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Chapter 6

EEG source localization

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Abstract

Since the discovery of electroencephalography (EEG), when it was hoped that EEG would offer "a window into the brain," researchers and clinicians have attempted to localize the neuronal activity in the brain that generates the scalp potentials measured noninvasively with EEG. Early explorations in the 1950s using electric field theory to infer the location and orientation of the current dipole in the brain from the scalp potential distribution triggered considerable efforts to quantitatively deduce these sources. Initially, dipole fitting, or dipole localization, was the method of choice and many studies used this approach in experimental and clinical studies with remarkable success. Later on, new methods were proposed that attempted to overcome the problem of having to fix the number of sources a priori; these methods are known as distributed source imaging techniques. The introduction and increasing availability of magnetic resonance imaging, allowing detailed realistic anatomy of the brain and head to be incorporated in source localization methods, has drastically increased the precision of such approaches. Today, source localization of EEG (and magnetoencephalography, or MEG) has reached a level of consistency and precision that allows these methods to be placed in the family of brain imaging techniques. The particular advantage that they have over other imaging methods is their high temporal resolution, which allows the origin of activity to be distinguished from its propagation and information flow in large-scale brain networks to be examined. This chapter gives an overview of these methods and illustrates them with several examples, thereby focusing on EEG source imaging in epilepsy and presurgical planning, as clinical applications with remarkable maturation.

INTRODUCTION

It is generally understood that the main generators of the electroencephalograph (EEG) are the postsynaptic potentials that take place on the pyramidal cortical neurons (Mitzdorf, 1985; Lopes da Silva, 1991). Synchronized activity of these synaptic currents leads to current flows in the head volume. Because the head is a conducting medium, volume conduction allows the propagation of these current flows to the scalp surface, where they give rise to electric potential differences between electrodes placed on different positions on the scalp (Brazier, 1949). By recording these potentials using an array of electrodes, topographical maps can be constructed that display the distribution of the scalp potential produced by the active neuronal population at any given moment in time. If only one brain area is active, the potential distribution on the scalp is rather simple and dipolar. However, if several brain areas are simultaneously active, complex patterns of scalp potentials arise, and the deduction of the underlying sources becomes a nontrivial task. In general, a priori assumptions are required, preferentially incorporating anatomical, physiological, and biophysical knowledge. An important

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development was to introduce anatomical constraints of the head to facilitate solving the EEG source localization problem (He et al., 1987; Hämäläinen and Sarvas, 1989). Further development has introduced physiological constraints of cortical sources to facilitate solving the distributed source imaging (Dale and Sereno, 1993; Pascual-Marqui et al., 1994). Such a priori constraints greatly improve the solvability and precision of the EEG source localization, albeit only an estimation of the underlying sources.

Historically, the first attempts of EEG source localization were based on the strong a priori assumption that only one source is active at a certain time point, that the head can be approximated as a sphere, and that the conductivity is homogeneous throughout the brain. In this case, nonlinear multidimensional optimization procedures allowed the position, orientation, and strength of an equivalent dipole in the brain to be found that best explained the observed scalp potential measurements. Soon, the conductivity difference between different tissues were incorporated in multilayer spherical head models, and finally realistic geometry head models based on magnetic resonance (MR) images were developed using boundary or finite element reconstruction of the scalp and the different tissues. Also, the inverse model developed from the strong constraint of one or a few dipoles with time-varying amplitudes to distributed source reconstruction methods that estimate the three-dimensional (3D) current density distribution in the whole brain volume. In the following text, the concepts and principles of EEG source localization are reviewed. More detailed methodological reviews can be found in He and Ding (2013), Pascual-Marqui et al. (2009), Michel et al. (2004b), Michel and He (2011). An illustration of the full pipeline for modern EEG source imaging is given in Fig. 6.1.

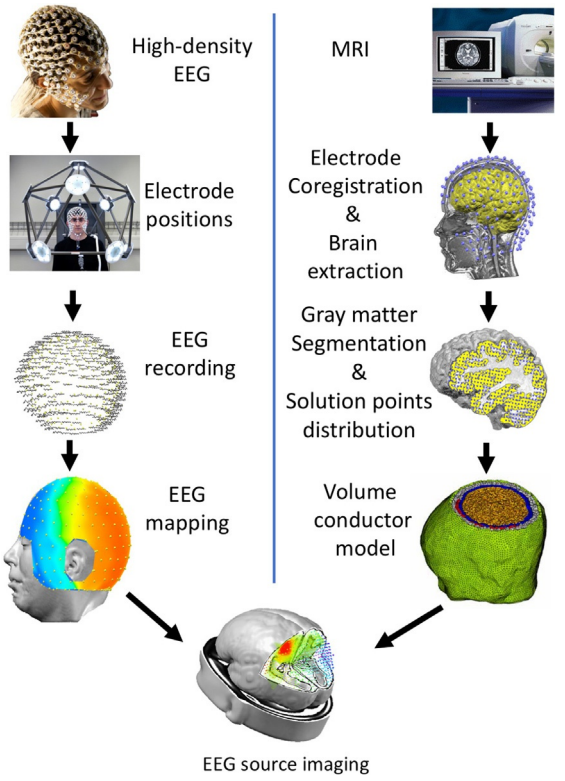

Fig. 6.1. Pipeline of modern EEG source imaging. High-density EEG (here 256 channels) is recorded with high temporal resolution. Exact electrode positions are assessed (here with a photogrammetry system from EGI Inc. as an example). The scalp potential map at each time instant is reconstructed from these recordings. Structural MRI of the subject is assessed. The electrodes are coregistered with the head surface. The brain is segmented and the solution points are distributed within the gray matter. A distributed inverse solution is then applied to the EEG map using the individual volume conductor model reconstructed from the MRI.

THE EEG FORWARD PROBLEM

The electric potential generated by synchronized postsynaptic potentials does not propagate homogeneously through the brain. Different tissues such as the scalp, skull, cerebrospinal fluid, and brain have different conductivity characteristics and therefore attenuate the current to a different extent. If the conductivity parameters are known and are correctly taken into account, Poisson's equation allows the potential to be determined at each scalp electrode generated by a known source in the brain (Malmivuo and Plonsey, 1995). Thereby, the source is generally modeled as an equivalent current dipole composed of a pair of current source and sink representing the postsynaptic currents flowing through the apical dendritic trees of cortical pyramidal cells. The calculation of the scalp potentials produced by such a source is commonly called the EEG forward problem.

The simplest solution to the EEG forward problem is that of an infinite homogeneous model, where the entire space is assumed to be occupied by a homogeneous conductive medium (Plonsey, 1969; He and Lian, 2005). More complicated but slightly more realistic models attribute different conductivity properties to different tissues of the head, represented as homogeneous shells in the spherical model (Rush and Driscoll, 1969; Cuffin and Cohen, 1979; Wang and He, 1998; Michel and Murray, 2012; He and Ding, 2013). Such models have been used in most of the initial source localization studies using equivalent dipole fitting. Many of them used conductivity values defined over 40 years ago by Rush and Driscoll (1969), where the skull resistivity was proposed to be 80 times higher than the resistivity of the scalp and the brain. Several more recent studies have showed that

these values are too high and that the conductivity ratio between skull and brain is only about 20:1 (Lai et al., 2005; Ryynanen et al., 2006). But not only is the skull resistivity smaller than previously assumed, the thickness of the skull varies across the head, and, more importantly, it varies across age, with thinner skull, and lower resistivity, in young children (Fig. 6.2A). This leads to a much higher spatial resolution of the EEG (less smearing) and has therefore important consequences regarding the number of electrodes needed to properly sample the scalp electric field, as discussed in Chapter 14.

While spherical head models with homogeneous conductivity properties of the different tissues provide an analytical solution of the EEG forward problem, such a head model is not realistic. The propagation of the electric potential from the brain to the scalp is modulated by the electric conductivity properties of the different tissues and by the geometry of the head. Exact knowledge of these properties and exact modeling of the different tissues are fundamental for correct source localization with EEG. With the use of individual magnetic resonance imaging (MRI), the head shape, the convolutions, and the thickness of the tissues can be modeled precisely and incorporated into what is called the forward solution, i.e., the relationship between a current source in the brain and the potential on the scalp. The most popular method introduced to solve the EEG forward problem is the boundary element method (BEM) (He et al., 1987; Hämäläinen and Sarvas, 1989). The use of the BEM permits the anatomic information of the head, as well as the major conductivity characteristics such as the brain, skull, and scalp, to be incorporated into EEG forward solutions. The BEM models the interfaces between each tissue of the head with a mesh of triangles, such as the air/scalp, scalp/skull, and skull/brain interfaces. Each type of tissue is considered electrically homogeneous and isotropic and different conductivity values are given for each of them. The finite element method (FEM), on the other hand, has been used to model tissue conductivity inhomogeneity and even conductivity anisotropic distributions within the white matter (Lee et al., 2009). These numerical techniques utilize the anatomical information provided by the MRI to segment different brain tissues and head structures.

Building a FEM head model is still a rather laborious effort. An alternative has been proposed by Spinelli et al. (2000), which combines the simple analytical solution of a spherical model but takes the head shape and the brain tissues into account. In a method called the spherical head model with anatomical constraints (SMAC), they proposed to determine the best-fitting sphere from the individual MRI and then use homogeneous transformation operators to warp the brain to this best-fitting sphere. The analytical solutions for a multishell spherical model can then be applied, but the solutions are directly calculated for this slightly deformed MRI. The method has subsequently been improved by an adaptive local spherical model (LSMAC), where local spheres with different radius are built for each electrode (Brunet et al., 2011). This model allows variation of the conductivity values for each electrode by taking the skull thickness under each electrode into account (Fig. 6.2B). In a series of 38 epileptic patients with focal epilepsy who underwent surgery, Birot et al. (2014) directly compared the BEM, the FEM, and the simpler LSMAC model in their accuracy to localize interictal spikes. Using the individual

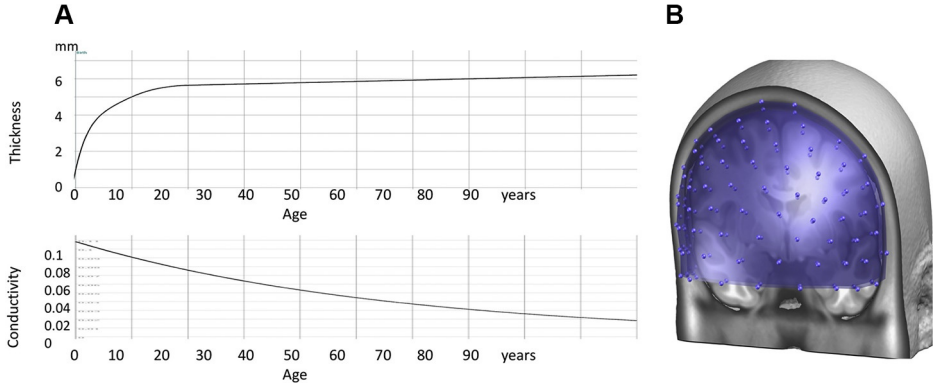

Fig. 6.2. The head as a volume conductor. Proper EEG source localization requires a correct model of the volume conductor because the different compartments have different conductivity properties. Most important is the resistivity of the skull. Its thickness as well as its conductivity varies with age. This important fact has to be considered when building the volume conductor model. (A) Skull thickness and skull conductivity relative to the brain across age. The values for conductivity are estimated from Roche (1953) and Lillie et al. (2016). The values for conductivity are estimated from Hoekema et al. (2003) and Latikka et al. (2001). (B) Estimating the local skull thickness from T1 MRI. The inner and outer estimated boundaries of the skull are shown as transparent layers. The *blue spheres* are positioned at the exact locations of the skull underneath each surface electrode (not shown here).

MRI and restricting the solution space to the gray matter, they showed that all three head models performed equally well with over 70% of the source maxima lying within the resection zone. No significant differences were found between the three head models in this particular clinical application.

THE EEG INVERSE PROBLEM

The basic problem of determining the intracranial sources that generate a given EEG (and magnetoencephalography, or MEG) measurement over the scalp is the challenge of the electromagnetic inverse problem. A solution to this problem can only be found if a priori assumptions about the sources are incorporated (Fender, 1987). Neurophysiologic knowledge about the sources of the EEG, biophysical knowledge about how electric activity spreads, anatomic knowledge of the conductive tissues, and knowledge or assumptions about distributions of neuronal activity are all contributors to such a priori constraints. Many different constraints have been introduced over the years and new constraints and assumptions are continuously formulated in the literature based on new available knowledge of signal generation. Such new models must be rigorously validated, leading to the legitimate question of the gold standard for validation (Michel et al., 2004b). Simulations are certainly helpful and important in this respect but bear the risk of simulating data that are most appropriate for the proposed model. Testing the results in recordings where the generators are well defined is another approach, but this can lead to the risk of preselection of data that are most suitable for the proposed approach and the question of how much the method can be generalized to other conditions than the one tested. For example, being able to properly localize the single source of an epileptic spike does not prove that the very same method can localize all nodes of a complex network in ongoing activities at rest. It is possible that one method works perfectly fine in one specific dataset, but another method is preferable for another set of data in another condition. A good knowledge of the properties, advantages, and limitations of each of the methods is mandatory.

In the following paragraphs, we describe some of today's most widely used inverse solution methods and explain the basic assumptions that each of these inverse solutions incorporate.

Dipole source localization

Localization of a limited number of equivalent dipoles was the first approach proposed to solve the EEG inverse problem. In this classical approach, the a priori assumption is that only one or a few areas in the brain are active and generate the scalp potential field. Under this constraint, the mathematically best solution can be found by nonlinear optimization (Scherg and von Cramon, 1985; He et al., 1987). The number of dipoles that can be reliably found is limited by the number of scalp electrodes and by the nonlinear complexity of the search algorithms with multiple sources. Advanced methods, such as decoupling the linear and nonlinear part of the estimation or searching for the best solutions over a certain time period with time-varying strength of the dipoles (MUSIC (Mosher et al., 1992); BESA (Scherg and von Cramon, 1985)) can increase the number of dipoles slightly. Nevertheless, if the number of dipoles is underestimated, the source localization is biased by the missing dipoles, and if too many dipoles are assumed, spurious sources will be introduced.

Despite the simplicity and limitation of this a priori assumption, dipole source localization can produce reasonable results under some particular conditions (Henderson et al., 1975), in particular in localizing the epileptic foci (Ebersole et al., 1995; Lantz et al., 1996) or primary sensory areas, such as the localization of the sensorimotor cortex in surgical candidates (Willemse et al., 2016), as discussed in more detail later. Dipole source localization is still widely used in the MEG community in these clinical applications (Stefan et al., 2003).

Distributed source imaging

In experimental EEG studies the dipole source localization approach has been largely replaced by distributed source imaging methods. These methods do not impose a constraint on the number of sources. Instead, a large number (usually more than 5000) of equivalent dipoles are distributed in fixed positions over the whole source space and the strength of each of these dipoles is estimated. Using anatomical information from the individual or a template MRI, the source space is usually constrained to the gray matter. Dale and Sereno (1993) proposed the cortical current density model in which the dipoles are constrained to the directions perpendicular to the cortical surface. Anatomical constraints reduce the number of parameters that have to be estimated. Still, the number of unknowns is obviously much larger than the number of knowns (recordings at electrodes), making the problem highly underdetermined if no additional constraints are imposed. Such constraints can be purely mathematical or can be based on biophysical or physiological information or incorporate knowledge from other structural or functional imaging modalities, such as diffusion tensor imaging or functional MRI.

The first and most general linear distributed inverse solution was introduced by Hämälainen (1984) and

Hämäläinen and Ilmoniemi (1994), named the minimum norm (MN) solution. The constraint proposed in this solution is that current distribution over all solution points has minimum energy (minimizing the least-square error, i.e., the L2-norm) and that the forward solution of this distribution optimally explains the measured data. Evidently, the constraint of minimal overall energy favors sources closer to the scalp electrodes and overlooks sources in deeper structures. Using different mathematical operations, depth-weighting strategies have been proposed to overcome the problem of favoring superficial sources (Wang et al., 1992; Greenblatt, 1993; Grave de Peralta Menendez and Gonzalez Andino, 1998).

A current widely used variation of the MN solution is called LORETA (low resolution electromagnetic tomography, introduced by Pascual-Marqui et al., 1994). The additional constraint added in this solution is the minimization of the Laplacian of the sources, leading to a smooth (low resolution) distribution of the 3D activity. This constraint has been justified by the physiologically plausible assumption that activity in neighbored voxels are correlated, an assumption that is challenged in some brain areas, for example, in the interhemispheric fissure. LORETA can lead to blurred and oversmoothed solutions in such cases. Improvements of this algorithm have been proposed by this and other authors, leading to algorithms named sLORETA (Pascual-Marqui, 2002), eLORETA (Pascual-Marqui et al., 2011), LAURA (Grave de Peralta Menendez et al., 2004), VARETA (Fernandez-Bouzas et al., 2004), and others.

Recently, various signal-processing techniques have been applied to further develop distributed source imaging algorithms. These include L1-norm algorithms, which are essentially based on the assumptions that neuronal sources are discrete and focal, therefore leading to solutions in favor of more focal localizations (instead of overly smoothed solutions as in the L2-norm) (Matsuura and Okabe, 1995; Uutela et al., 1999; Huang et al., 2006; Bai et al., 2007; Ding and He, 2008).

In addition to spatial source imaging in which EEG measurements at a given time instant are used to localize and image the underlying brain activity, spatiotemporal source imaging methods have also been developed (Yang et al., 2011; Lu et al., 2012). Such spatiotemporal source imaging has practical importance in imaging seizure sources, which are essentially oscillatory sources with a high degree of temporal correlation. A particular approach is to integrate the independent component analysis (ICA) with source imaging, in which seizure EEG measurements are decomposed using ICA, source imaging performed on a selected set of these independent components, and then recombined to obtain the estimated seizure sources (Yang et al., 2011; Lu et al., 2012).

Beamforming (Vrba and Robinson, 2001) is another spatiotemporal method for source imaging. The idea behind this method is to refocus the signal captured at the scalp to its originating location, by finding weights pertaining to each location of the source space, such that the variance of the current dipole at every location is minimal. Beamforming techniques have the same smoothing issue as the MN solution, and are known to face challenges when underlying sources have correlation with each other.

Scanning techniques are another class of methods that attempt to solve for the dipole distribution by scanning through all the possible locations of the source space to determine the most likely locations of the dipoles. MUSIC (Mosher et al., 1992) is a well-known scanning approach. Some variants of MUSIC are the recursively applied and projected MUSIC (RAP-MUSIC) (Mosher and Leahy, 1999) and the first principle vector (FINE) (Xu et al., 2004) localization method. Scanning methods will have decreased performance for coherent and correlated sources, specifically when the sources are close to each other.

Brain network analysis

EEG (and MEG) source localization has been widely used to identify brain regions implicated in information processing and execution of tasks and to localize dysfunctional areas in different neurologic and psychiatric diseases. However, whole-brain imaging methods, particularly fMRI, have led to an increasing recognition that brain functions and dysfunctions are based on interactions between different regions forming large-scale networks. The question of how such interactions are organized, how the regions communicate with each other, how areas transmit and receive information, and how such communication is disturbed in mental disease has become a key topic of research in neuroscience (Ioannides, 2007). Because of the sluggishness of the hemodynamic process, fMRI is limited with respect to the interpretation of neuronal interactions (Otte and Halsband, 2006). EEG (and MEG) with its high temporal resolution is more suitable for studying network dynamics and connectivity. Many different techniques with different properties have been developed for this purpose (Lopes da Silva et al., 1989; Lachaux et al., 1999; Stam and Van Dijk, 2002; Wendling et al., 2009), most interestingly time-varying methods that estimate the direction of interactions using effective connectivity measures in the framework of Wiener–Granger causality or dynamic causal modeling (Urbano et al., 1998; Strogatz, 2001; Brovelli et al., 2004; David et al., 2006; Lin et al., 2009; Martino et al., 2011; Porcaro et al., 2013; Plomp et al., 2014). They were mainly

applied to evaluate the relationships between pairs of electrodes on the scalp, which bears the problem of volume conduction (Brunner et al., 2016; Van De Steen et al., 2016) and reference dependency (Chella et al., 2016) and limits the interpretability in terms of brain areas that are connected. It was therefore proposed to perform functional connectivity analysis on the source domain after solving the source imaging (inverse) problem. This approach leads to a more adequate description of interactions between brain regions. Functional connectivity analysis such as structural equation modeling (Astolfi et al., 2004), the directed transfer function (Babiloni et al., 2005; Wilke et al., 2009b), partial directed coherence (Coito et al., 2015; Plomp et al., 2015), and graph theory (Astolfi et al., 2007a) have been applied on the estimated current density waveforms, allowing a direct mapping of brain functional networks from the high temporal resolution EEG (or MEG).

Fig. 6.3 illustrates the approach of functional connectivity imaging from EEG or MEG (from Sohrabpour et al., 2016). The combined electric source imaging (ESI) and directional functional connectivity analysis

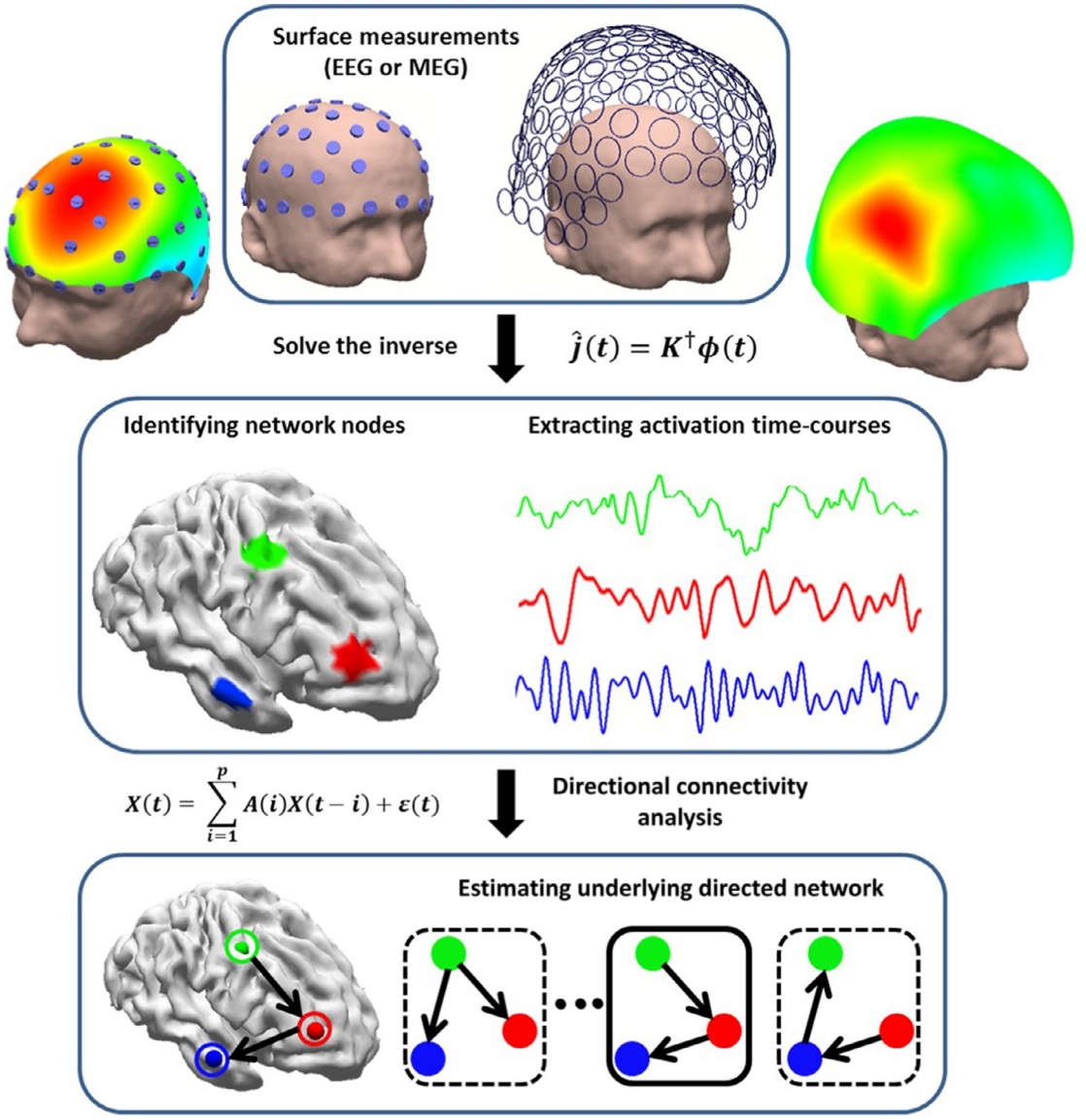

Fig. 6.3. Mapping and imaging the functional connectivity from EEG/MEG. The combined ESI and directional functional connectivity analysis identifies nodes and internodal connections of the network under study. ESI can objectively determine the network nodes and extract activation time-courses and feed them to a directional functional-connectivity analysis, such as Granger causality analysis, to determine the directional connectivity patterns. From Sohrabpour A, Ye S, Worrell GA et al. (2016). Noninvasive electromagnetic source imaging and granger causality analysis: an electrophysiological connectome (eConnectome) approach. IEEE Trans Biomed Eng 63: 2474–2487.

identifies nodes and internodal connections of the network under study. ESI can objectively determine the network nodes and extract activation time-courses and feed them to a directional functional-connectivity analysis, such as Granger causality analysis, to determine the directional connectivity patterns.

Currently, many different methods for estimating functional connectivity are available and have been applied to EEG and MEG on the sensor and source level. Since they have different properties, their suitability for a given data set has to be carefully evaluated and validation studies using simulations and benchmark data are still needed (David et al., 2004; Astolfi et al., 2007b; Wendling et al., 2009; Haufe et al., 2013; Plomp et al., 2014).

CLINICAL APPLICATIONS OF EEG SOURCE IMAGING

Given the increasing interest in large-scale, whole-brain networks and their temporal dynamics, EEG source imaging methods have become a method of choice in many research laboratories, often combined with other functional or structural imaging methods (Michel and He, 2011; Michel and Murray, 2012).

EEG source imaging is also increasingly used in clinical applications to localize functionally abnormal brain areas and/or to localize eloquent cortex for surgical planning. One of the key applications is epilepsy, and more precisely in the presurgical evaluation of patients with pharmaco-resistant focal epilepsy. EEG source imaging has proven to be an important tool to localize the epileptic foci and to decide about the possibility for surgical resection or guide the placement of intracranial electrodes.

In the following we describe selected examples of studies applying EEG source imaging in clinical and experimental studies, albeit only a subjective selection of exemplar cases. Studies using MEG instead of EEG are also described, considering these two modalities as measuring the same sources and using the same localization methods, albeit with some differences in sensitivity to different types of sources (Ahlfors et al., 2010; Malmivuo, 2011).

Epilepsy

The main aim of EEG source imaging in epileptic patients is the determination of the epileptogenic focus. This helps in making decisions about surgically resecting or ablating the focus or it can guide the location of intracranial electrodes if considered necessary.

Early applications of epileptic focus localization with EEG used equivalent dipole modeling (Ebersole and Wade, 1990; Ebersole, 1998). Subsequently, many different groups demonstrated the accuracy of dipole fitting to epileptic spikes in comparison to intracranial recordings or to the resected zone in operated patients (Lantz et al., 1994; Scherg and Ebersole, 1994; Gavaret et al., 2006; Ebersole and Hawes-Ebersole, 2007; Gavaret et al., 2009; Rose and Ebersole, 2009). Several commercially available EEG analysis packages added this tool to their analysis software. Dipole fitting also became the standard in clinical MEG systems where it has been approved by the FDA and is still widely used (Schwartz et al., 2010; Braeutigam, 2013). However, there are obvious limits to the anatomical precision of such single-point dipoles, particularly if spatially extended or multiple sources generated the spike seen on the scalp (Alarcon et al., 1994; Shindo et al., 1998; Ebersole and Hawes-Ebersole, 2007). Most importantly, however, is the increasing acknowledgment that epilepsy is a network disease with fast propagation of epileptic activity within large-scale networks (Richardson, 2012). Identifying these network nodes and the temporal dynamics within these networks requires distributed source imaging methods that allow identification of multiple sources. Also, methods that permit the definition of the epileptic activity extent are of interest and have recently been proposed (Chowdhury et al., 2013; Heers et al., 2016).

Accurate localization of interictal spikes using distributed electric source imaging methods (often abbreviated as ESI) has been demonstrated in many studies over the last 15 years (for an early application, see Michel et al., 1999). Sperli et al. (2006) analyzed the standard (20 electrodes) clinical EEG of 30 operated and seizure-free children with ESI. They reported correct localization on a lobar level in 90% of the cases, whereas PET and SPECT revealed only 82% and 70% correct localization, respectively. However, they also showed that a higher number of electrodes (in their case 128) increased localization precision, particularly in temporal lobe epilepsy. Using such high-density EEG recordings, Michel et al. (2004a) demonstrated correct localization on a lobar level in 93.7% of 32 patients. In the 24 patients who were operated, ESI localized the maximum within the resected zone, i.e., on a sublobar level, in 79%. Brodbeck et al., 2010 analyzed 10 operated patients with normal MRI and showed correct localization within the resected margins in 8 of them. Zumsteg et al. (2005) performed ESI analysis in 15 mesial temporal lobe epilepsy patients and compared them with simultaneously recorded data from foramen ovale electrodes. They showed that 14 of the 19 different local field patterns seen by the foramen ovale electrodes could be correctly identified with ESI. These results indicate that even mesial temporal sources can be recorded by scalp EEG and properly localized by ESI, a conclusion that has also been made by Lantz et al. (2001) in simultaneous EEG and

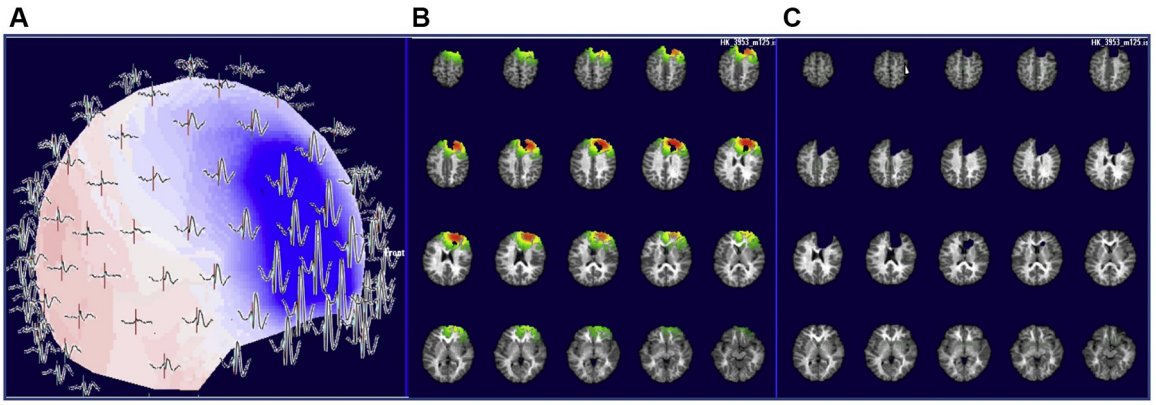

Fig. 6.4. Localization of epileptic spikes with EEG source imaging. This example shows an averaged epileptic spike recorded with 128-channel EEG. The scalp potential map at 50% of the rising phase of the spike is shown (A). The sources in the brain at this time point are estimated with a distributed inverse solution (LORETA) and the patient's MRI as head model. Maximal activity is found in the vicinity of a right frontal lesion (B). The patient was subsequently operated on and the postoperative MRI is shown (C). The EEG source maximum was correctly localized within the resected area in this postoperatively seizure-free patient. Such assessment of correctness of the source estimation by comparing it with the area of surgical resection has been the basis of several studies that evaluated the sensitivity of EEG source imaging (see, for example, Brodbeck et al., 2010).

intracranial EEG recordings. In addition, Brodbeck et al. (2009) showed that ESI accuracy is not vulnerable to eventual conductivity inhomogeneities due to lesions. Despite large cerebral lesions, ESI correctly localized spike activity within the resected zone in 12 of 14 patients (Fig. 6.4).

Given all these promising studies, Plummer et al. (2008) concluded in a comprehensive review that ESI deserves a place in the routine workup of patients with localization-related epilepsy, but that a prospective validation study conducted on larger clinical groups is still required. In 2011, Brodbeck et al. (2011) presented such a prospective study of 152 operated patients with >1 year postoperative follow-up, allowing them to look at sensitivity and specificity of ESI for epileptic focus localization. The study demonstrated a sensitivity of 84% and a specificity of 88% if the EEG was recorded with a large number of electrodes (128–256 channels) and the individual MRI was used as head model (SMAC head model). These values compared favorably with those of structural MRI, PET, and ictal/interictal SPECT (Fig. 6.5). The sensitivity and specificity of ESI decreased significantly with a low number of electrodes (<32 channels) and a template head model. Using this database as well as additional data, Lascano et al. (2015) evaluated the predictive value of all conventional imaging studies used (PET, SPECT, MRI) in the presurgical evaluation and included high-density ESI in this study; 190 patients with focal epilepsy who underwent surgery were included in the study, all recorded with high-density EEG (128–256 channels). These results showed that structural MRI and high-density EEG source imaging were the only two favorable outcome predictors. Patients who had concordant structural MRI and HD-ESI results had 92.3% probability of favorable outcome. An independent study by Feng et al. (2015) on 43 temporal lobe epilepsy patients recorded with 256-channel EEG confirmed these results by showing a sensitivity of 91.4% and a specificity of 75% on a sublobar level. While the precision of source imaging might be less relevant in patients where large resections are made, the question of how precisely ESI localizes the epileptic focus becomes relevant in small resections or ablations. Megevand et al. (2014) specifically evaluated the question of localization precision with HD-ESI in 38 patients who later underwent intracranial EEG monitoring. They measured the distance between the ESI maximum and the nearest intracranial electrodes in the irritative zone. They reported a median distance from the ESI maximum to the nearest intracranial electrode that showed maximal spike discharges of 15 mm.

While there are now more and more convincing results on the yield of the ESI for localizing the epileptic spikes, there is constant criticism that the true identification of the seizure onset zone requires the analysis of ictal and not only interictal activity (Blume et al., 2001; Janszky et al., 2001).

In their 38 patients with intracranial recordings, Megevand et al. (2014) showed that the median distance between the interictal zone and electrodes that were identified as belonging to the seizure onset zone was 0 mm with an interquartile range of 0–14 mm. Consequently, the localization of the spike with HD-ESI also correctly identified the seizure onset zone in most of the patients and the median distance between the ESI maximum based on spikes and the seizure onset zone was 17 mm.

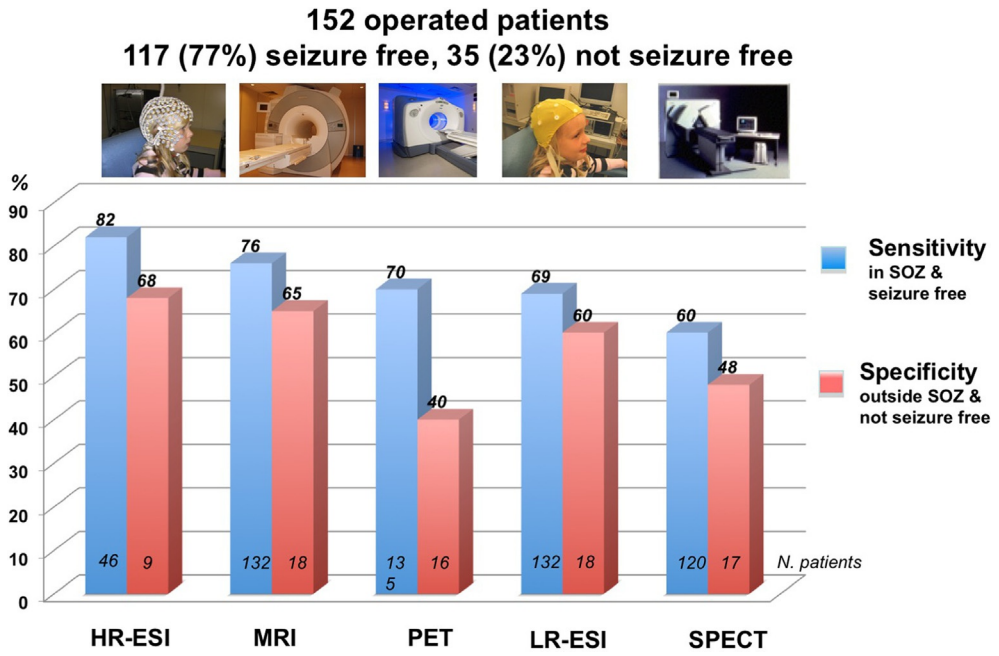

Fig. 6.5. Sensitivity and specificity of EEG source imaging. This study by Brodbeck et al. (2011) evaluated the clinical yield of different imaging modalities in the presurgical workup of patients with pharmaco-resistant epilepsy. A total of 152 patients with at least 1 year of postsurgical follow-up were included. Sensitivity of a method was determined by evaluating whether the localization proposed by the method was within the resected zone in postoperatively seizure-free patients, while specificity was determined by evaluating whether the localization was outside the resected area in patients in whom the surgery was not reducing the seizures. High-resolution EEG (128–256 electrodes) source imaging (HR-ESI) showed highest sensitivity and specificity. EEG source imaging based on standard clinical EEG (19–29 electrodes) (LR-ESI) showed much lower yield.

The problem with localizing the seizure onset zone with ESI is that fast propagation of seizure activity can lead to wrong identification of the seizure onset zone. Early studies applied phase-corrected frequency source analysis to determine which area started first with the most prominent initial ictal frequency (Lantz et al., 1999; Blanke et al., 2000). In Lantz et al., the source reconstruction of the predominant frequency was concordant with the intracranial findings in seven of nine cases (Lantz et al., 1999). However, this type of simple frequency analysis is not able to catch very fast propagation because the time resolution is lost. Time–frequency analysis might be more promising in this respect, as recently shown by Pellegrino et al. (2016). Yang et al. (2011) used independent component analysis in the time–frequency domain to determine maps that represented the rhythmic discharges at seizure onset. Localization of the sources of these maps closely corresponded to the seizure onset zone determined with intracranial recordings. Fig. 6.6 illustrates one example of direct seizure imaging in two patients with temporal lobe epilepsy and frontal lobe epilepsy. Nemtsas et al. (2017) filtered the high-density EEG in the dominant frequency of the rhythms at seizure onset and showed correct source localization of this dominant frequency in the resected zone in five of six postoperatively seizure-free patients. They also showed a 93% concordance between ictal and interictal source localization, again indicating that spike focus localization corresponds to the seizure onset zone in the majority of the cases. While these frequency-based methods are very promising, they only work in patients where the seizure onset is characterized by continuous synchronized rhythmic discharges. The functional connectivity imaging has also shown merits in localizing seizure sources. Ding et al. (2007) reported a study of 20 seizures in a group of patients. The application of Granger causality analysis to sources estimated using a scanning technique resulted in a concordant outcome as compared with structure MRI and SPECT in the same patients. Staljanssens et al. (2017) recently proposed an alternative approach based on functional connectivity analysis in the source space and identification of the source with the highest number of outgoing connections as the seizure onset zone. While this approach showed promising results in high-density EEG (>200 electrodes), it was remarkably less successful with lower channel counts (<128 electrodes).

Another subject of high interest for the clinical workup of patients concerns high-frequency oscillations (HFOs), mostly in the range of 80–500 Hz. There is now

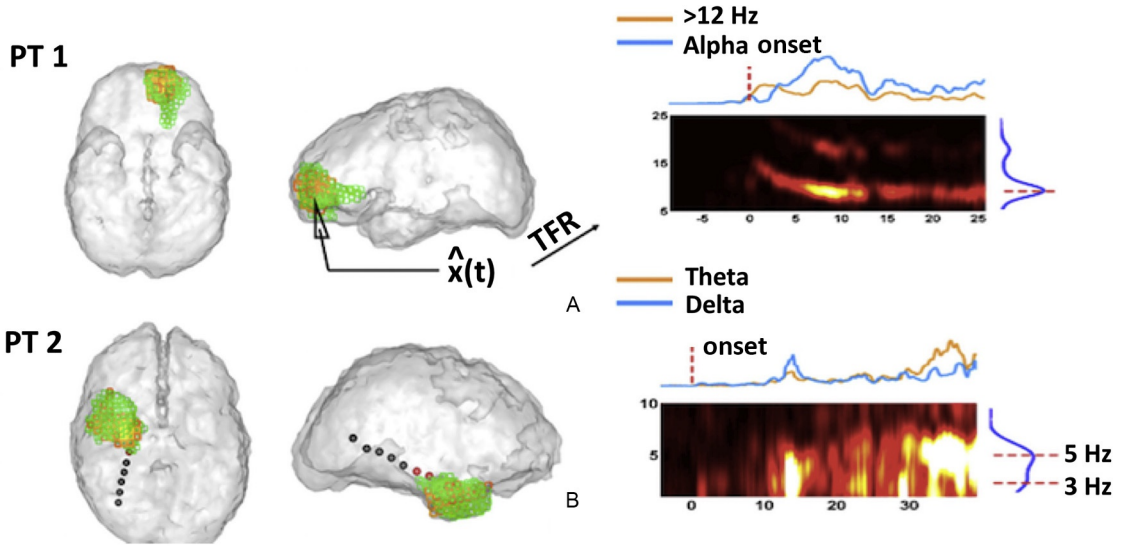

Fig. 6.6. EEG source imaging of seizures: Examples of electric source imaging (ESI) of the seizure onset zone from high-density EEG with the aid of independent component analysis. The *yellow color* refers to noninvasive ESI results from seizure components identified by time–frequency analysis. The *green color* illustrates surgical resected areas quantified by postoperative MRI in the patients. (A) and (B) refer to results in two patients. The patients were seizure free at 1-year follow-up postsurgery. Modified from Yang L, Wilke C, Brinkmann B et al. (2011). Dynamic imaging of ictal oscillations using non-invasive high-resolution EEG. Neuroimage 56: 1908–1917.

a large body of research on HFOs, indicating that HFOs are more frequently found in or close to the seizure onset zone in the intracranial EEG and even correlate with surgical outcome (Jacobs et al., 2010). HFOs are very focal and of low amplitude and therefore difficult to detect with scalp EEG, but recent reports indicate that this might be possible (Wu et al., 2008; Andrade-Valenca et al., 2011; Von Ellenrieder et al., 2016), particularly when high-density EEG is used (Zelmann et al., 2014). Lu et al. (2014), Kuhnke et al. (2018) confirmed the detection of focal HFO events with high-density EEG and showed that they can be correctly localized with EEG source imaging. The importance of high-resolution EEG recordings becomes evident in these studies, a point that is discussed in detail in Chapter 14.

The increasing recognition of epilepsy as a network disease (Richardson, 2012) has triggered studies that look at functional connectivity between the different nodes of these pathological networks (Hassan et al., 2017). Wilke and colleagues showed that Granger causality or graph theory can substantially facilitate resolving the seizure onset zone from intracranial EEG during interictal spikes and seizures (Wilke et al., 2009a,b, 2011). Ding et al. (2007) demonstrated that such methods (in this case, direct transfer function) applied to the source-space data can successfully localize the seizure focus and distinguish it from propagated activities. Coito et al. (2015) used another directed connectivity measure in the source-space (partial directed coherence) to study epileptic networks in left vs right temporal lobe epilepsy. They showed clear differences between the two patient groups, with more bilateral networks in right as compared to left temporal epilepsy. Interestingly, the same group (Coito et al., 2016) also showed that the same pathological networks were active in the EEG at rest without any visible EEG abnormalities and distinguished them from a control group. This study indicates that epileptic networks might be active even outside of epileptic activity and might explain neuropsychological and cognitive dysfunctions of epileptic patients even when seizures are controlled.

Fig. 6.7 shows an example of localizing the primary epileptic sources using EEG and MEG source imaging and directional functional connectivity in a patient with temporal lobe epilepsy (Sohrabpour et al., 2016). Two types of interictal spikes (both observed in EEG and MEG) were observed in this patient. One type of the extracted spikes localized to the temporal region (21 spikes in EEG and 23 spikes in MEG), and the other type to the left parietal-occipital region (8 spikes in EEG and 8 spikes in MEG) when the inverse problem was solved for the peak of the averaged spike. The regions of interest (ROIs) found using both EEG spikes and MEG spikes overlap well with each other. The arrow between the two panels of Fig. 6.7A indicates the information flow derived from connectivity analysis, directing from the primary source to the secondary source where the epileptic activity propagates after being generated by the primary source. This can also be seen from the information flow direction and comparison of total outflow volume

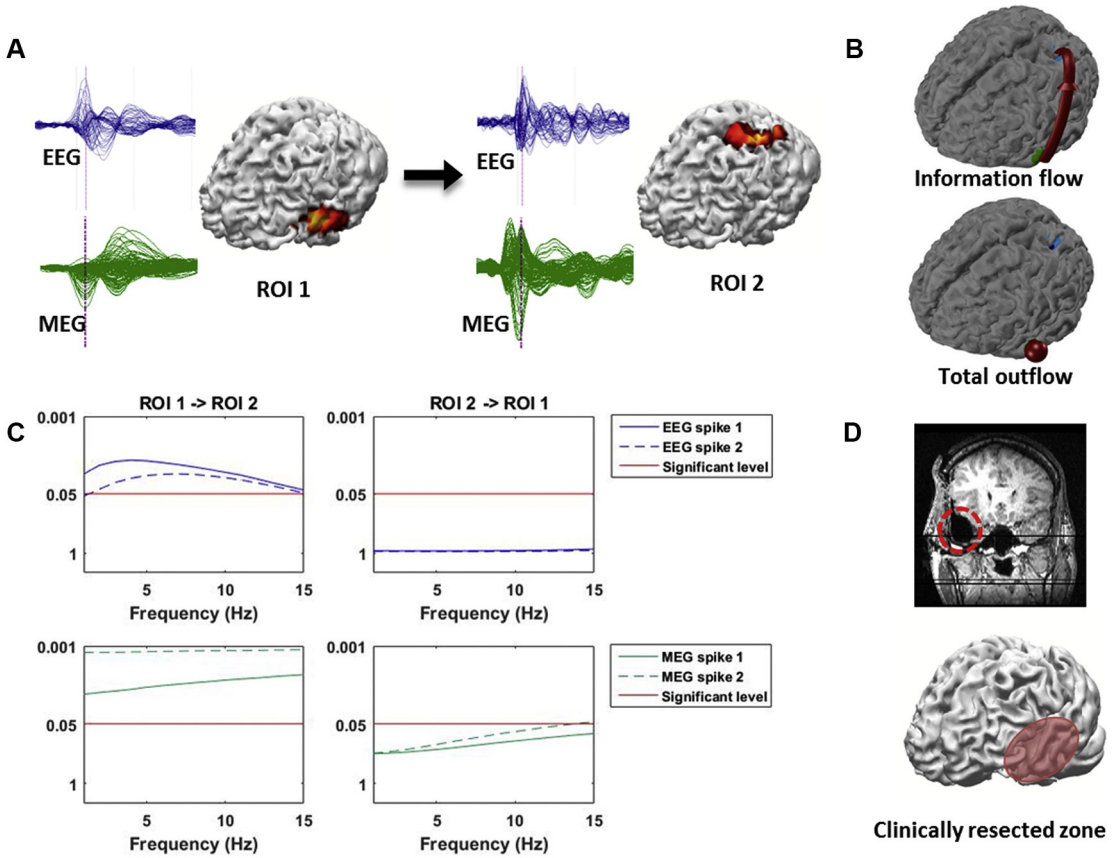

Fig. 6.7. Identifying epileptic networks from interictal spikes in a patient with temporal lobe epilepsy. (A) Spikes (*blue* from EEG, *green* from MEG), estimated sources, and directional causality of two regions of interest. (B) Information flow direction and comparison of total outflow volumes between the two ROIs depicted on cortex model. (C) Statistical testing results of DTF values between the two ROIs. DTF values above the red line are significant with a corresponding P value <0.05. (D) Surgical resection marked by *red dotted line* on postoperative MR image and *red oval* on the cortex model. This patient suffered from left temporal lobe epilepsy and is seizure-free after the resection. From Sohrabpour A, Ye S, Worrell GA et al. (2016). Noninvasive electromagnetic source imaging and granger causality analysis: an electrophysiological connectome (eConnectome) approach. IEEE Trans Biomed Eng 63: 2474–2487.

(between the two nodes) in Fig. 6.7B. In this patient, ROI 1 shows significant information flow to ROI 2, while no such significance can be observed from ROI 2 to ROI 1. Thus, ROI 1, which is located in the left temporal lobe, was identified as the primary source. Fig. 6.7D shows the postoperative MR image with the red line marking out the surgically resected area. The results indicate that source imaging results and connectivity analysis results from E/MEG coincide well with the clinical findings and can be used to localize primary epilepsy source responsible for seizure generation.

Surgical planning

Another important potential clinical use of EEG/MEG source imaging is the localization of eloquent cortex in the planning of brain surgery, whether for resection of brain tumors or epileptic foci. While maximization of resection is key to the success of surgery, the extent of resection should not threaten neurological functions or quality of life. Therefore, resections in the vicinity of eloquent zones require the precise localization of both the lesion and the eloquent areas (i.e., sensorimotor cortex, language areas) during presurgical planning, in order to make the surgery both as radical and as precise as possible. Various efforts have been made to expand the limits of resective brain surgery with intraoperative mapping of functions such as motor or language through direct cortical stimulation (DCS) (Ojemann et al., 1989; Duffau et al., 2003), or intraoperative imaging with low field MRI and tractography (Prabhu et al., 2011; Seifert et al., 2011). The most established noninvasive method for presurgical mapping of eloquent cortex is fMRI, particularly for the localization of sensorimotor areas

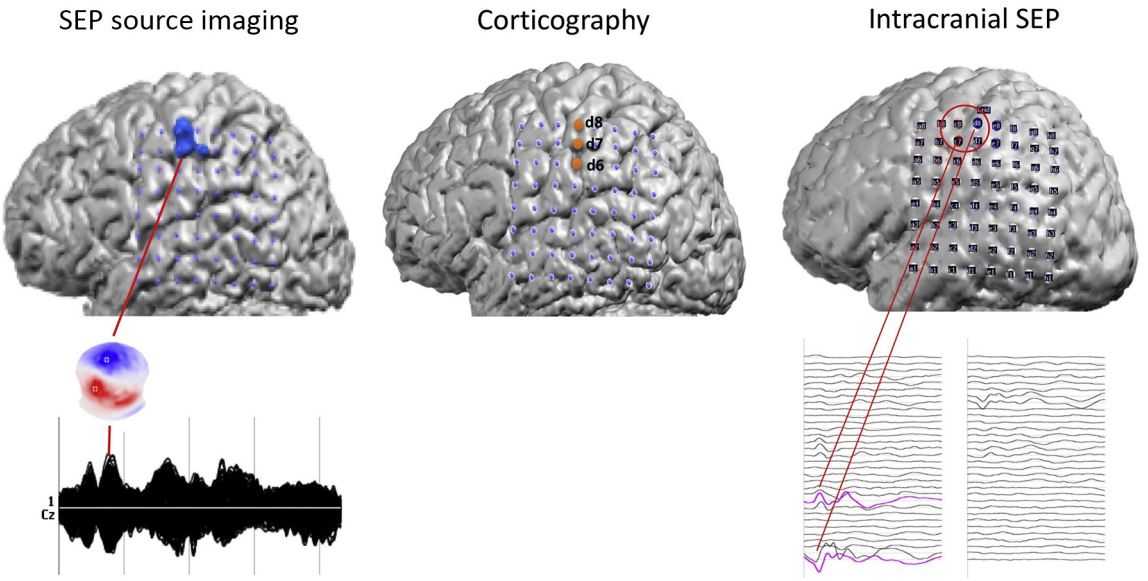

Fig. 6.8. Localization of eloquent cortex with EEG source imaging. The localization of the somatosensory cortex in an individual patient was compared between source imaging of the somatosensory evoked potential (SEP), corticography based on direct electrical stimulations of the contacts on a subdural grid, and intracranial recordings of SEPs (determining phase reversal). High correspondence between these three methods was found. For more details and comparison with fMRI, see the study on a large group of patients by Lascano et al. (2014).

(Krings et al., 2001; Majos et al., 2005) where the spatial precision is in the range of 2–5 mm (Roessler et al., 2005). However, some drawbacks are reported (Sunaert, 2006). Besides a relatively high drop-out rate for technical reasons (movement artifacts, distortions, system instabilities, etc.) the most important problem in the context of brain lesions is the possibility that altered vasoactivity can lead to neurovascular uncoupling and missing the blood-oxygenation level dependent activation (Holodny et al., 2000; Schreiber et al., 2000). Consequently, absence of an fMRI activity in a given area does not necessarily indicate that this region is not implied in the function (Sunaert, 2006). EEG/MEG source imaging might be more promising in this respect. However, the use of MEG and EEG source imaging in localization of eloquent cortex in presurgical planning is less common. High-resolution MEG systems have been on the market somewhat longer and have therefore been used for this purpose in some studies, particularly for localization of sensory and motor cortex. These studies, using single dipole localization approaches, showed generally good localization results (Gallen et al., 1995; Rezai et al., 1996; Ganslandt et al., 1999; Makela et al., 2006; Willemse et al., 2016). Recently, precise localization of somatosensory cortex has been demonstrated with HD-EEG and source imaging in individual realistic head models (Lascano et al., 2014). Subjects were stimulated with pneumatic stimulation of the thumb and somatosensory evoked potentials (SEPs) were calculated and localized using a distributed inverse solution. The results were compared with fMRI and (in a subset of epilepsy patients) with intracranial SEP and DCS (Fig. 6.8). The study showed that ESI of the SEP precisely localizes primary somatosensory cortex with very small interindividual variability. Comparison of ESI and fMRI showed small differences of 3–7 mm except in the medial-lateral direction, because the SEP maximum at 40-ms latency was systematically localized deeper in the cortex than the fMRI maximum. This is explained by the fact that the early peak of the SEP results from the activation of Area 3b, comprising the anterior wall of the postcentral gyrus, while fMRI, lacking the temporal resolution, was dominated by activation of areas 1 and 2 and therefore obtained a more lateral and more posterior activation than the SEP. Comparison of the noninvasive with the invasive methods revealed that fMRI was slightly closer to the intracranial SEP, while ESI was closer to the DCS location. An independent study by Klamer et al. (2015) confirmed the excellent localization precision of the somatosensory cortex with high-density EEG when compared to fMRI as gold standard and again showed a more medial localization of EEG. Interestingly, these authors compared high-density EEG source imaging (256 channel) with MEG using the same stimulation protocol. They found that EEG localized significantly closer to the fMRI than MEG, but only if individual realistic head models were used, confirming again the importance of realistic head models for EEG source imaging, as discussed previously.

Source localization of sensory evoked potentials (EPs) has a high potential to not only localize eloquent cortex, but also to identify and localize brain lesions in various neurological diseases. In a recent review on the clinical use of EPs Lascano et al. (2017) concluded that "EPs based on multichannel electroencephalography recordings, known as high-density EPs, help to better differentiate between healthy subjects and patients and, moreover, they provide valuable spatial information regarding the site of the lesion."

CONCLUSIONS

This chapter describes the fundamental principles and the development of EEG source localization. It shows that the localization of brain neuronal activity based on scalp EEG has matured from a rough estimation of an equivalent dipole in a sphere to an anatomically precise localization of the current density distribution. Several important developments led to this maturation: high-density electrode arrays, MRI-based individual head models, and distributed inverse solution methods are among the most important. EEG source imaging allows not only precise localizing of sources at given time instances, but the high time resolution of EEG also permits looking at information flow within large-scale brain networks and gaining new insights in the way the areas of such networks communicate with each other.

The use of EEG source imaging based on high-density EEG is a current standard in many experimental laboratories that study normal brain function. But the method has also found its way into several clinical laboratories where it is used to localize abnormal brain functions and networks. Most important is the use of EEG source imaging in presurgical epilepsy evaluation. While EEG remains the cornerstone of epilepsy diagnosis, the advanced analysis of these signals using the methods described in this chapter places the EEG on the same level as other brain imaging methods used in the evaluation of this disease. Applications of these methods in other pathologies as well as in presurgical functional mapping of eloquent cortex are now within reach.

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REFERENCES

Ahlfors SP, Han J, Belliveau JW et al. (2010). Sensitivity of MEG and EEG to source orientation. Brain Topogr 23: 227–232.

Alarcon G, Guy CN, Binnie CD et al. (1994). Intracerebral propagation of interictal activity in partial epilepsy: implications for source localisation. J Neurol Neurosurg Psychiatry 57: 435–449.

Andrade-Valenca LP, Dubeau F, Mari F et al. (2011). Interictal scalp fast oscillations as a marker of the seizure onset zone. Neurology 77: 524–531.

Astolfi L, Cincotti F, Mattia D et al. (2004). Estimation of the effective and functional human cortical connectivity with structural equation modeling and directed transfer function applied to high-resolution EEG. Magn Reson Imaging 22: 1457–1470.

Astolfi L, Cincotti F, Mattia D et al. (2007a). Time-varying cortical connectivity by adaptive multivariate estimators applied to a combined foot-lips movement. Conf Proc IEEE Eng Med Biol Soc 2007: 4402–4405.

Astolfi L, Cincotti F, Mattia D et al. (2007b). Comparison of different cortical connectivity estimators for high-resolution EEG recordings. Hum Brain Mapp 28: 143–157.

Babiloni F, Cincotti F, Babiloni C et al. (2005). Estimation of the cortical functional connectivity with the multimodal integration of high-resolution EEG and fMRI data by directed transfer function. Neuroimage 24: 118–131.

Bai X, Towle VL, He EJ et al. (2007). Evaluation of cortical current density imaging methods using intracranial electrocorticograms and functional MRI. Neuroimage 35: 598–608.

Birot G, Spinelli L, Vulliemoz S et al. (2014). Head model and electrical source imaging: a study of 38 epileptic patients. Neuroimage Clin 5: 77–83.

Blanke O, Lantz G, Seeck M et al. (2000). Temporal and spatial determination of EEG-seizure onset in the frequency domain. Clin Neurophysiol 111: 763–772.

Blume WT, Holloway GM, Wiebe S (2001). Temporal epileptogenesis: localizing value of scalp and subdural interictal and ictal EEG data. Epilepsia 42: 508–514.

Braeutigam S (2013). Magnetoencephalography: fundamentals and established and emerging clinical applications in radiology. ISRN Radiol 2013, 529463.

Brazier MAB (1949). A study of the electrical fields at the surface of the head. Electroencephalogr Clin Neurophysiol Suppl 2: 38–52.

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

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

Brodbeck V, Spinelli L, Lascano A et al. (2011). Electroencephalographic source imaging: a prospective study of 152 operated epileptic patients. Brain 134: 2887–2897.

Brovelli A, Ding M, Ledberg A et al. (2004). Beta oscillations in a large-scale sensorimotor cortical network: directional influences revealed by Granger causality. Proc Natl Acad Sci USA 101: 9849–9854.

Brunet D, Murray MM, Michel CM (2011). Spatiotemporal analysis of multichannel EEG: CARTOOL. Comput Intell Neurosci 2011, 813870.

Brunner C, Billinger M, Seeber M et al. (2016). Volume conduction influences scalp-based connectivity estimates. Front Comput Neurosci 10: 121.

Chella F, Pizzella V, Zappasodi F et al. (2016). Impact of the reference choice on scalp EEG connectivity estimation. J Neural Eng 13, 036016.

Chowdhury RA, Lina JM, Kobayashi E et al. (2013). MEG source localization of spatially extended generators of epileptic activity: comparing entropic and hierarchical Bayesian approaches. PLoS One 8: e55969.

Coito A, Plomp G, Genetti M et al. (2015). Dynamic directed interictal connectivity in left and right temporal lobe epilepsy. Epilepsia 56: 207–217.

Coito A, Genetti M, Pittau F et al. (2016). Altered directed connectivity in temporal lobe epilepsy in the absence of interictal spikes: a high density EEG study. Epilepsia 57: 402–411.

Cuffin BN, Cohen D (1979). Comparison of the magnetoencephalogram and electroencephalogram. Electroencephalogr Clin Neurophysiol 47: 132–146.

Dale AM, Sereno MI (1993). Improved localization of cortical activity by combining EEG and MEG with MRI cortical surface reconstruction: a linear approach. J Cogn Neurosci 5: 162–176.

David O, Cosmelli D, Friston KJ (2004). Evaluation of different measures of functional connectivity using a neural mass model. Neuroimage 21: 659–673.

David O, Kiebel SJ, Harrison LM et al. (2006). Dynamic causal modeling of evoked responses in EEG and MEG. Neuroimage 30: 1255–1272.

Ding L, He B (2008). Sparse source imaging in electroencephalography with accurate field modeling. Hum Brain Mapp 29: 1053–1067.

Ding L, Worrell GA, Lagerlund TD et al. (2007). Ictal source analysis: localization and imaging of causal interactions in humans. Neuroimage 34: 575–586.

Duffau H, Capelle L, Denvil D et al. (2003). Usefulness of intraoperative electrical subcortical mapping during surgery for low-grade gliomas located within eloquent brain regions: functional results in a consecutive series of 103 patients. J Neurosurg 98: 764–778.

Ebersole JS (1998). EEG and MEG dipole source modeling. In: J Engel, TA Pedley (Eds.), Epilepsy: a comprehensive textbook. Lippincott-Raven, Philadelphia.

Ebersole JS, Hawes-Ebersole S (2007). Clinical application of dipole models in the localization of epileptiform activity. J Clin Neurophysiol 24: 120–129.

Ebersole JS, Wade PB (1990). Spike voltage topography and equivalent dipole localization in complex partial epilepsy. Brain Topogr 3: 21–34.

Ebersole JS, Hawes S, Scherg M (1995). Intracranial EEG validation of spike propagation predicted by dipole models. Electroencephalogr Clin Neurophysiol 95: 18.

Fender D (1987). Source localization of brain electrical activity. In: ASGA Remond (Ed.), Methods of analysis of brain electrical and magnetic signals, Elsevier Science Publishers, Amsterdam.

Feng R, Hu J, Pan L et al. (2015). Application of 256-channel dense array electroencephalographic source imaging in presurgical workup of temporal lobe epilepsy. Clin Neurophysiol 127: 108–116.

Fernandez-Bouzas A, Harmony T, Fernandez T et al. (2004). Variable resolution electromagnetic tomography (VARETA) in evaluation of compression of cerebral arteries due to deep midline brain lesions. Arch Med Res 35: 225–230.

Gallen CC, Schwartz BJ, Bucholz RD et al. (1995). Presurgical localization of functional cortex using magnetic source imaging. J Neurosurg 82: 988–994.

Ganslandt O, Fahlbusch R, Nimsky C et al. (1999). Functional neuronavigation with magnetoencephalography: outcome in 50 patients with lesions around the motor cortex. Neurosurg Focus 6: e3.

Gavaret M, Badier JM, Marquis P et al. (2006). Electric source imaging in frontal lobe epilepsy. J Clin Neurophysiol 23: 358–370.

Gavaret M, Trebuchon A, Bartolomei F et al. (2009). Source localization of scalp-EEG interictal spikes in posterior cortex epilepsies investigated by HR-EEG and SEEG. Epilepsia 50: 276–289.

Grave de Peralta Menendez R, Gonzalez Andino SL (1998). A critical analysis of linear inverse solutions. IEEE Trans Biomed Eng 45: 440–448.

Grave de Peralta Menendez R, Murray MM, Michel CM et al. (2004). Electrical neuroimaging based on biophysical constraints. Neuroimage 21: 527–539.

Greenblatt RE (1993). Probabilistic reconstruction of multiple sources in the neuroelectromagnetic inverse problem. Inverse Prob 9: 271–284.

Hämälainen MS (1984). Interpreting measured magnetic fields of the brain: estimates of current distributions, Helsinki University of Technology, Espoo.

Hämäläinen M, Ilmoniemi RJ (1994). Interpreting measured magnetic fields of the brain: minimum norm estimates. Med Biol Eng Comput 32: 25–42.

Hämäläinen M, Sarvas J (1989). Realistic conductor geometry model of the human head for interpretation of neuromagnetic data. IEEE Trans Biomed Eng 36: 165–171.

Hassan M, Merlet I, Mheich A et al. (2017). Identification of interictal epileptic networks from dense-EEG. Brain Topogr 30 (1): 60–76. https://doi.org/10.1007/s10548-016-0517-z.

Haufe S, Nikulin VV, Muller KR et al. (2013). A critical assessment of connectivity measures for EEG data: a simulation study. Neuroimage 64: 120–133.

He B, Ding L (2013). Electrophysiological neuroimaging. In: B He (Ed.), Neural engineering, Springer, New York.

He B, Lian J (2005). Electrophysiological neuroimaging: solving the EEG inverse problem. In: B He (Ed.), Neural engineering, Kluwer Academic Publishers, Norwell, USA.

He B, Musha T, Okamoto Y et al. (1987). Electric dipole tracing in the brain by means of the boundary element method and its accuracy. IEEE Trans Biomed Eng 34: 406–414.

Heers M, Chowdhury RA, Hedrich T et al. (2016). Localization accuracy of distributed inverse solutions for

electric and magnetic source imaging of interictal epileptic discharges in patients with focal epilepsy. Brain Topogr 29: 162–181.

Henderson CJ, Butler SR, Glass A (1975). The localization of equivalent dipoles of EEG sources by the application of electrical field theory. Electroencephalogr Clin Neurophysiol 39: 117–130.

Hoekema R, Wieneke GH, Leijten FS et al. (2003). Measurement of the conductivity of skull, temporarily removed during epilepsy surgery. Brain Topogr 16: 29–38.

Holodny AI, Schulder M, Liu WC et al. (2000). The effect of brain tumors on BOLD functional MR imaging activation in the adjacent motor cortex: implications for image-guided neurosurgery. AJNR Am J Neuroradiol 21: 1415–1422.

Huang MX, Dale AM, Song T et al. (2006). Vector-based spatial-temporal minimum L1-norm solution for MEG. Neuroimage 31: 1025–1037.

Ioannides AA (2007). Dynamic functional connectivity. Curr Opin Neurobiol 17: 161–170.

Jacobs J, Zijlmans M, Zelmann R et al. (2010). High-frequency electroencephalographic oscillations correlate with outcome of epilepsy surgery. Ann Neurol 67: 209–220.

Janszky J, Fogarasi A, Jokeit H et al. (2001). Spatiotemporal relationship between seizure activity and interictal spikes in temporal lobe epilepsy. Epilepsy Res 47: 179–188.

Klamer S, Elshahabi A, Lerche H et al. (2015). Differences between MEG and high-density EEG source localizations using a distributed source model in comparison to fMRI. Brain Topogr 28: 87–94.

Krings T, Reinges MH, Erberich S et al. (2001). Functional MRI for presurgical planning: problems, artefacts, and solution strategies. J Neurol Neurosurg Psychiatry 70: 749–760.

Kuhnke N, Schwind J, Dümpelmann M et al. (2018). High frequency oscillations in the ripple band (80–250 Hz) in scalp EEG: higher density of electrodes allows for better localization of the Seizure Onset Zone. Brain Topogr 31 (6): 1059–1072. https://doi.org/10.1007/s10548-018-0658-3.

Lachaux JP, Rodriguez E, Martinerie J et al. (1999). Measuring phase synchrony in brain signals. Hum Brain Mapp 8: 194–208.

Lai Y, Van Drongelen W, Ding L et al. (2005). Estimation of in vivo human brain-to-skull conductivity ratio from simultaneous extra- and intra-cranial electrical potential recordings. Clin Neurophysiol 116: 456–465.

Lantz G, Ryding E, RosÉN I (1994). Three dimensional localisation of interictal epileptiform activity with dipole analysis: comparison with intracranial recordings and SPECT findings. J Epilepsy 7: 117–129.

Lantz G, Holub M, Ryding E et al. (1996). Simultaneous intracranial and extracranial recording of interictal epileptiform activity in patients with drug resistant partial epilepsy: patterns of conduction and results from dipole reconstructions. Electroencephalogr Clin Neurophysiol 99: 69–78.

Lantz G, Michel CM, Seeck M et al. (1999). Frequency domain EEG source localization of ictal epileptiform activity in patients with partial complex epilepsy of temporal lobe origin. Clin Neurophysiol 110: 176–184.

Lantz G, Grave de Peralta Menendez R, Gonzalez Andino S et al. (2001). Noninvasive localization of electromagnetic epileptic activity. II. Demonstration of sublobar accuracy in patients with simultaneous surface and depth recordings. Brain Topogr 14: 139–147.

Lascano AM, Grouiller F, Genetti M et al. (2014). Surgically relevant localization of the central sulcus with high-density somatosensory-evoked potentials compared with functional magnetic resonance imaging. Neurosurgery 74: 517–526.

Lascano AM, Perneger T, Vulliemoz S et al. (2015). Yield of MRI, high-density electric source imaging (HD-ESI), SPECT and PET in epilepsy surgery candidates. Clin Neurophysiol 125: 150–155.

Lascano AM, Lalive PH, Hardmeier M et al. (2017). Clinical evoked potentials in neurology: a review of techniques and indications. J Neurol Neurosurg Psychiatry 88: 688–696.

Latikka J, Kuurne T, Eskola H (2001). Conductivity of living intracranial tissues. Phys Med Biol 46: 1611–1616.

Lee WH, Liu Z, Mueller BA et al. (2009). Influence of white matter anisotropic conductivity on EEG source localization: comparison to fMRI in human primary visual cortex. Clin Neurophysiol 120: 2071–2081.

Lillie EM, Urban JE, Lynch SK et al. (2016). Evaluation of skull cortical thickness changes with age and sex from computed tomography scans. J Bone Miner Res 31: 299–307.

Lin FH, Hara K, Solo V et al. (2009). Dynamic Granger-Geweke causality modeling with application to interictal spike propagation. Hum Brain Mapp 30: 1877–1886.

Lopes da Silva F (1991). Neural mechanisms underlying brain waves: from neural membranes to networks. Electroencephalogr Clin Neurophysiol 79: 81–93.

Lopes da Silva F, Pijn JP, Boeijinga P (1989). Interdependence of EEG signals: linear vs. nonlinear associations and the significance of time delays and phase shifts. Brain Topogr 2: 9–18.

Lu Y, Yang L, Worrell GA et al. (2012). Dynamic imaging of seizure activity in pediatric epilepsy patients. Clin Neurophysiol 123: 2122–2129.

Lu Y, Worrell GA, Zhang HC et al. (2014). Noninvasive imaging of the high frequency brain activity in focal epilepsy patients. IEEE Trans Biomed Eng 61: 1660–1667.

Majos A, Tybor K, Stefanczyk L et al. (2005). Cortical mapping by functional magnetic resonance imaging in patients with brain tumors. Eur Radiol 15: 1148–1158.

Makela JP, Forss N, Jaaskelainen J et al. (2006). Magnetoencephalography in neurosurgery. Neurosurgery 59: 493–510; discussion 510–1.

Malmivuo J (2011). Comparison of the properties of EEG and MEG in detecting the electric activity of the brain. Brain Topogr 25: 1–19.

Malmivuo J, Plonsey R (1995). Bioelectromagnetism: principles and applications of bioelectric and biomagnetic fields, Oxford University Press, New York.

Martino J, Honma SM, Findlay AM et al. (2011). Resting functional connectivity in patients with brain tumors in eloquent areas. Ann Neurol 69: 521–532.

Matsuura K, Okabe Y (1995). Selective minimum-norm solution of the biomagnetic inverse problem. IEEE Trans Biomed Eng 42: 608–615.

Megevand P, Spinelli L, Genetti M et al. (2014). Electric source imaging of interictal activity accurately localises the seizure onset zone. J Neurol Neurosurg Psychiatry 85: 38–43.

Michel C, He B (2011). EEG mapping and source imaging. In: D Schomer, FH Lopes da Silva (Eds.), Niedermeyer's electroencephalography, sixth edn. Lippincott Williams & Wilkins, Philadelphia.

Michel CM, Murray MM (2012). Towards the utilization of EEG as a brain imaging tool. Neuroimage 61: 371–385.

Michel CM, Grave de Peralta R, Lantz G et al. (1999). Spatio-temporal EEG analysis and distributed source estimation in presurgical epilepsy evaluation. J Clin Neurophysiol 16: 239–266.

Michel CM, Lantz G, Spinelli L et al. (2004a). 128-channel EEG source imaging in epilepsy: clinical yield and localization precision. J Clin Neurophysiol 21: 71–83.

Michel CM, Murray MM, Lantz G et al. (2004b). EEG source imaging. Clin Neurophysiol 115: 2195–2222.

Mitzdorf U (1985). Current source-density method and application in cat cerebral cortex: investigation of evoked potentials and EEG phenomena. Physiol Rev 65: 37–100.

Mosher JC, Leahy RM (1999). Source localization using recursively applied and projected (RAP) MUSIC. IEEE Trans Signal Process 47: 332–340.

Mosher JC, Lewis PS, Leahy RM (1992). Multiple dipole modeling and localization from spatio-temporal MEG data. IEEE Trans Biomed Eng 39: 541–557.

Nemtsas P, Birot G, Pittau F et al. (2017). Source localization of ictal epileptic activity based on high-density scalp EEG data. Epilepsia 58: 1027–1036.

Ojemann G, Ojemann J, Lettich E et al. (1989). Cortical language localization in left, dominant hemisphere. An electrical stimulation mapping investigation in 117 patients. J Neurosurg 71: 316–326.

Otte A, Halsband U (2006). Brain imaging tools in neurosciences. J Physiol Paris 99: 281–292.

Pascual-Marqui RD (2002). Standardized low-resolution brain electromagnetic tomography (sLORETA): technical details. Methods Find Exp Clin Pharmacol 24 (Suppl. D): 5–12.

Pascual-Marqui RD, Michel CM, Lehmann D (1994). Low resolution electromagnetic tomography: a new method for localizing electrical activity in the brain. Int J Psychophysiol 18: 49–65.

Pascual-Marqui RD, Sekihara K, Brandeis D et al. (2009). Imaging the electrical neuronal generators of EEG/MEG. In: CM Michel, T Koenig, D Brandeis, LRR Gianotti, J Wackermann (Eds.), Electrical neuroimaging, Cambridge University Press, Cambridge.

Pascual-Marqui RD, Lehmann D, Koukkou M et al. (2011). Assessing interactions in the brain with exact low-resolution electromagnetic tomography. Philos Trans A Math Phys Eng Sci 369: 3768–3784.

Pellegrino G, Hedrich T, Chowdhury R et al. (2016). Source localization of the seizure onset zone from ictal EEG/MEG data. Hum Brain Mapp 37: 2528–2546.

Plomp G, Quairiaux C, Michel CM et al. (2014). The physiological plausibility of time-varying Granger-causal modeling: normalization and weighting by spectral power. Neuroimage 97: 206–216.

Plomp G, Hervais-Adelman A, Astolfi L et al. (2015). Early recurrence and ongoing parietal driving during elementary visual processing. Sci Rep 5, 18733.

Plonsey R (1969). Bioelectric phenomena, McGraw-Hill, New York.

Plummer C, Harvey AS, Cook M (2008). EEG source localization in focal epilepsy: where are we now? Epilepsia 49: 201–218.

Porcaro C, Coppola G, Pierelli F et al. (2013). Multiple frequency functional connectivity in the hand somatosensory network: an EEG study. Clin Neurophysiol 124: 1216–1224.

Prabhu SS, Gasco J, Tummala S et al. (2011). Intraoperative magnetic resonance imaging-guided tractography with integrated monopolar subcortical functional mapping for resection of brain tumors. Clinical article. J Neurosurg 114: 719–726.

Rezai AR, Hund M, Kronberg E et al. (1996). The interactive use of magnetoencephalography in stereotactic image-guided neurosurgery. Neurosurgery 39: 92–102.

Richardson MP (2012). Large scale brain models of epilepsy: dynamics meets connectomics. J Neurol Neurosurg Psychiatry 83: 1238–1248.

Roche AF (1953). Increase in cranial thickness during growth. Hum Biol 25: 81–92.

Roessler K, Donat M, Lanzenberger R et al. (2005). Evaluation of preoperative high magnetic field motor functional MRI (3 Tesla) in glioma patients by navigated electrocortical stimulation and postoperative outcome. J Neurol Neurosurg Psychiatry 76: 1152–1157.

Rose S, Ebersole JS (2009). Advances in spike localization with EEG dipole modeling. Clin EEG Neurosci 40: 281–287.

Rush S, Driscoll DA (1969). EEG electrode sensitivity—an application of reciprocity. IEEE Trans Biomed Eng 16: 15–22.

Ryynanen OR, Hyttinen JA, Malmivuo JA (2006). Effect of measurement noise and electrode density on the spatial resolution of cortical potential distribution with different resistivity values for the skull. IEEE Trans Biomed Eng 53: 1851–1858.

Scherg M, Ebersole JS (1994). Brain source imaging of focal and multifocal epileptiform EEG activity. Neurophysiol Clin 24: 51–60.

Scherg M, von Cramon D (1985). A new interpretation of the generators of BAEP waves I-V: results of a spatio-temporal dipole model. Electroencephalogr Clin Neurophysiol 62: 290–299.

Schreiber A, Hubbe U, Ziyeh S et al. (2000). The influence of gliomas and nonglial space-occupying lesions on blood-oxygen-level-dependent contrast enhancement. AJNR Am J Neuroradiol 21: 1055–1063.

Schwartz ES, Edgar JC, Gaetz WC et al. (2010). Magnetoencephalography. Pediatr Radiol 40: 50–58.

Seifert V, Gasser T, Senft C (2011). Low field intraoperative MRI in glioma surgery. Acta Neurochir Suppl 109: 35–41.

Shindo K, Ikeda A, Musha T et al. (1998). Clinical usefulness of the dipole tracing method for localizing interictal spikes in partial epilepsy. Epilepsia 39: 371–379.

Sohrabpour A, Ye S, Worrell GA et al. (2016). Noninvasive electromagnetic source imaging and Granger causality analysis: an electrophysiological connectome (eConnectome) approach. IEEE Trans Biomed Eng 63: 2474–2487.

Sperli F, Spinelli L, Seeck M et al. (2006). EEG source imaging in paediatric epilepsy surgery: a new perspective in presurgical workup. Epilepsia 47: 981–990.

Spinelli L, Andino SG, Lantz G et al. (2000). Electromagnetic inverse solutions in anatomically constrained spherical head models. Brain Topogr 13: 115–125.

Staljanssens W, Strobbe G, Holen RV et al. (2017). Seizure onset zone localization from ictal high-density EEG in refractory focal epilepsy. Brain Topogr 30: 257–271.

Stam CJ, Van Dijk BW (2002). Synchronization likelihood: an unbiased measure of generalized synchronization in multivariate data sets. Phys. D Nonlin Phenom 163: 236–251.

Stefan H, Hummel C, Scheler G et al. (2003). Magnetic brain source imaging of focal epileptic activity: a synopsis of 455 cases. Brain 126: 2396–2405.

Strogatz SH (2001). Exploring complex networks. Nature 410: 268–276.

Sunaert S (2006). Presurgical planning for tumor resectioning. J Magn Reson Imaging 23: 887–905.

Urbano A, Babiloni C, Onorati P et al. (1998). Dynamic functional coupling of high resolution EEG potentials related to unilateral internally triggered one-digit movements. Electroencephalogr Clin Neurophysiol 106: 477–487.

Uutela K, Hamalainen M, Somersalo E (1999). Visualization of magnetoencephalographic data using minimum current estimates. Neuroimage 10: 173–180.

Van De Steen F, Faes L, Karahan E et al. (2016). Critical comments on EEG sensor space dynamical connectivity analysis. Brain Topogr. [Epub ahead of print].

Von Ellenrieder N, Pellegrino G, Hedrich T et al. (2016). Detection and magnetic source imaging of fast oscillations (40-160 Hz) recorded with magnetoencephalography in focal epilepsy patients. Brain Topogr 29: 218–231.

Vrba J, Robinson SE (2001). Signal processing in magnetoencephalography. Methods 25: 249–271.

Wang Y, He B (1998). A computer simulation study of cortical imaging from scalp potentials. IEEE Trans Biomed Eng 45: 724–735.

Wang JZ, Williamson SJ, Kaufman L (1992). Magnetic source images determined by a lead-field analysis: the unique minimum-norm least-squares estimation. IEEE Trans Biomed Eng 39: 665–675.

Wendling F, Ansari-Asl K, Bartolomei F et al. (2009). From EEG signals to brain connectivity: a model-based evaluation of interdependence measures. J Neurosci Methods 183: 9–18.

Wilke C, Van Drongelen W, Kohrman M et al. (2009a). Identification of epileptogenic foci from causal analysis of ECoG interictal spike activity. Clin Neurophysiol 120: 1449–1456.

Wilke C, Van Drongelen W, Kohrman M et al. (2009b). Neocortical seizure foci localization by means of a directed transfer function method. Epilepsia 51: 564–572.

Wilke C, Worrell G, He B (2011). Graph analysis of epileptogenic networks in human partial epilepsy. Epilepsia 52: 84–93.

Willemse RB, Hillebrand A, Ronner HE et al. (2016). Magnetoencephalographic study of hand and foot sensorimotor organization in 325 consecutive patients evaluated for tumor or epilepsy surgery. Neuroimage Clin 10: 46–53.

Wu JY, Koh S, Sankar R et al. (2008). Paroxysmal fast activity: an interictal scalp EEG marker of epileptogenesis in children. Epilepsy Res 82: 99–106.

Xu XL, Xu B, He B (2004). An alternative subspace approach to EEG dipole source localization. Phys Med Biol 49: 327–343.

Yang L, Wilke C, Brinkmann B et al. (2011). Dynamic imaging of ictal oscillations using non-invasive high-resolution EEG. Neuroimage 56: 1908–1917.

Zelmann R, Lina JM, Schulze-Bonhage A et al. (2014). Scalp EEG is not a blur: it can see high frequency oscillations although their generators are small. Brain Topogr 27: 683–704.

Zumsteg D, Friedman A, Wennberg RA et al. (2005). Source localization of mesial temporal interictal epileptiform discharges: correlation with intracranial foramen ovale electrode recordings. Clin Neurophysiol 116: 2810–2818.