EEG source imaging in epilepsy—practicalities and pitfalls

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Abstract | EEG source imaging (ESI) is a model-based imaging technique that integrates temporal and spatial components of EEG to identify the generating source of electrical potentials recorded on the scalp. Recent advances in computer technologies have made the analysis of ESI data less time-consuming, and have rekindled interest in this technique as a clinical diagnostic tool. On the basis of the available body of evidence, ESI seems to be a promising tool for epilepsy evaluation; however, the precise clinical value of ESI in presurgical evaluation of epilepsy and in localization of eloquent cortex remains to be investigated. In this Review, we describe two fundamental issues in ESI; namely, the forward and inverse problems, and their solutions. The clinical application of ESI in surgical planning for patients with medically refractory focal epilepsy, and its use in source reconstruction together with invasive recordings, is also discussed. As ESI can be used to map evoked responses, we discuss the clinical utility of this technique in cortical mapping—an essential process when planning resective surgery for brain regions that are in close proximity to eloquent cortex.

Kaiboriboon, K. *et al. Nat. Rev. Neurol.* **8**, 498–507 (2012); published online 7 August 2012; doi:10.1038/nrneurol.2012.150

Introduction

In 1929, Hans Berger's study describing the first human EEG recording was published.[1] Since then, the adaptation of EEG to clinical use and subsequent utility of this technique to measure neuronal activity in epilepsy has been exponential. EEG is an important tool for precisely identifying the irritative zone, defined as the area of cortex that generates interictal sharp waves or spikes, and the ictal onset zone, the area of cortex that generates epileptic seizures (Figure 1).

Traditionally, analysis of EEG recordings relies mainly on visual inspection. Simple visual analysis of EEG tracings is usually adequate for a clinician to identify the type of epilepsy. For epilepsy surgery evaluation, however, conventional EEG analysis often cannot be used to identify the irritative zone and/or the ictal onset zone with the required precision.[2] Consequently, computational techniques that can depict the presumed source of EEG activity—a process termed EEG source imaging (ESI)—have been developed. Although studies on the relationship between the source of neural activity and its potentials began long before the first EEG was recorded,[3] the application of ESI in a clinical setting (Box 1) has only become practical in the past two decades with the advent of digital EEG.[4]

In this Review, we discuss the current clinical utility of ESI in surgical planning for focal epilepsy, describing the available computational models, and highlighting the practicalities and pitfalls of this approach to epileptic source localization. The role of ESI in identifying the source of evoked potentials, which could potentially aid in mapping of eloquent cortex, is also discussed. An improved understanding of the ESI process and advances in computational technology will enhance the utility of ESI in presurgical investigation of patients with refractory focal epilepsy.

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Competing interests
The authors declare no competing interests.

Principles of ESI

In theory, determining the exact location of an electrical source in the brain from only scalp-recorded EEG data —the so-called inverse problem—is impossible.[3] However, if the characteristics of the volume conductor (in the case of EEG, the brain and head structures) and the location of the source are known, the scalp voltage field can be accurately predicted—the so-called forward problem. Consequently, the only way to solve the inverse problem is to solve the forward problem by postulating *a priori* models for both the source and the volume conductor.[5] Solving the forward and inverse problems is not straightforward and requires two independent mathematical algorithms: a volume conductor model for the forward problem and source model for the inverse problem (Figure 2).[6–8] The choice of model used to obtain these solutions is extremely important as both solutions crucially influence the results of ESI.[9–12]

The forward problem

As previously mentioned, the forward problem of EEG refers to the difficulty in predicting the surface field potential (the EEG recording) for a given source within the conductor (namely, the head and its internal structures). This problem can be solved by specifying a set of known conditions for the head model and then calculating the potential at the recording electrodes.[6] In general, for a source of specified location, orientation and magnitude,

only one field potential is possible on the surface of the conductor. The forward solution, therefore, is unique. However, solving the forward problem or estimating field distribution on the scalp is extremely difficult owing to the inhomogeneity of brain structures (such as the sulci and gyri) and the anisotropic properties of the brain and surrounding tissues (cerebrospinal fluid, meninges, skull and scalp). Calculation of conductivities in each tissue along the signal path in the brain is difficult and, currently, an inexact science.[13]

Head models

Two broad categories of head or volume conductor models are used: the spherical shell model and the realistic head model. The spherical shell model, which assumes that conductive property throughout the head is uniform, is the simplest. However, as the human head is not spherical and its conductivity is not spatially uniform, the accuracy of ESI based on this model is limited. The incorporation of different conductivity parameters in spherical multiple shell models (two-shell to four-shell) and consideration of local anisotropies can improve the accuracy of shell-model-based ESI to some extent.

Theoretically, more-sophisticated realistic head models that are based on high-resolution MRI scans of individual patients should offer better solutions than are obtained with use of the spherical shell model. The most popular techniques for realistic head models are the boundary element method (BEM), the finite element method (FEM), and the finite difference method (FDM). BEM uses triangulations of the interfaces between brain compartments of equal isotropic conductivities as a geometric model.[14,15] By contrast, FEM allows tessellation of the brain and, therefore, the individual anisotropic conductivity of each element (tissue or fluid) is taken into account.[11,16] In FDM, the conducting volume is divided into cubic grids and each cubic element has a different conductivity.[17] Recently, a sensor-weighted overlapping sphere head model,[18] a spherical model with an anatomical constrains transformation method,[19] and 3D forward-field interpolation[20] have been developed in an attempt to combine the computational efficiency of the spherical model with a more accurate depiction of the head shape.

Issues with conductivity

Owing to the variability of brain-to-skull conductivity values, several methods have been proposed to minimize the uncertainty of conductivity. These include the reduced conductivity dependence method,[21] which reformulates the cost function (relating to differences between the measured and calculated potentials), and selects only the set of electrodes that are least affected by the unknown conductivity; the conductivity tensor map,[22] which infers the conductivity tensor from the diffusion tensor; and electrical impedance tomography,[23] which enables estimation of the electrical properties of the brain. These methods can potentially be applied to both spherical and realistic head models to enhance the accuracy of source localization.[24,25] However, they have rarely been used in clinical practice, and no technique that can produce an accurate high-resolution image of conductivity *in vivo* is currently available.

Key points

- EEG source imaging (ESI) is a model-based imaging technique that integrates temporal and spatial components of EEG to identify the source of scalp-recorded potentials
- The choice of forward and inverse solutions can crucially influence the outcome of source localization using ESI
- A realistic head model using an individual's MRI offers the best forward solution
- A high total number of electrodes or concentration of electrodes over the region of interest can improve the accuracy of ESI
- Attention to technical recording details, including co-registration of electrode positions on MRI and modelling of the initial phase of epileptic spikes, is crucial for accurate source localization using ESI
- On the basis of current evidence, ESI is a promising tool for epilepsy evaluation, but further studies in large epilepsy cohorts are needed to demonstrate its clinical value

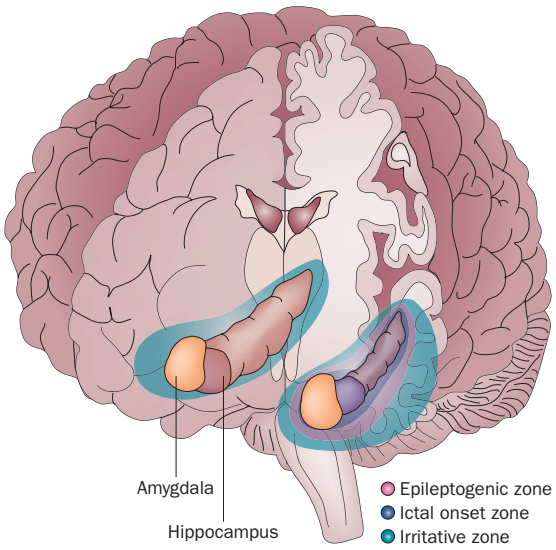

Figure 1 | The irritative and ictal onset zones in relation to the epileptogenic zone.

Which volume conduction model provides the most accurate source localization remains an open question. Only a limited number of simulation studies have demonstrated that more-complex realistic head models perform better than less-complex realistic models or spherical head models in ESI.[6,26,27] Whether the complex realistic head models are cost-effective, and if they provide more-accurate localization than the less-complex volume conduction models, remains to be determined with direct clinical testing.

The inverse problem

The inverse problem—the problem of identifying the source of a given surface field potential—is encountered frequently by electroencephalographers in routine clinical practice. In contradistinction to the forward problem, a potentially infinite number of sources within the brain can produce similar scalp-recorded field potentials. As previously stated, *a priori* assumptions of the source and the volume conductor are required to solve the inverse problem.[5] These assumptions are important because

Box 1 | Utility of EEG source imaging in epilepsy

- Identification of the irritative zone (spikes and/or sharp waves)
- Presurgical assessment of patients with refractory focal epilepsy
- Accurate definition of focal epilepsies
- Identification of the ictal onset zone (EEG seizure onset)
- Identification of seizure networks (seizure propagation)
- Identification of eloquent cortex (visual, auditory and somatosensory regions)

they determine whether the solution can only superficially explain the data or whether it provides meaningful neurophysiological information regarding the probable source.

Single dipole model

The most commonly used source model in the clinical setting is the single equivalent current dipole (ECD). The basic assumption of this model is that at any given instant, the detected potential represents activity from a single, infinitely small area of active cortex.[8] Under this assumption, the dipole model will essentially never reflect biological fact, and will only approximate reality in a limited number of conditions, such as epileptic spikes or the early component of the auditory evoked potential.[8,28] In the ECD model, the voltage field map at a given instant is modelled by the best-fitting single dipole. The map is then compared with the measured potential map to identify the best location of the source: the solution with the least-square source estimation or the minimum squared error is accepted as the best source-localization result. Each subsequent field measurement can also be modelled by another single dipole using the same method, which results in data from a series of dipoles with different locations and orientations—the so-called moving dipole model.[29,30] These sequentially modelled single dipoles are assumed to approximate source propagation.[31]

Multiple dipole model

Adding complexity to source localization, one can assume that a given scalp-recorded voltage field can represent activities from more than one source. In this case, a more advanced dipole model, such as the spatiotemporal multiple source model, can be applied.[32] This technique involves fixation of the location and orientation of numerous dipoles over a given time interval, with the entire block of data used to calculate the least-square fit. One advantage over the moving single dipole is that the multiple dipole model aims to identify the lowest number of dipoles that can explain the measured scalp voltage field over time.[28] Nevertheless, the critical issue for the spatiotemporal dipole model, as well as for the other multiple dipole models, is the correct estimation of the number of sources. Selection of the wrong number of dipoles and the setting of inappropriate initial parameters can lead to imprecise localization.[33] Several techniques with the capacity to scan brain sources without an *a priori* knowledge of the optimal number of dipoles over a given data period have been developed; these include multiple signal classification,[34] recursively applied and projected multiple signal classification (RAP-MUSIC),[35] common spatial pattern decomposition,[36] a combination of independent component analysis and RAP-MUSIC,[37] and the first principle vector (FINES) approach.[38]

Distributed source model

The distributed source model is another commonly used approach to solve the inverse problem. This method does not require an *a priori* assumption on the number of dipoles. Instead, it is based on the assumption that multiple sources can be simultaneously active across many locations at any given time.[39] The distributed model reconstructs cerebral activity at each point on a 3D grid. Conceptually, each point in the solution space represents a mini dipole and is considered as a possible location of a current source. These mini dipoles have fixed positions; only their orientation and strength can vary. However, an infinite number of mini-dipole combinations can lead to the generation of a similar scalp potential map. The distributed models, therefore, require further assumption in order to identify the optimal or most likely solution,[11] with different choice and implementation of these assumptions having been made in the literature. For example, low-resolution electromagnetic tomography (LORETA) is based on the concept that neighbouring neuronal populations are more likely to undergo synchronous depolarization during spontaneous discharge or an evoked response than are non-neighbouring neurons.[40] LORETA, therefore, tends to generate a broad solution as neighbourhood sources are assumed to have similar strength.

Several other solutions for the inverse problem have been proposed, and are reviewed elsewhere.[11] Each method depends on certain and different sets of *a priori* assumptions. The most important question is how trustworthy these solutions are, and which one should be chosen. Research in the late 1990s demonstrated reasonable and comparable results with the use of different inverse solutions, including the spatiotemporal dipole model and the linear and nonlinear distributed source models.[41–46] A more recent study found no statistically significant differences in source localization derived from different inverse models, and identified the optimal method for single dipole modelling as a combined approach using the moving and rotating algorithms.[12] Nevertheless, it is important to remember that dipole localization represents the centre of gravity of the source and not the spatial distribution of the irritative zone. For this reason, the location identified using the dipole model is often deeper than the actual source, whereas the dipole orientation represents the net orientation of the source.[31] Consequently, the cortical area that lies in the direction of the dipole's orientation is the probable source. As the distributed model displays the area of activated cortex, it has been argued that a combination of dipole and distributed models could help elucidate the source better than either approach alone.[47]

ESI software

In the past few years, marked advances in analytical approaches to ESI have been made, aiming to improve

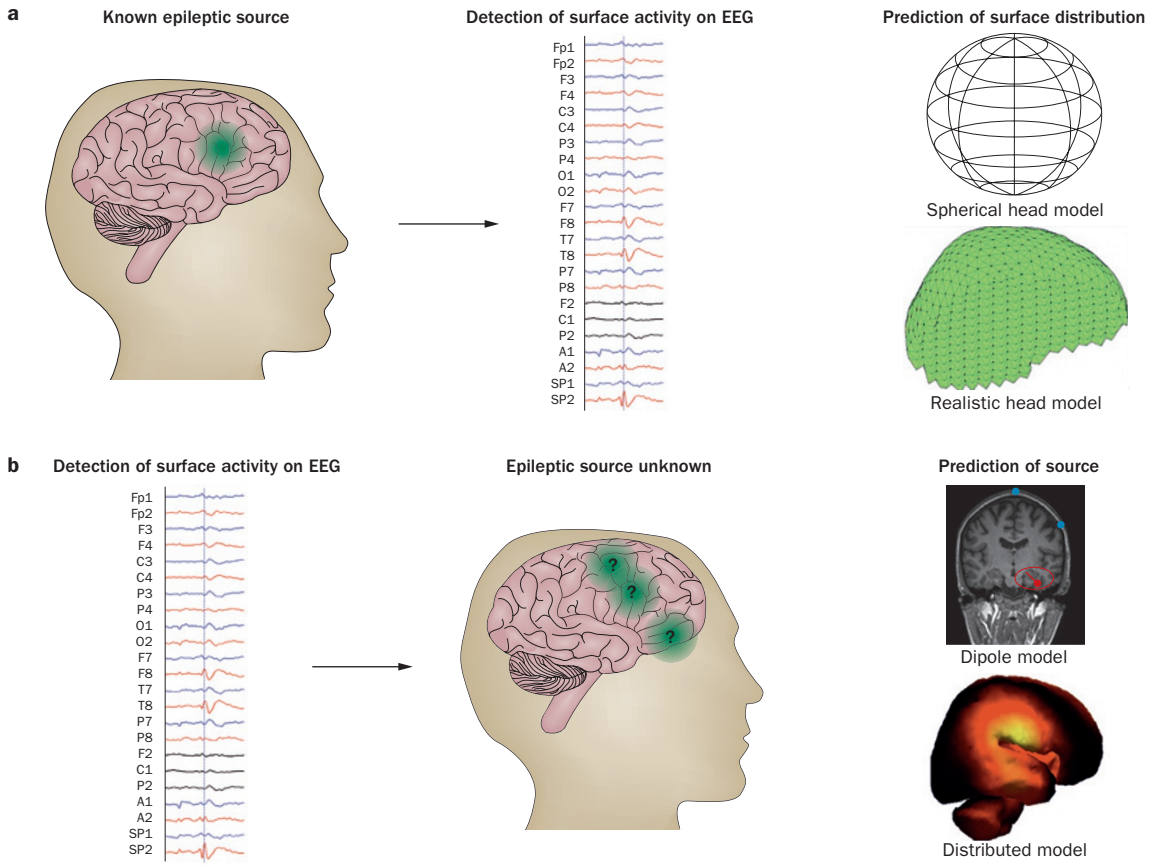

Figure 2 | The forward and inverse problems. **a** | The forward problem: a known epileptic source within the brain produces a surface distribution of activity. Several properties of the human head and brain make prediction of this surface distribution difficult, although models (known as volume conduction models or head models) have been used for this purpose with varying degrees of success. **b** | The inverse problem: a surface distribution of EEG activity has infinite solutions for a source of this activity, and several models can be used to predict the source location.

accuracy and performance of source localization. These efforts led to the development of several robust analytics software packages,[48] each with distinct features and advantages (Supplementary Table 1 online). Integration of these software packages (such as a combination of statistical parametric mapping and FieldTrip,[49] or mix and match of toolboxes at different stages of processing) will increase the flexibility and capability of EEG analysis. Nonetheless, most, if not all, of the software packages are complex, non-user-friendly programs that require some basic knowledge of signal processing and, in some cases, knowledge of MATLAB programming to fully understand and use them. The need for powerful and flexible yet user-friendly applications cannot be overstated. Without such programs, ESI will remain as an interesting but esoteric research tool.

Practicalities and pitfalls of ESI

Several important steps are inherent to the process of obtaining accurate ESI results (Figure 3). For example, errors of 1–2 cm can displace source localization from the orbitofrontal lobe to the temporal lobe, the occipital lobe to the parietal lobe or, indeed, the right mesial frontal region to the left. Such an error margin is unacceptable when epilepsy surgery is considered. In addition to choosing appropriate forward and inverse solutions, meticulous attention to technical recording detail is crucial.

Number and location of electrodes

Studies show that higher numbers of electrodes result in smaller dipole-localization errors,[50,51] and a maximum of 2–3 cm of interelectrode distance is required to avoid distortion of potential distributions on the scalp.[52,53] The relationship between the number of electrodes and the precision of source localization is nonlinear, achieving a plateau at around 100 electrodes for distributed inverse models.[11] Nonetheless, several clinical studies that used both dipole and distributed inverse models on data recorded from the most commonly used international 10–20 system set-up (corresponding to a 5.3–7.4 cm interelectrode distance[54]) showed good and reliable results.[12,55–59] Moreover, nonuniform sampling—placing more electrodes over the region of interest—can alleviate issues with under-sampling and improve the accuracy of ESI results.[60]

Electrode and MRI co-registration

As the source location is calculated relative to the electrode positions, co-registration of electrical source with the anatomical space is an important step in ESI. Given

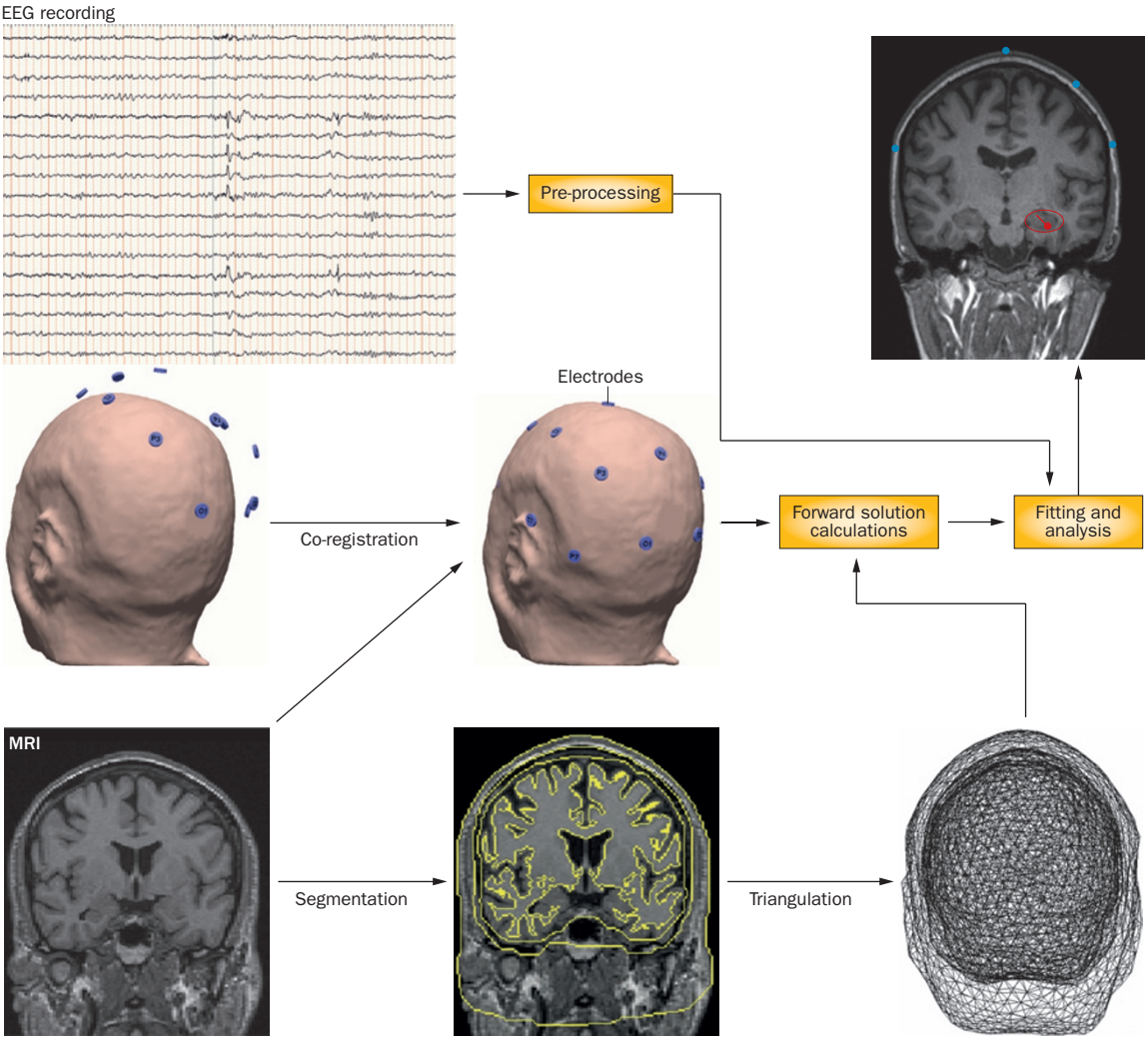

Figure 3 | Flow diagram of the ESI process. Source imaging with realistic head models requires three inputs: EEG recording, patient's MRI, and digitized coordinates of EEG electrodes. Abbreviation: ESI, EEG source imaging.

that head shapes and sizes vary among individuals, knowing where the recording electrodes are located in the individual's head is important, as incorrect assumption about the electrode positions can lead to an inaccurate ESI result. Several methods of electrode localization, such as electromagnetic digitization, ultrasound digitization, MRI localization of electrodes, and the geodesic photogrammetry system, have been introduced.[61] Electromagnetic digitizers, such as FASTRAK® (Polhemus, Colchester, USA), are the most commonly used methods to localize electrode positions in clinical practice.[61,62] These systems are, however, sensitive to error and therefore require repeated measurement.

MRI segmentation and tessellation

Solving the EEG inverse problem using realistic head models relies on accurate computation of the head model (or forward solution). As electrical conductivities of tissues are inhomogeneous, reconstructed surfaces of different head regions are necessary.[63] Moreover, the influence of skull defects and brain lesions on surface electrical potential has been demonstrated.[64] The individual's own MRI rather than the template MRI of the software program should, therefore, be used to calculate the forward solution.

Preprocessing of EEG

Noisy EEG data can lead to unreliable ESI results, so careful attention to minimize artefact contamination is essential. Noise reduction techniques should be applied once the EEG has been recorded. In principle, a few noisy EEG channels can be omitted from the calculation. The application of filters and/or averaging of the activity of interest can also improve signal-to-noise ratio (SNR).[42] Averaging of non-monomorphic spikes, however, could lead to inaccuracies in the ESI result.[65] More-sophisticated techniques, such as principal component analysis and independent component analysis, can be helpful in identifying the number and relative contribution of components in the EEG signal separate from noise in the data.[12]

Modelling the initial phase of a spike

Some reports suggest that the early component of an epileptic spike is likely to represent the location and field

of the source.[31,39] The authors of these studies concluded that the peak of the epileptiform discharge actually reflected a propagated activity. Modelling of the spike peak, therefore, could be misleading (Figure 4). However, the early component of the spike is, by definition, of much smaller amplitude than the peak, and accurate modelling is further complicated by high noise contamination at this stage.[42]

Statistical analysis of ESI

The adequacy of a given ESI result can be determined by goodness of fit (GOF) and the confidence ellipsoid volume. GOF is a measure of how well the electrical potential of the calculated source matches the actual potential, with 100% being a perfect fit. In general, a maximum variance of 10% or a minimum GOF of 90% is acceptable for clinical purposes.[31] As EEG data inherently include noise, a perfect fit does not guarantee accurate source localization. The confidence ellipsoid volume helps in defining a region that, with a certain probability, contains the sources (a large volume indicates low SNR),[66] and is, consequently, a good indicator of the noise level.

Clinical studies

ESI of the interictal spike

Interictal epileptiform activity is a complex phenomenon, and propagation of activity from the source to remote cortical regions can occur within milliseconds.[67,68] The information provided by EEG-spike source localization, even if technically accurate, may not reflect the actual source of the observed spikes. Moreover, the irritative zone (where interictal spikes are generated) could be distant and/or completely separate from the seizure onset zone and the epileptogenic zone (Figure 1).[69] These inherent limitations make clinical validation of ESI in spike localization challenging. In our opinion, the best and probably the only—although imperfect—way to assess the accuracy of ESI in localization of epileptic spikes is to compare the result of EEG source modelling to that of simultaneous spikes recorded from intracranial EEG (Figure 5). However, one must keep in mind that intracranial EEG recording might not offer complete source characterization owing to the limited number of intracranial electrodes used.

To date, several studies attempting to determine the accuracy of ESI for source localization of interictal spikes have been reported (Supplementary Table 2 online).[12,51,56,57,59,70–82] However, data from intracranial and scalp EEG recordings, where available, were not obtained simultaneously.[55,70–73] Small sample size, lack of blinding with regard to the patient's clinical data during the fitting process, and a lack of standardized methodology, are all major limitations in most of this research, and prevent comparisons between the studies. Overall, the studies consistently showed ESI had a high positive predictive value.[57,74–77] In the largest study, the accuracy and contribution of ESI was compared with other, more-established, noninvasive presurgical work-up methods in 152 patients with intractable epilepsy.[77] Sensitivity and specificity of ESI was comparable to that of PET, ictal and interictal single-photon emission CT, and MRI. In addition, no significant differences were observed in sensitivity and specificity between ESI techniques for temporal and extratemporal lobe epilepsy.[77] Whether ESI adds any information to visual EEG analysis that ultimately influences surgical decision-making remains to be investigated; notably, the clinical value of ESI for epilepsy surgery evaluation is much more difficult to determine than its accuracy. More-thorough analyses in large cohorts are needed to examine the clinical validity and value of ESI. At present, ESI seems to be a promising technique that can positively contribute to visual EEG analysis in localization of epileptic spikes, and deserves a role in epilepsy surgery evaluation.

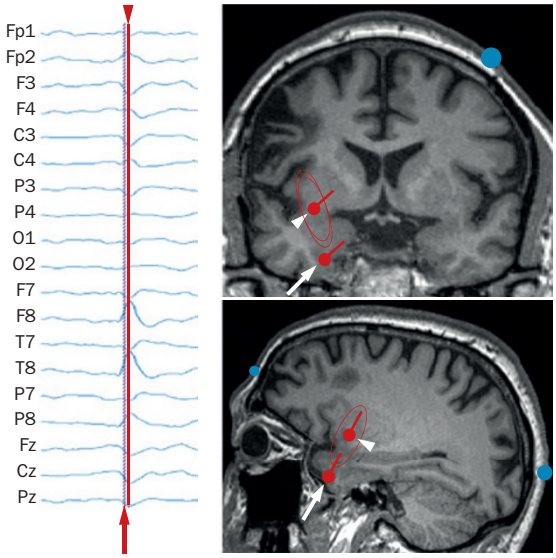

Figure 4 | Source localization of the initial phase of epileptic spikes. Modelling of the spike peak could be misleading due to propagation of the discharges (arrowhead). A rising phase of the spike (arrow) is more likely to represent the initial spike source.

ESI of the ictal onset

One advantage of EEG over magnetoencephalography is the fact that prolonged EEG can be routinely performed to record seizures and identify the seizure onset focus. However, analysis of ictal data using source modelling techniques is complex, time-consuming and labour-intensive. In some studies, successful source modelling was reported in only 30–40% of patients.[83,84] Ictal source modelling is difficult for several reasons. First, certain types of seizures generate substantial muscle and movement artefacts, which results in low SNR. Second, ictal rhythm can only be recorded at the scalp when there is sufficient synchronization of cerebral activity; by that point, the cortex adjacent to or distant from the seizure onset zone is already involved.[69,85] In addition, some seizures might show detectable scalp EEG changes very late into the seizure, as observed in intracranial EEG studies. Ictal ESI, therefore, identifies not only the ictal onset zone but also the cortex to which seizure discharges spread during an early ictal event.

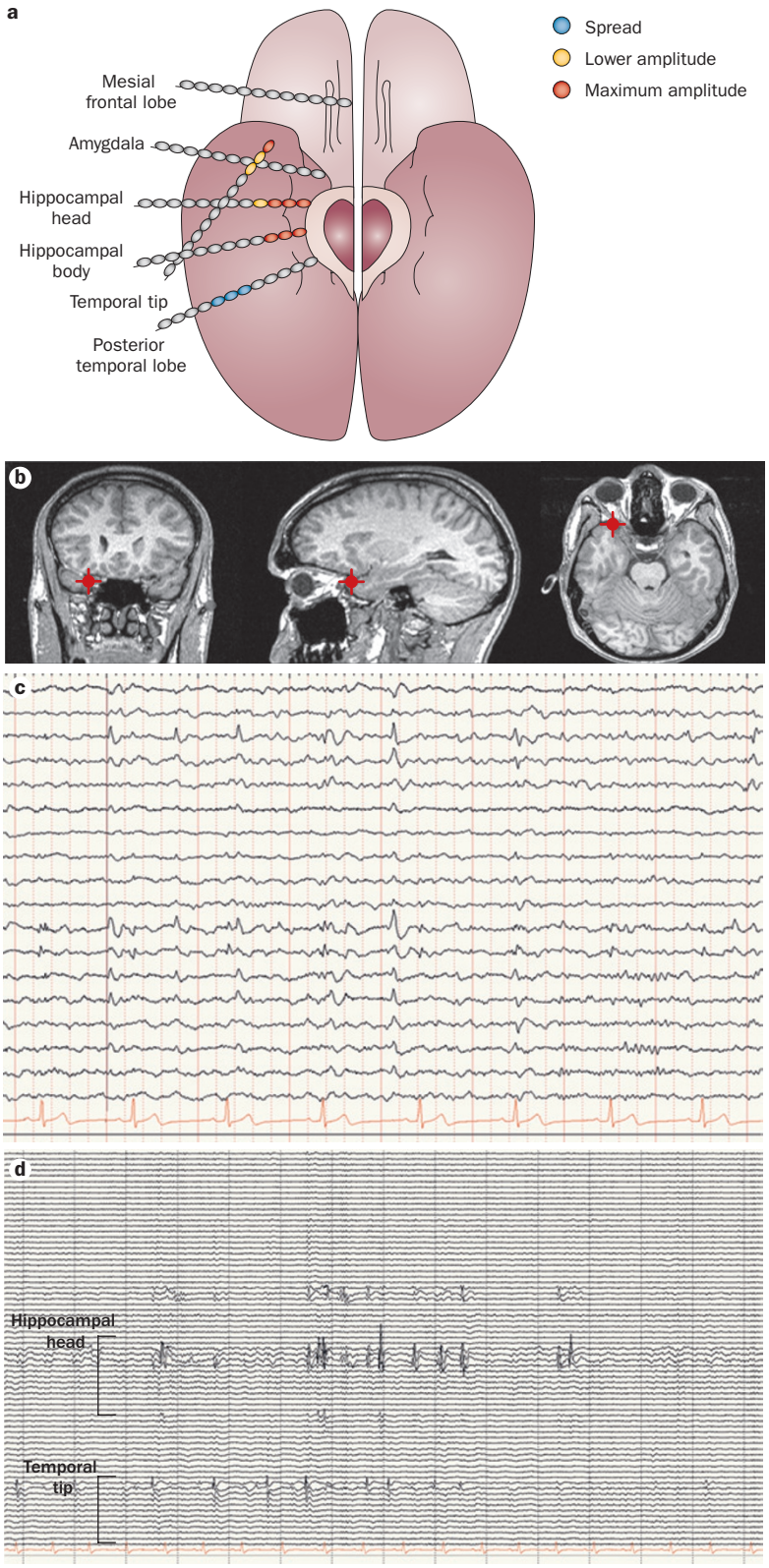

Figure 5 | Validation of EEG source imaging with simultaneous scalp and intracranial EEG. **a**,**b** | Stereotactic depth recordings in the temporal pole and mesial temporal structures of the brain (a) can be used to confirm ESI-based localization of the source to the temporal pole (b). **c**,**d** | Temporal spikes on surface EEG (c) are observed simultaneously with hippocampal and temporal pole spikes in intracranial EEG (d). Abbreviation: ESI, EEG source imaging.

Few studies have evaluated the accuracy of ictal ESI (Supplementary Table 3 online).[84,86–91] Early studies in which single or multiple dipoles were fitted in the time or frequency domain showed a high correlation between the dominant source component and the location of seizure onset.[83,84,86,92] Given that ictal activity evolves spatiotemporally over time, some investigators have suggested that dynamic analysis of ictal discharges in a given time window should be performed to accurately determine the origin and propagation of ictal activities.[87,93–96] For distributed source models, it is recommended that the window of analysis should be at least 100 ms.[87] Interestingly, the duration of the time window does not seem to affect the result in dipole models.[87] As the seizure progresses from seconds to minutes, localization of the source would require a substantial number of inverse problems to be solved. More recently, a dynamic spatiotemporal approach—decomposing the seizure into several components and then localizing and recombining the source of each of these components—was found to effectively decrease the complexity of ictal source analysis.[95] This approach is, therefore, well-suited for imaging of continuous oscillatory activities. Notably, analysis of ictal ESI has been limited to continuous rhythmic activity. Whether source modelling of more-obscure ictal patterns can provide precise ictal source localization remains to be investigated, and prospective studies to evaluate the reliability and specificity of ictal ESI in large numbers of patients are needed.

ESI of nonepileptiform abnormalities

In addition to ictal and interictal epileptiform activities, analysis of nonepileptiform activity in an attempt to identify regions of cortical dysfunction has been explored. Two studies using dipole models showed that source analysis of focal slow activity corresponded well to anatomical lesions[97] and to the location of epileptiform abnormalities.[98] A study evaluating interictal EEG background using frequency-domain distributed source analysis showed good spatial concordance of ESI and intracranial EEG recordings.[99] However, one should note that nonepileptiform abnormalities, even in patients with epilepsy, are not necessarily related to the underlying epileptic condition. ESI of background activity, therefore, is nonspecific and may not provide useful information for epilepsy surgery evaluation.

Source reconstruction of electrocorticography

Source imaging techniques have also been applied to electrocorticography (ECoG).[100] Despite the complexity of potential distributions and the concerns of cortical sampling associated with ECoG, studies using this technique for source reconstruction obtained reliable results with the most commonly used forward and inverse solutions.[100–102] However, accurate source reconstruction can only be obtained from ECoG recording when the sources are well-covered by subdural electrode arrays.[101,102] Over the past few years, a combination of ECoG source reconstruction and causal or connectivity analysis has provided valuable information in defining the epileptogenic

zone.[103–106] Whether these techniques can add clinically relevant information to traditional analysis of ECoG recordings—and to what extent—remains to be explored.

ESI of eloquent cortex

A variety of evoked potentials have been subjected to ESI with varying degrees of success. The clinical focus has mainly been on the identification of eloquent cortex, namely the primary somatosensory, visual and auditory cortices, using the somatosensory evoked potential, the visual evoked potential, and the auditory evoked potential, respectively. Accurate localization of the primary somatosensory cortex has substantial value in presurgical work-up and surgery in patients with medically intractable epilepsy when the epileptogenic zone is close to the primary somatosensory cortex.[107–110] Localization of this region can aid surgical planning for resection or the placement of intracranial EEG electrodes, particularly where the pericentral cortex may be distorted owing to space-occupying lesions or malformations of cortical development. Additionally, the capacity of a given source imaging program to accurately source image-evoked potential components (of which the cortical generators are well known) engenders greater faith in the program's accuracy in source imaging of epileptic spikes or seizures. Surprisingly, both the literature and study designs have paid relatively scant attention to this aspect of ESI.[111]

Conclusions

Tremendous progress has been made in the technique of ESI in recent years, and more than 10 software programs to aid in this process have been introduced. This software is, however, mathematically complex and non-intuitive. Consequently, only a handful of clinical studies—most of which involved fewer than 30 patients—have been published. More user-friendly and easy-to-use ESI software is needed before this technique can be translated to routine clinical practice. As computer technology progresses, we believe that such ESI software will be available in the next few years. At present, more-advanced ESI methods show promise, and the development of user-friendly programs should open the path for extensive clinical studies in large cohorts to demonstrate the value of ESI in presurgical evaluation of patients with epilepsy and in precise localization of eloquent cortex.

Review criteria

We searched PubMed and MEDLINE for articles using the terms "electroencephalography" and "source localization", as well as "source modelling", "source imaging" or "ESI". Only papers and abstracts published in English were reviewed initially. Further references were found manually from reference lists of pertinent original articles or the authors' personal databases.

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Acknowledgements
K. Kaiboriboon and M. Hamaneh are supported by the Epilepsy Foundation. M. Hamaneh is also supported by the Coulter Foundation.

Author contributions
K. Kaiboriboon researched data for the article. K. Kaiboriboon and S. D. Lhatoo provided substantial contributions to discussion of content and wrote the article. K. Kaiboriboon, H. O. Lüders, M. Hamaneh, J. Turnbull and S. D. Lhatoo contributed equally to review and editing of the manuscript before submission.

Supplementary information
Supplementary information is linked to the online version of the paper at www.nature.com/nrneurol