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Research Article

Electric Source Imaging and its Clinical Applications: A Review

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Abstract

Electric Source Imaging (ESI) is an emerging technique that identifies the source of brain electrical activity by utilizing the spatial and temporal components of EEG recorded on the scalp. ESI appears to be a promising methodology for epilepsy evaluation as well as other neurological disorders based on the present body of research; nevertheless, the precise clinical relevance of ESI localization remains to be explored. This review paper aims to present the basic theoretical aspects of ESI and its clinical applications along with the currently available softwares for implementing this cutting-edge technology by examining some of the key studies performed in the field, with emphasis given to clinical work published in the recent years.

Keywords: Epilepsy; Presurgical Evaluation; Source Localisation; Forward and Inverse Solution

Introduction

Epilepsy is a common chronic neurological disorder with millions of people affected worldwide. It is characterized by recurrent seizures, defined as the period of sign or symptoms that occurs due to the uncontrolled/abnormal electrical activity in the brain [1,2]. If seizures persist after 2 years of treatment and/or after treatment with 2-3 appropriately selected medications in sufficiently high individually tolerated doses with satisfactory patient compliance, epilepsy is deemed refractory or pharmaco resistant [3] and these patients usually as polytherapy often uses heavy dose of antiepileptic drugs [AEDs].Thus the burden of drug toxicity and the insufficient control of seizures imposes significant impact on the quality of life of the patient and increases the morbidity and mortality rate. In those patients with drug resistant/medically refractory epilepsy surgical removal of the region which is responsible for the generation of seizures [epileptogenic zone] is the only means to achieve seizure freedom or to significantly reduce the severity and frequency of the occurrence of seizures [4-6].Therefore the primary aim of epilepsy surgery is to define the resection borders of the epileptogenic area while keeping the “eloquent cortex” intact (i.e. cortical region vital for a certain neurological function) [7].This entails a thorough presurgical workup to identify the epileptogenic zone. Presurgical evaluation involves various invasive and non-invasive techniques such as multichannel EEG and video monitoring, high resolution magnetic resonance imaging [MRI], functional MRI, single photon emission computed tomography [SPECT], positron emission tomography [PET] and several neurological, neuropsychological test to identify the zone [8]. If the aforementioned methods show concordant information without any overlap of the regions responsible for speech or language, movement, sensation then the clinicians infer the location of epileptogenic zone from the potential surgical candidates.

Electric source imaging [ESI], a highly recommended technique based on scalp EEG which allows the estimation of source of electrical activity of the underlying brain region plays a vital role in the presurgical evaluation of epilepsy [9]. Advancements in science

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and technology has allowed a wide expansion of ESI technique in recent years. This cutting-edge technology can be used to evaluate the dynamics of the epileptic network with great temporal resolution, boosting our understanding of neurophysiological mechanism of epileptic seizures. The following review aims to explore the fundamentals of ESI and its current role in epilepsy and other clinical practice.

Principles of ESI

The concept of electrical source localization has been explored since the inception of the EEG [10]. Though ESI aims to localize the source of scalp-recorded potentials, in theory, solving the inverse problem which is the determination of precise location of an electrical source in the brain solely from scalp-recorded EEG data is impossible [11]. The forward problem must be resolved first in order to tackle the EEG inverse problem. Accuracy of source localisation highly depends on the accurate forward head modelling [12]. It is accomplished by various advanced mathematical formulations [13]. Key steps involved in EEG source imaging is explained using figure 1.

According to poisons equations the propagation of current flow generated by the synchronised post-synaptic potentials of pyramidal neurons in the brain causes the electric potential variations between electrodes placed on different scalp locations [14]. This propagation, however is not uniform and is attenuated by the high resistance of the skull. And so when solving the forward problem [determination of potential at the electrode location generated by a known source in the brain], this attenuation factor has to be considered significantly and then modelled [15]. Also, as the head is not exact spherical in shape, distance of each scalp electrode to the centre of the head also varies. Therefore the exact electrode location of each should be known [16]. Hence the solution of forward problem is determined by specifying a set of conditions for the model [17]. It is this conditions which makes each model different from one another. The head modelling can range from a simple spherical shell model [analytical] to complex realistic model [numerical] which can model the brain, CSF, skull and scalp surfaces. It is highly suggested to use the anatomical information derived from individual MRI scan to be used for modelling as it has proven to be more efficient in terms of resolution, resulting in an improved solution for the inverse problem. The commonly used technique for realistic modelling/numerical is finite element method (FEM), finite difference method (FDM) and boundary element method (BEM). Among these methods FEM has proven to be having better resolution but with higher computational complexity [18] as it covers a wider region and BEM is comparatively simpler compared with FEM and FDM [19]. At the same time, FEM and FDM tackles the inhomogeneity problem of brain. Solving the forward problem computes a specific potential field at the scalp surface for the specified electrical source, thereby giving a unique solution [20].

Once the proper head model has been built and lead field is constructed, next step is to solve the inverse problem which is ill posed. It is the process of determining the intracranial source which produces the EEG potential on different electrode locations. This is a major challenge in ESI as it does not have a unique solution [21] i.e., a very large number of different source distributions can produce the same potential field on the scalp.

Generally there are two approaches for solving the inverse problem. They are parametric [dipole] and non-parametric/imaging/distributed source model/distributed inverse solution approaches. The main difference between the two lies in the a priori assumption of the number of fixed dipoles [22]. In non-parametric approach, it is presumed that the sources are aligned perpendicular to the cortical sources and are considered as intracellular currents within the pyramidal neurons in cortical surface. Therefore dipole sources with fixed orientation and fixed location is used to represent the tessellation elements distributed on the cortical surface or the entire brain volume [23]. i.e., the brain electrical activity is reconstructed on each point of the solution space and each solution point is considered as a location of the current source. As the only calculation is the estimation of the amplitude of these dipole sources, the source estimation is linear in distributed/non-parametric modelling. Whereas in the dipolar approach, fixed number of dipoles are assumed a priori whose location and direction are unknown.ie it is assumed that the surface measurements can be modelled using smaller number of current sources [24]. As the number of unknown elements in this model is less than or equal to the known/independent measurements, this is a nonlinear approach of solving the inverse problem [25]. There are a variety of algorithms introduced in both parametric and non-parametric approaches. Some of the commonly used approaches in non-parametric are minimum norm, weighted Minimum Norm, Laplacian weighted minimum norm (LORETA), Local autoregressive average (LAURA), EPIFOCUS etc. and in parametric approach commonly used algorithms include equivalent current dipole, Multiple Signal Classification (MUSIC), beam forming methods [26]. However, there is no proven gold standard that would provide an assessment of the goodness of inverse solutions.

EEG signals, whereas the forward solution calculates a potential distribution map with the advancements in technologies, many softwares both academic and commercial have been developed which improved the accuracy and performance of source localisation by implementing different forward and inverse [head and source] models. Some of the most commonly used academic software packages [27] include EEGLAB, FIELDTRIP, CARTOOL, SPM etc and commercial softwares include BESA, GEOSOURCE, CURRY, BRAIN VOYAGER. Forward and inverse models used in each of these software are included in table 1. Most of these softwares are developed in MATLAB environment and are compatible with laptop computers as well as standard desktop computers with its own unique features such as larger user community, user interaction emphasised through GUI, group level ICA etc. However most of these software packages require the user to have basic knowledge of programming languages to fully understand and use the software.

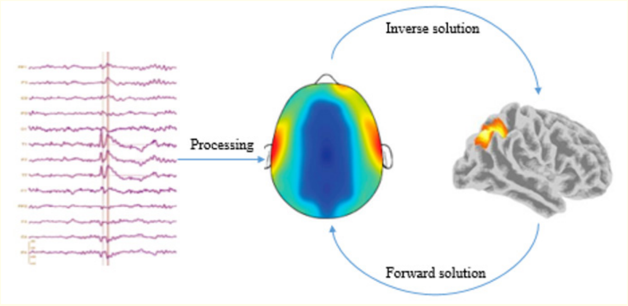

Figure 1: Key steps in Electric Source Imaging; Inverse solution localises the sources from the processed.

Software	Forward model	Source model	Interface/ language
Academic softwares			
BRAINSTORM [28]	Single sphere, Overlapping spheres, Realistic head model [BEM & FEM]	Minimum norm imaging Beamforming [LCVM] Dipole modelling	Matlab (and Java)
CARTOOL [29]	Spherical model [Spherical Model with Anatomical Constraints and Locally Spherical Model with Anatomical Constrains], Realistic head model	WMN, LORETA, LAURA, EPIFOCUS	C++
EEGLAB [30]	Spherical model [Single layer sphere, spheroid and 3-4-layer sphere], Realistic head model [BEM, FEM]	Minimum norm estimate LORETA, Beamforming MUSIC	MATLAB
FIELDTRIP [31]	Spherical model [single sphere, multiple concentric spheres with up to 4 shell], Realistic head model [BEM, FEM]	Minimum norm estimate, Beamforming	MATLAB
SPM [32]	Spherical head model, Template head model, Realistic head model [BEM, FEM]]	Beamforming, Bayesian source estimation	MATLAB
Commercial softwares			
BESA [33]	Multi-shell ellipsoidal head models, Template head model, Realistic head model [BEM, FEM]	Minimum norm image, LORETA, sLORETA, swLORETA, LAURA RAP-MUSIC	MATLAB
BRAIN VOYAGER [34]	Spherical head model, Realistic head model	Beamformer, Minimum Norm, LORETA, LAURA	C++
CURRY [35]	Spherical shell head model Realistic head model [BEM, FEM]	Minimum norm, sLORETA, swLORETA, SWARM, ssLOFO, FOCUSS, L1 Norm, Lp Norm, LORETA, LAURA, MUSIC, RAP-MUSIC	MATLAB
GEOSOURCE [36]	Spherical head model Realistic head model [FDM]	MNLS, LORETA, sLORETA, and LAURA	MATLAB

Table 1: Different softwares available for head and source modelling.

BEM: Boundary Element Method; FEM: Finite Element Method; FDM: Finite Difference Method; LCMV: Linear Constraint Minimum Variance; WMN: Weighted Minimum Norm Solution; LORETA: Low Resolution Electromagnetic Tomography; sLORETA: Standardised Low Resolution Electromagnetic Tomography; LAURA: Local Autoregressive Average; MUSIC: Multiple Signal Classification; MNLS: Minimum Norm Least Squares; SWARM: sLORETA-Weighted Accurate Minimum Norm.

Interictal or ictal signal?

ESI uses interictal spikes as the major contributor of signal to localise the epileptogenic zone during presurgical evaluation. As the accuracy of ESI technique depends on the SNR [signal to noise ratio], similar spikes has to be averaged before the actual ESI computation begins [37]. Also the propagation of epileptiform activity can affect accuracy of source localisation. Hence the exact time point at which the ESI is performed also matters. The accuracy of ESI for source localization of interictal spikes has been the subject of numerous studies that have been published so far [38-40].

Even though ESI based on interictal spikes has proved its performance in localisation in most patients, performing ESI of seizure onset is intriguing. As the EEG pattern varies from one seizure to other, instead of averaging the seizure onsets ESI of EEG at the seizure starting point is a possible approach. In many studies the accuracy of ictal ESI is comparable with interictal spike ESI [41-43]. However source imaging using ictal EEG is complex and time consuming due to many reasons. Often ictal EEG is susceptible to muscle and movement artifacts resulting in low signal to noise ratio. Besides that ictal EEG can be recorded only if there is enough synchronization of cerebral activity. In addition, often ictal ESI pinpoints not only the ictal onset zone but also the brain region where seizure discharges propagate during an early ictal event [44].

Current relevance of ESI

The combination of high temporal resolution of EEG and spatial evaluation of sources provided by ESI imparts non-invasive monitoring of brain areas that a single modality cannot. Even though electric source imaging technique has proven its clinical application and usefulness, it still remains underutilized. This underutilisation is mainly due to the use of reduced number of electrodes in clinical practice [usually ranges from 16 to 60] and availability of many algorithms for solving inverse problem which are not been standardised. However the main application of ESI lies in localising the epileptogenic zone and hence in the presurgical evaluation of epilepsy. In determining the efficacy and accuracy of ESI, it is often compared against a gold standard or desired outcome in diagnostic imaging [45].

In a study of 152 patients with refractory focal epilepsy, ESI based on 128-256 high resolution channel recordings showed specificity above 80% [46]. The diagnostic accuracy of ESI was comparable to that of MRI and PET. Another study of epileptic patients showed sensitivity of 84% and specificity of 84% when ESI was performed based on high resolution EEG, as it compared with standard EEG recording showed only 66% sensitivity [47]. ESI also has application in pediatric epilepsy. In a study of 30 children with epilepsy, ESI could correctly localise the epileptogenic zone in 27 with 90% accuracy which is then compared favourably with PET and ictal SPECT [48]. Another cohort study of 30 to 60 paediatric patients pinpointed the specificity of electric source imaging and feasibility of low-density EEG recordings during the ESI analysis [49].

Studies have showed that the application of ESI can also be extended to certain neurodegenerative diseases such as Alzheimers since the brain activation in the cognitive region alters with disease progression. In a recent study, eloreta technique has been used for the diagnosis of Alzheimers disease [50].In another study, sLORETA technique of ESI has been used to asses OCD [Obsessive-Compulsive Disorder] and thereby to evaluate the activity of intracortical EEG sources in OCD patients [51].Furthermore, in patients of diabetes mellitus [DM] a study has been conducted using the sloreta techniques of source localisation and diaclosed that the structural and function changes in DM is due to the central cortical areas of gamma band and frontal region activity of delta band [52]. More interestingly, ESI is also effectual in identifying the area responsible for sleep spindle generation and the areas and activities associated during NREM sleep stages. It can also be used for estimating the brain areas affected by sleep arousal disorders [53,54].

Conclusion

In this paper we have outlined the fundamentals of ESI with the currently available software for solving forward and inverse problems and its clinical applications. We have reviewed literatures to point that ESI is an effective teqnique to be used in clinical applications of several neurological disorders in localising the brain sources, especially in the presurgical evaluation of epilepsy. Apart from the cost benefits of ESI technique, the non-invasive nature of source localisation brings healthcare advantages such as surgical site infection risks as intracranial invasive recordings can be eliminated. Through this review we also tried to point out the research progress of ESI in both clinical and cognitive applications and hence we believe that this cost-effective technique will earn a place in the routine clinical practice of several neurological disorders in foreseeable future.

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