilepsy evaluation, systematic reviews and meta-analyses are available [14–16].

2. Basic principles of electric source imaging

Performing ESI means solving an inverse problem that is ill-posed: a particular configuration of the electric potential field at the surface of a conductor could theoretically be generated by an infinite variety of configurations of electric charges within that conductor. Thus, additional assumptions are necessary. One possibility is to restrict the location of ESI solutions to the cerebral cortex, given that it is the cortex that generates interictal spikes and seizures. For instance, in distributed source localization algorithms, ESI is typically computed for a few thousand cortical solution points. Furthermore, the ESI solution is "smoothed", since the EEG signal recorded at the scalp results from synchronized activity in relatively large patches of cerebral cortex. In the case of distributed source localization, the activity of neighboring solution points is forced to be similar [17]. As such, ESI does not provide a direct picture or measurement of the brain's activity, but rather estimates the location of the cerebral source that generated that activity. For more detailed information on the basic principles and technical aspects of ESI, reviews are available [8,18,19].

ESI has amply proven its accuracy and its usefulness in the clinical context of the presurgical epilepsy evaluation, as we will review. International guidelines on the presurgical epilepsy evaluation are beginning to mention the importance of ESI or magnetic source imaging [20]. Nevertheless, ESI remains underutilized, since only 12 of 24 surveyed European epilepsy centers reported using it in their presurgical evaluation [21]. We also discuss potential barriers to the more widespread dissemination of ESI in epilepsy surgery centers, and how to remediate them.

3. Establishing the clinical usefulness of ESI

In determining whether ESI is accurate and helpful in clinical practice, its results must be measured against an appropriate gold standard. Two questions must be addressed: how accurately does ESI estimate the cerebral sources of epilepsy-related EEG activity, and how does ESI help delineate the epileptogenic zone, the cerebral region whose removal will lead to freedom from seizures? Another approach to determine whether ESI is useful is to assess whether it changes the management plan of patients considering epilepsy surgery.

3.1. Accuracy of ESI with respect to intracranial EEG

Intracranial EEG (iEEG) refers to the surgical insertion of electrodes directly over or into the brain, which then capture epilepsy-related signals with a spatial resolution of a few millimeters [22]. iEEG helps to refine hypotheses regarding the putative epileptogenic zone by locating the irritative zone, which is the cerebral region that generates interictal spikes, as well as the seizure onset zone, from where the seizures originate [6]. There is some controversy in the literature regarding the yield of ESI of interictal EEG alone or if ictal recordings are mandatory. In a retrospective study of 38 patients who underwent high-density EEG-based ESI of interictal spikes and later iEEG evaluation, the median distance between the ESI maximum and the nearest iEEG electrode involved in the irritative zone was 15 mm. The median distance between the irritative and seizure onset zones was 0 mm, confirming that localizing the source of interictal spikes provides an excellent estimate of the source of seizures. Accordingly, the median distance between the ESI maximum and the nearest electrode involved in seizure onset is similar and was 17 mm [23]. Importantly, the accuracy of ESI did not depend on whether the epilepsy originated from the medial temporal lobe, the temporal neocortex, or extratemporal cortex, suggesting that it is useful for localization in all types of epilepsies. In that cohort, including the ESI maximum in the resected brain volume was associated with a higher probability of post-operative seizure freedom. While the comparator was neurophysiological signals directly from the human cortex, it should be underlined that this comparator is not perfect given that only a subset of possible sources are sampled with intracranial electrodes. Another caveat is that the irritative and seizure onset zones located by iEEG can be discordant in a minority of patients [23,24].

Other studies where scalp EEG was recorded simultaneously with iEEG showed that only a fraction of the epilepsy-related signals generated by the brain reach the head surface. The proportion of surface-detected interictal spikes was higher if more surface electrodes were used [25–27]. Thus, performing ESI with high electrode-count systems and recording for several hours can increase the yield of the technique.

3.2 ESI and post-operative outcomes

A clinically relevant way of determining the usefulness of ESI and comparing it with that of other modalities such as magnetic resonance imaging (MRI) or positron emission tomography (PET) is to check whether the brain region of the ESI was resected in patients who then became seizure-free. An ESI result within the resection cavity counts as a true positive, while an ESI result outside it is a false negative. Conversely, in patients whose seizures persist after resective surgery despite an ESI result within the resection cavity is a false positive, while an ESI result outside it is a true negative [28]. Using this approach in a cohort of 82 patients, the sensitivity of hdEEG-based ESI was 92% and its specificity 45% [29]. The diagnostic performance of ESI compared favorably with that of MRI and PET (Table 2). Importantly, the inclusion of both the ESI result and the epileptogenic lesion delineated by MRI was associated with a probability of being seizure free (positive predictive value) of 92%.

Another study that focused on patients with temporal lobe epilepsy only found a similarly high sensitivity of hdEEG-based ESI (91%; [30]). A recent systematic review also highlighted the high sensitivity of ESI and magnetoencephalography source imaging [15]. Taken together, these studies argue that the accuracy of ESI is sufficiently high to warrant its inclusion in the routine work-up of candidates for epilepsy surgery, as also recommended by the International Federation of Clinical Neurophysiology [31].

The relatively low specificity numbers for ESI (see Table 2) might at first appear surprising. We first emphasize that these numbers are not markedly different from those of the other modalities used in the presurgical evaluation. Further, when only the ESI maximum is considered as a single point (as in [29]), the computation of sensitivity and specificity values artificially reduces the specificity of ESI while boosting that of modalities that provide volumetric estimates of the putative epileptogenic zone: if, for instance, PET shows a widespread hypometabolism that is not entirely included in the resected volume, and the patient does not become seizure-free, it is counted as a true negative. This situation is less likely to occur for the point-like ESI maximum. Innovations in source localization algorithms are being developed to allow ESI to model the extent of sources in addition to their location [32,33].

3.3 ESI and changes to the patient's management plan

The role of ESI in the presurgical epilepsy evaluation can be studied prospectively by comparing the management plan of patients before and after ESI results are revealed. A recent study showed that ESI was instrumental in changing the management plan of 34% of patients (28 of 82) [34]. The single largest contribution of ESI was to prompt the insertion of additional iEEG electrodes. The influence of ESI in influencing the management plan is comparable to that of magnetoencephalography [35,36]. Another recent study combined ESI and magnetic source imaging and also found that the results of these techniques altered the management plan in 34% of patients (29 of 85) [37]. Notably, the additional iEEG electrodes implanted because of the electromagnetic source imaging results were the ones to localize the irritative and seizure onset zones in 8 of 10 patients (80%). These prospective studies highlight the practical relevance of ESI in management decisions regarding the planning of epilepsy surgery. Importantly, even if the accuracy of ESI as determined using the gold standards of iEEG or post-operative outcomes is not higher than that of other modalities like PET or MRI (as summarized above), these studies demonstrate that ESI provides non-redundant information in a substantial proportion of patients.

3.4 Usefulness of ESI in select patient populations

ESI could play a particularly important role in particular subgroups of patients considering epilepsy surgery. Perhaps most clinically relevant are patients where the MRI is considered negative, either because it shows no lesion or because it shows diffuse, large or multifocal abnormalities not entirely amenable to resection. In relatively small cohorts, the technical accuracy of ESI was shown to be conserved in patients with a normal MRI [38] as well as in those with large brain lesions [39]. Those studies did not directly contrast the performance of ESI in MRI-negative vs. MRI-positive patients. A more recent study, where the results of ESI were validated with iEEG, showed that the concordance between ESI and iEEG was actually higher for patients with MRI-negative epilepsy than for those with a lesion on the MRI [40]. This study illustrates the fact that the relationship between the putative epileptogenic lesion seen on the MRI, the irritative zone generally identified by ESI (although see below for ictal ESI) and the seizure onset zone revealed by iEEG is complex. No single method currently stands above the others in terms of performance; in difficult circumstances like MRI-negative epilepsy, gathering information from a variety of modalities brings complementary information that informs the clinicians and patients' decisions.

4. Practical aspects of ESI

4.1 How many electrodes?

The density and extent of coverage of the head by the EEG electrodes are important in determining an appropriate sampling of the electric potential field recorded at the head surface. Intuitively, more electrodes are better. Indeed, the accuracy of interictal spike ESI increased significantly when moving up from about 30 to about 60 electrodes, with more incremental improvement with further increasing electrode counts [41–43]. Modern hdEEG systems allow recording signals from 128 to 256 electrodes with less than an hour of preparation. Importantly, coverage must extend below the hairline, including face and neck, to capture sources on the inferior surfaces of the cerebral hemispheres. Simulation studies showed that the advantage of higher electrode counts is abolished if coverage is limited to the upper part of the head [44]. The importance of coverage is such that the International Federation of Clinical Neurophysiology now recommends a minimum of 25 electrodes for routine EEG recordings, extending to the inferior frontal, temporal and occipital regions [31].

4.2 Which signal?

The majority of research on ESI in the presurgical evaluation uses interictal spikes as the signal to localize. The accuracy of ESI depends on the signal-to-noise ratio (SNR) of the EEG: therefore, similar spikes should be averaged together before ESI computation. The accuracy of ESI is compromised if spikes differ in their morphology, which may reflect different sources or propagation patterns. Interictal epileptiform discharges last anywhere from 20 to 300 ms, and significant propagation of the underlying cerebral activity is known to occur during the time course of a spike [45,46]. Therefore, the exact time point at which ESI is performed matters: too early, and the SNR might be insufficient to obtain a reliable ESI result; too late, and significant propagation might occur (Figure 1). ESI is most commonly performed at the half-rising point of the spike. Using this time point, all subjects were correctly localized in a study on 16 subjects [45]. A recent study challenges this practice and suggests localizing spikes as early as possible after their onset [47]; however, this may result in poor SNR. Future larger studies are necessary to determine the optimal time point for ESI.

Interictal spikes can be marked manually upon reviewing the EEG recording, or detected and clustered together automatically by dedicated software [48]. Both approaches require expertise in clinical neurophysiology in order to avoid localizing spiky features of the EEG signal that are physiological or artefacts and do not correspond to interictal epileptiform discharges. Longer recording durations yield larger numbers of interictal spikes [49], and also increase the probability of sampling a seizure. This must be balanced by the increasing workload of processing longer recordings, an issue that could itself be alleviated by automatizing some processing steps (see below).

4.3 Ictal ESI

Even though the cerebral sources of interictal spikes and of seizures colocalize in most patients [23,29], performing ESI of seizure onsets is also appealing. Given that the EEG pattern often varies from one seizure to the other, averaging seizure onsets is not an option. Instead, ESI of the EEG at the beginning of a seizure, a few seconds before movement artefacts obscure it, is a possible approach, using frequency analysis [50,51]. A variety of methods have been developed for that purpose; interestingly, these methods produce rather convergent ESI results [52]. Overall, in the small studies published so far, the accuracy of ictal onset ESI seems to be roughly comparable to that of interictal spike ESI [47,50–55], although the two approaches have not yet been compared prospectively in a large patient group. Similar to interictal ESI, the number of electrodes matters for ictal ESI: in a cohort of 10 patients, 76 electrodes performed better than 32 or fewer [56].

4.4 Which head model?

The head model describes how the electric potential generated by a given solution point of the ESI traverses the various tissues of the head (brain, skull, scalp, etc.) and reaches the EEG electrodes (the so-called forward problem). There are several technical approaches to design the head model, from simple concentric spheres to anatomically realistic geometrical parcellations of the head. In the practical case of interictal spike ESI, a comparison of three approaches (concentric spheres, boundary element model, and finite element model) found very minor differences that did not impact on the accuracy of ESI [57]. That being said, it is essential to use the patient's own head anatomy when building the head model rather than a head template, which lowers the accuracy of ESI [28]. Using the patient's own cerebral MRI has the advantage that the presence of large lesions without neuronal tissue is acknowledged by the head model, so no solution points are placed within CSF or cavity [39].

5. ESI as an automated procedure

Performing hdEEG recordings and ESI requires expertise and time as well as dedicated hardware and software. If these resources are unavailable, clinically useful information can still be obtained from the routine EEG recordings obtained in the epilepsy monitoring, provided that the electrode coverage extends to the inferior temporal regions as recommended [31]. In recent studies, a semi-automated pipeline of interictal spike detection and clustering followed by ESI using 25 to 31-electrode EEG recordings [58] has been described. Using the patient's own MRI, the algorithm had favorable sensitivity (88%) and specificity (63%) [59,60]. Long EEG recordings (several hours to several days), and consequently the high numbers of interictal spikes available for ESI, might improve the SNR enough to partially compensate for lower spatial sampling (e.g. of only 40 electrodes) but this remains to be shown in a prospective study.

6. Conclusion

We have reviewed the literature to show that ESI can readily be applied to epilepsy-related EEG signals and that the diagnostic accuracy of ESI rivals that of MRI and PET. ESI (and magnetic source imaging) can bring additional information that directly influences management in about 20-30% of patients [34–37,61,62]. Furthermore, concordant results between multiple noninvasive modalities is associated with a higher chance of post-operative seizure freedom [29]. Despite the good performance of ESI, its use in clinical practice remains limited [21]. However, the perceived difficulties with ESI should not detract epilepsy centers from offering the technique to their patients, either by specialized in-house teams or as an outsourced activity.

7. Expert opinion

ESI is the only technique that allows the direct identification of neuronal activity using a tool available in every epilepsy center or neurology clinic: the electroencephalogram (EEG). The EEG visualizes and records directly the correlate of epileptogenic activity, which can then be processed by source localization algorithms to obtain a 3D view of the source inside the patient's brain. Its usefulness before surgical decisions has been shown in a number of retrospective and prospective clinical studies. There is an emerging consensus that over 64 electrodes are preferable. Newer systems allow a set-up of up to 256 electrodes within 30 minutes, which is more practicable than attaching each electrode individually. One limitation of ESI in its current implementation is the lack of standardization for the collection and data analysis; however, a comparison of the different algorithms did not reveal important localization differences. The major limitation for the widespread use of ESI is the fact that it entails several steps of EEG and MRI data preparation, which requires some expertise and is difficult to integrate into the clinical flow by the practicing neurologist, neurosurgeon or pediatric neurologist. Given that MEG machines usually come with dedicated maintenance staff, like physicists, MSI analysis is often carried out by the same MEG team. However, the main advantages of hdEEG are the possibility of prolonged recordings (e.g. sleep), which make the acquisition of ictal data more likely, and the portability of hdEEG systems which can be moved to specific clinical units, like pediatric neurology or intensive care. In addition, the relatively low price and running costs of EEG systems (a few tens of thousands to a few hundred thousand dollars, versus several million dollars for MEG systems) make them an affordable addition to the arsenal of techniques available to epilepsy centers around the world.Current research in ESI is focusing, among others, on new approaches to process the hdEEG signal and reveal the underlying organization of epilepsy-related brain networks [33,63]. Advanced techniques, including analyses of directed connectivity between brain regions, can be performed using hdEEG and ESI. These techniques estimate how the activity of a given cortical area influence that of others. They have the potential to reveal how certain cortical regions are responsible for the generation of epilepsy-related activity versus its propagation. Furthermore, by studying how the epilepsy-generating regions influence and perturb the activity in downstream areas, it might become possible to understand why some epilepsy patients suffer from neuropsychological deficits that involve functional areas remote from the epileptogenic cortex [64,65]. Another line of research concerns the identification of EEG biomarkers of epilepsy-related activity even in the absence of overt EEG abnormalities. The idea here is that epilepsy-related brain networks are strongly interconnected even when they are not generating interictal spikes or seizures [66] and that ongoing activity in these networks might be detectable using hdEEG [67].

The accuracy of ESI in localizing epilepsy-related EEG activity has been established by comparing it with the gold standards of intracranial EEG and surgical outcomes [23,29]. This work has increased the confidence of the clinical community in using ESI to localize cerebral activity, and this confidence also extends to other settings where these gold standards are not available [18]. ESI can also contribute to mapping so-called eloquent cortex, the cortical areas that are involved in critical functions like motor control or speech perception and production and should be spared by the surgeon. ESI of somatosensory-evoked potentials recorded with hdEEG accurately localizes sensorimotor cortex around the central sulcus [68]. More recently, ESI and MSI have been applied successfully to identify which cerebral hemisphere is dominant for language [69,70]. Studies on the accurate localization of cortical regions indispensable for speech or memory with hdEEG are still pending, but the situation is likely to evolve favorably with refinements in data analysis and knowledge of the size and number of modules of the underlying networks.

In the coming years, we predict that ESI will be fully integrated into the workflow of most comprehensive epilepsy centers, and could even become a requisite for the highest-level centers. Easy-to-handle localization programs will be built into clinical-grade hdEEG systems, and dedicated services allowing uncomplicated outsourcing of ESI will be developed. Currently initiatives from the International Federation of Clinical Neurophysiology and the International League against Epilepsy to standardize recording and analysis of hdEEG and ESI will facilitate these processes. Once these improvements are established, ESI will be extended to frequency analysis as a regular clinical tool so that focal or diffuse slowing (or faster rhythms) can be localized. This could become an additional useful tool in the investigation of epilepsy, but also in neurodegenerative, neurodevelopmental and psychiatric diseases, and may carry important information on the type and prognosis of the brain disease.

Key issues

- Electric source imaging of high-density EEG signals has been demonstrated to localize accurately the source of epilepsy-related EEG activity such as interictal spikes and seizures.
- Including ESI in the assessment of patients with drug-resistant focal epilepsy who are candidates for epilepsy surgery enriches the amount of information available. This additional information meaningfully influences the clinical management of these patients when deciding on an operation or planning an intracranial EEG evaluation. Furthermore, ESI might play a role in selecting patients for surgery by helping predict surgical outcomes in terms of freedom from seizures.
- As of today, ESI remains a technically demanding investigation. However, improvements in the development of hardware for high-density EEG and of software for signal analysis are ongoing. Consequently, the technique could soon become a routine tool available in every clinical neurophysiology laboratory and epilepsy center.

Declaration of competing interests

PM is supported by the Swiss National Science Foundation (grant 167836). MS has shares in Epilog. MS was speaker for Philips and Desitin. MS is supported by the Swiss National Science Foundation (grants 163398, 180365).

References

[1] Beghi E, Giussani G, Nichols E, et al. Global, regional, and national burden of epilepsy, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2019;18:357–375.

[2] Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE Official Report: A practical clinical definition of epilepsy. Epilepsia. 2014;55:475–482.

[3] Kwan P, Brodie MJ. Early identification of refractory epilepsy. N. Engl. J. Med. 2000;342:314–319.

[4] Wiebe S, Blume WT, Girvin JP, et al. A Randomized, Controlled Trial of Surgery for Temporal-Lobe Epilepsy. N. Engl. J. Med. 2001;345:311–318.

[5] Rugg-Gunn F, Miserocchi A, McEvoy A. Epilepsy surgery. Pract. Neurol. BMJ Publishing Group; 2020. p. 4–14.

[6] Rosenow F, Lüders H. Presurgical evaluation of epilepsy. Brain. 2001;124:1683–1700.

[7] Mégevand P, Seeck M. Electroencephalography, magnetoencephalography and source localization: their value in epilepsy. Curr. Opin. Neurol. 2018;31:176–183.

[8] Michel CM, Murray MM, Lantz G, et al. EEG source imaging. Clin. Neurophysiol. 2004;115:2195–2222.

[9] Duncan JS. Selecting patients for epilepsy surgery: Synthesis of data. Epilepsy Behav. 2011;20:230–232.

[10] Engel J. The current place of epilepsy surgery. Curr. Opin. Neurol. 2018;31:192–197.

[11] Boon P, De Cock E, Mertens A, et al. Neurostimulation for drug-resistant epilepsy: A systematic review of clinical evidence for efficacy, safety, contraindications and predictors for response. Curr. Opin. Neurol. 2018;31:198–210.

[12] Cheng JY, French JA. Intelligent use of antiepileptic drugs is beneficial to patients. Curr. Opin. Neurol. 2018;31:169–175.

[13] Englot DJ, Birk H, Chang EF. Seizure outcomes in nonresective epilepsy surgery: an update. Neurosurg. Rev. 2017;40:181–194.

[14] Lau M, Yam D, Burneo JG. A systematic review on MEG and its use in the presurgical evaluation of localization-related epilepsy. Epilepsy Res. 2008;79:97–104.

[15] Mouthaan BE, Rados M, Boon P, et al. Diagnostic accuracy of interictal source imaging in presurgical epilepsy evaluation: A systematic review from the E-PILEPSY consortium. Clin. Neurophysiol. 2019;130:845–855.

[16] Sharma P, Seeck M, Beniczky S. Accuracy of Interictal and Ictal Electric and Magnetic Source Imaging: A Systematic Review and Meta-Analysis. Front. Neurol. 2019;10:1250.

[17] Buzsáki G, Anastassiou CA, Koch C. The origin of extracellular fields and currents — EEG, ECoG, LFP and spikes. Nat. Rev. Neurosci. 2012;13:407–420.

[18] Michel CM, Brunet D. EEG source imaging: A practical review of the analysis steps. Front. Neurol. 2019;10:325.

[19] He B, Sohrabpour A, Brown E, et al. Electrophysiological Source Imaging: A Noninvasive Window to Brain Dynamics. Annu. Rev. Biomed. Eng. 2018;20:171–196.

[20] Rosenow F, Bast T, Czech T, et al. Revised version of quality guidelines for presurgical epilepsy evaluation and surgical epilepsy therapy issued by the Austrian, German, and Swiss working group on presurgical epilepsy diagnosis and operative epilepsy treatment. Epilepsia. 2016;1–6.

[21] Mouthaan BE, Rados M, Barsi P, et al. Current use of imaging and electromagnetic source localization procedures in epilepsy surgery centers across Europe. Epilepsia. 2016;57:770–776.

[22] Dubey A, Ray S. Cortical Electrocorticogram (ECoG) is a local signal. J. Neurosci. 2019;39:2917–2918.

[23] Mégevand P, Spinelli L, Genetti M, et al. Electric source imaging of interictal activity accurately localises the seizure onset zone. J. Neurol. Neurosurg. Psychiatry. 2014;85:38–43.

[24] Bartolomei F, Trébuchon A, Bonini F, et al. What is the concordance between the seizure onset zone and the irritative zone? A SEEG quantified study. Clin. Neurophysiol. 2016;127:1157–1162.

[25] Tao JX, Ray A, Hawes-Ebersole S, et al. Intracranial EEG substrates of scalp EEG interictal spikes. Epilepsia. 2005;46:669–676.

[26] Ramantani G, Dümpelmann M, Koessler L, et al. Simultaneous subdural and scalp EEG correlates of frontal lobe epileptic sources. Epilepsia. 2014;55:278–288.

[27] Yamazaki M, Tucker DM, Fujimoto A, et al. Comparison of dense array EEG with simultaneous intracranial EEG for interictal spike detection and localization. Epilepsy Res. 2012;98:166–173.

[28] Brodbeck V, Spinelli L, Lascano AM, et al. Electroencephalographic source imaging: A prospective study of 152 operated epileptic patients. Brain. 2011;134:2887–2897.

[29] Lascano AM, Perneger T, Vulliemoz S, et al. Yield of MRI, high-density electric source imaging (HD-ESI), SPECT and PET in epilepsy surgery candidates. Clin. Neurophysiol. 2016;127:150–155.

[30] Feng R, Hu J, Pan L, et al. Application of 256-channel dense array electroencephalographic source imaging in presurgical workup of temporal lobe epilepsy. Clin. Neurophysiol. 2016;127:108–116.

[31] Seeck M, Koessler L, Bast T, et al. The standardized EEG electrode array of the IFCN. Clin. Neurophysiol. 2017;128:2070–2077.

[32] Heers M, Chowdhury RA, Hedrich T, et al. Localization Accuracy of Distributed Inverse Solutions for Electric and Magnetic Source Imaging of Interictal Epileptic Discharges in Patients with Focal Epilepsy. Brain Topogr. 2016;29:162–181.

[33] Mégevand P, Hamid L, Dümpelmann M, et al. New horizons in clinical electric source imaging. Zeitschrift fur Epileptol. 2019;32:187–193.

[34] Foged MT, Martens T, Pinborg LH, et al. Diagnostic added value of electrical source imaging in presurgical evaluation of patients with epilepsy: A prospective study. Clin. Neurophysiol. 2020;131:324–329.

[35] Sutherling WW, Mamelak AN, Thyerlei D, et al. Influence of magnetic source imaging for planning intracranial EEG in epilepsy. Neurology. 2008;71:990–996.

[36] Knowlton RC, Razdan SN, Limdi N, et al. Effect of epilepsy magnetic source imaging on intracranial electrode placement. Ann. Neurol. 2009;65:716–723.

[37] Duez L, Tankisi H, Hansen PO, et al. Electromagnetic source imaging in presurgical workup of patients with epilepsy: A prospective study. Neurology. 2019;92:e576–e586.

[38] Brodbeck V, Spinelli L, Lascano AM, et al. Electrical source imaging for presurgical focus localization in epilepsy patients with normal MRI. Epilepsia. 2010;51:583–591.

[39] Brodbeck V, Lascano AM, Spinelli L, et al. Accuracy of EEG source imaging of epileptic spikes in patients with large brain lesions. Clin. Neurophysiol. 2009;120:679–685.

[40] Abdallah C, Maillard LG, Rikir E, et al. Localizing value of electrical source imaging: Frontal lobe, malformations of cortical development and negative MRI related epilepsies are the best candidates. NeuroImage Clin. 2017;16:319–329.

[41] Lantz G, Grave de Peralta R, Spinelli L, et al. Epileptic source localization with high density EEG: How many electrodes are needed? Clin. Neurophysiol. 2003;114:63–69.

[42] Sohrabpour A, Lu Y, Kankirawatana P, et al. Effect of EEG electrode number on epileptic source localization in pediatric patients. Clin. Neurophysiol. 2015;126:472–480.

[43] Tamilia E, AlHilani M, Tanaka N, et al. Assessing the localization accuracy and clinical utility of electric and magnetic source imaging in children with epilepsy. Clin. Neurophysiol. 2019;130:491–504.

[44] Song J, Davey C, Poulsen C, et al. EEG source localization: Sensor density and head surface coverage. J. Neurosci. Methods. 2015;256:9–21.

[45] Lantz G, Spinelli L, Seeck M, et al. Propagation of interictal epileptiform activity can lead to erroneous source localizations: a 128-channel EEG mapping study. J. Clin. Neurophysiol.

2003;20:311–319.
[46] Mălîia MD, Meritam P, Scherg M, et al. Epileptiform discharge propagation: Analyzing spikes from the onset to the peak. Clin. Neurophysiol. 2016;127:2127–2133.
[47] Plummer C, Vogrin SJ, Woods WP, et al. Interictal and ictal source localization for epilepsy surgery using high-density EEG with MEG: a prospective long-term study. Brain. 2019;142:932–951.
[48] Scheuer ML, Bagic A, Wilson SB. Spike detection: Inter-reader agreement and a statistical Turing test on a large data set. Clin. Neurophysiol. 2017;128:243–250.
[49] Burkholder DB, Britton JW, Rajasekaran V, et al. Routine vs extended outpatient EEG for the detection of interictal epileptiform discharges. Neurology. 2016;86:1524–1530.
[50] Nemtsas P, Birot G, Pittau F, et al. Source localization of ictal epileptic activity based on high-density scalp EEG data. Epilepsia. 2017;58:1027–1036.
[51] Pellegrino G, Hedrich T, Chowdhury R, et al. Source localization of the seizure onset zone from ictal EEG/MEG data. Hum. Brain Mapp. 2016;37:2528–2546.
[52] Beniczky S, Rosenzweig I, Scherg M, et al. Ictal EEG source imaging in presurgical evaluation: High agreement between analysis methods. Seizure. 2016;43:1–5.
[53] Staljanssens W, Strobbe G, Van Holen R, et al. EEG source connectivity to localize the seizure onset zone in patients with drug resistant epilepsy. NeuroImage Clin. 2017;16:689–698.
[54] Staljanssens W, Strobbe G, Holen R Van, et al. Seizure Onset Zone Localization from Ictal High-Density EEG in Refractory Focal Epilepsy. Brain Topogr. 2017;30:257–271.
[55] Habib MA, Ibrahim F, Mohktar MS, et al. Ictal EEG Source Imaging for Presurgical Evaluation of Refractory Focal Epilepsy. World Neurosurg. 2016;88:576–585.
[56] Lu Y, Yang L, Worrell GA, et al. Seizure source imaging by means of FINE spatio-temporal dipole localization and directed transfer function in partial epilepsy patients. Clin. Neurophysiol. 2012;123:1275–1283.
[57] Birot G, Spinelli L, Vulliémoz S, et al. Head model and electrical source imaging: A study of 38 epileptic patients. NeuroImage Clin. 2014;5:77–83.
[58] Epilog NV. Epilog [Internet]. 2020.
[59] van Mierlo P, Strobbe G, Keereman V, et al. Automated long-term EEG analysis to localize the epileptogenic zone. Epilepsia Open. 2017;322–333.
[60] Baroumand AG, van Mierlo P, Strobbe G, et al. Automated EEG source imaging: A retrospective, blinded clinical validation study. Clin. Neurophysiol. 2018;129:2403–2410.
[61] Stefan H, Hummel C, Scheler G, et al. Magnetic brain source imaging of focal epileptic activity: A synopsis of 455 cases. Brain. 2003;126:2396–2405.
[62] De Tiège X, Carrette E, Legros B, et al. Clinical added value of magnetic source imaging in the presurgical evaluation of refractory focal epilepsy. J. Neurol. Neurosurg. Psychiatry. 2012;83:417–423.
[63] Pittau F, Mégevand P, Sheybani L, et al. Mapping epileptic activity: sources or networks for the clinicians? Front. Neurol. 2014;5:218.
[64] Coito A, Plomp G, Genetti M, et al. Dynamic directed interictal connectivity in left and right temporal lobe epilepsy. Epilepsia. 2015;56:207–217.
[65] Coito A, Genetti M, Pittau F, et al. Altered directed functional connectivity in temporal lobe epilepsy in the absence of interictal spikes: A high density EEG study. Epilepsia. 2016;57:402–411.
[66] Iannotti GR, Grouiller F, Centeno M, et al. Epileptic networks are strongly connected with and without the effects of interictal discharges. Epilepsia. 2016;57:1086–1096.
[67] Grouiller F, Thornton RC, Groening K, et al. With or without spikes: localization of focal epileptic activity by simultaneous electroencephalography and functional magnetic resonance imaging. Brain. 2011;134:2867–2886.
[68] Lascano AM, Grouiller FF, Genetti MM, et al. Surgically relevant localization of the central sulcus

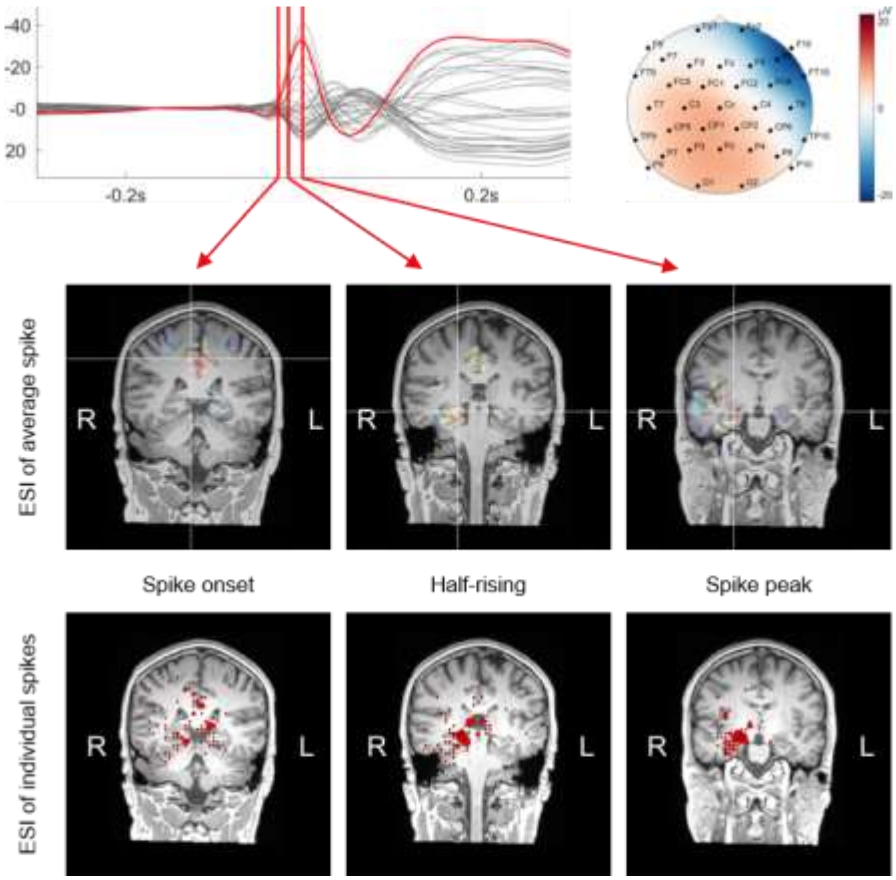
with high-density somatosensory-evoked potentials compared with functional magnetic resonance imaging. Neurosurgery. 2014;74:517–526.

[69] Pirmoradi M, Jemel B, Gallagher A, et al. Verbal memory and verbal fluency tasks used for language localization and lateralization during magnetoencephalography. Epilepsy Res. 2016;119:1–9.

[70] Trimmel K, Sachsenweger J, Lindinger G, et al. Lateralization of language function in epilepsy patients: A high-density scalp-derived event-related potentials (ERP) study. Clin. Neurophysiol. 2017;128:472–479.

Figures and tables

Figure 1: Propagation of activity during interictal spikes and average versus individual spikes



This 27-year-old patient suffered from drug-resistant epilepsy for 4 years. MRI was unremarkable. Ictal video-EEG suggested right temporal seizure onsets, but PET and SPECT were not concordant. Intracranial EEG (sampling the right temporal, prefrontal, insular and cingular regions) confirmed a right medial temporal seizure onset zone. A right-sided anterior temporal lobar resection was performed. Pathological examination disclosed hippocampal gliosis. Six months later, the patient is seizure-free. ESI of the patient's typical interictal spikes (right-sided anterior temporal, with maximal amplitude at electrode F8) is performed at its onset, at the point during its rising period where amplitude reaches 50% of its maximum (half-rising), and at its peak. Notice how the ESI, which is initially cingular at onset, progresses to the medial temporal lobe at later time points. The signal-to-noise ratio of individual spikes is very low at their onset, which shows in the broad distribution of ESI (spanning both cerebral hemispheres) and explains the false localization. At later time points, ESI of individual spikes is more similar to that of the average spike. This image is generated by the Epilog software (https://www.epilog.care/).

Table 1: List of terms

Interictal spike (interictal epileptiform discharge)	A brief (<= 200 ms) period of sharp-looking abnormal EEG activity, unnoticed by the patient, which is a biomarker of epilepsy
Irritative zone	The cerebral region generating interictal spikes
Seizure onset zone	The cerebral region from which seizures originate
Epileptogenic zone	The cerebral region whose removal leads to freedom from seizures
Resection cavity	The cerebral region that is removed during epilepsy surgery. If the patient then becomes seizure-free, it can be supposed that the epileptogenic zone was included in the resection cavity.

Table 2. Diagnostic performance of ESI, MRI, and PET with respect to outcome from epilepsy surgery

Modality	Sensitivity	Specificity	Positive predictive value	Negative predictive value
ESI	92% (57/62)	45% (9/20)	84% (57/68)	64% (9/14)
MRI	78% (116/148)	62% (26/42)	88% (116/132)	45% (26/58)
PET	71% (102/144)	56% (23/41)	85%(102/120)	35% (23/65)

Data from [29].