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The Role of Electrical Source Imaging in Pediatric Epilepsy and Pre-Surgical Evaluation

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SUMMARY

Epilepsy is a neurological disorder involving frequent and involuntary seizures. Caused by an imbalance of electrical activity in the brain, epilepsy is typically treated with anti-epileptic drugs to reduce or cure symptoms. Unfortunately, there are individuals who do not respond to medication. When all other treatment options have been exhausted, doctors might recommend surgery to remove the area of the brain thought to be the cause of seizures (the epileptogenic zone). This area is determined by a thorough pre-surgical evaluation employing a variety of diagnostic imaging technologies. The goal of this evaluation is to identify the epileptogenic zone. Unfortunately, the use of invasive tests can potentially scar brain tissue and traditional methods of determining the epileptogenic zone can potentially be inaccurate. Electrical source imaging (ESI) is a non-invasive imaging software proposed as an additional tool to be included within the pre-surgical evaluation of children with epilepsy. ESI combines the patient's brain scans and recordings of electrical activity to identify the potential sources of seizures. Despite evidence supporting its use, ESI is underutilized in clinical settings and within pediatric research. The following review looks into the literature surrounding ESI and advocates for its inclusion within the pre-surgical evaluation of children with epilepsy.

ABSTRACT

Children with drug-resistant epilepsy undergo an extensive pre-surgical evaluation to determine the part of the brain thought to be the cause of seizures. The employment of non-invasive diagnostic imaging tools plays an important role in establishing surgical candidacy, preventing the need for invasive procedures. Electrical source imaging (ESI) has been explored as a modern alternative to traditional diagnostic techniques in pre-surgical workup. Through computational analysis of recorded electric potentials and individualized head scans, ESI provides a non-invasive method of obtaining more accurate localizations. However, its use within the clinical setting is limited. The following review looks to examine the literature surrounding ESI and advocates for its inclusion within the pre-surgical workup of children.

Keywords: Electrical source imaging (ESI), electrical source localization, epilepsy, pediatrics, pre-surgical evaluation, epileptogenic zone

INTRODUCTION

Epilepsy is a neurological disorder that is commonly treated with anti-epileptic drugs to control seizures and improve quality of life. A large proportion of children diagnosed with epilepsy do not respond to medication and are often referred for surgery as a curative measure.[1] This involves a detailed and extensive pre-surgical evaluation to identify the epileptogenic zone, a hypothetical region of the cortex that, once resected, provides the patient with seizure freedom.[2] However, this area is only confirmed retroactively if the resection provides seizure freedom. Non-invasive imaging techniques are used to determine this region via the presence of anatomical or physiological anomalies.[3] Clinicians are able to infer the location of the epileptogenic zone and identify surgical candidates if these tests show concordant information and there is no overlap with the parts of the brain responsible for sensation, movement, language, or speech.[2]

The electroencephalogram (EEG) is one such diagnostic tool that plays a pivotal role in understanding the abnormal neuronal activity observed in epilepsy. EEGs measure and record the synchronous firing of cortical neurons using electrodes placed on the scalp.[4] Video analysis of EEG recordings is a crucial first step during the pre-surgical evaluation of children.[5] Traditionally, these recordings are visually analyzed for distinctive waveforms and spike patterns to approximate sources of epileptic activity within the brain. The ictal onset and irritative zone are two regions of interest that can be defined through EEG analysis. The ictal onset zone is defined by the EEG waves that occur at the beginning of the seizure (the ictal phase), while the irritative zone is identified by the spikes that occur between seizures (the interictal phase).[2]

EEGs play a pivotal role during the early stages of pre-surgical evaluation, helping neurologists build towards a general understanding of the epileptogenic zone. However, visual analysis of these recordings lacks the accuracy required to define the resection margins. Computational analysis, known as electrical, or EEG, source imaging (ESI), has shown promise in overcoming these limitations. Through a set of mathematical algorithms, ESI maps potential sources of EEG activity onto a magnetic resonance imaging (MRI) head model of the patient.[6,7]

The field of ESI has expanded exponentially in recent years. Advancements in software technology have allowed for more robust and rapid source localization of EEG recordings. Utilizing readily accessible information in MRI scans and EEG recordings, ESI presents itself as a safe and effective tool within pre-surgical workup. Ictal ESI determines the ictal onset zone from ictal EEG waves, while interictal ESI determines the irritative zone using interictal EEG spikes. In conjunction with other functional imaging techniques, ESI is a highly recommended modality that can improve the localization of the epileptogenic zone.[8]

In spite of a growing body of evidence and a need for non-invasive diagnostic tools, ESI is underutilized within the field of pediatric epilepsy. EEGs used for ESI analysis are typically recorded with large electrode arrays containing 100 to 200 electrodes. These high-density (HD) recordings have shown to yield more accurate results and provide greater spatial resolution with increased electrodes.[3,9] However, their use is impractical and cumbersome for long-term EEG monitoring.[10] Low-density (LD) recordings employing 20 to 30 electrodes, demonstrate similar accuracy to HD-EEG and presents an encouraging alternative for pediatric epileptology.[11-14]

There is a lack of studies looking at the use of low-density ESI in children during pre-surgical workup and, to date, none comparing ictal to interictal ESI.

The following review aims to examine the current role of electrical source imaging in clinical epileptology and its practicalities as a diagnostic tool in pediatric surgery.

FUNDAMENTALS OF ESI

The concept of electrical source localization has been explored since the inception of the EEG.[15] With recent advances in ESI, researchers have gained a better understanding of how electric fields are generated and propagated deep within the cortex. ESI attempts to localize the source of scalp-recorded potentials by solving for a set of forward and inverse problems.

The inverse problem addresses the guiding question behind source localization: determining the source of electrical activity in the brain from a given EEG recording. The answer to this problem is theoretically impossible as there can be an infinite number of potential sources for the recorded electrical potential. In light of this, a forward problem is created where the scalp potential is determined from a hypothetical source in the brain. As a single, unique potential can be calculated, the forward problem is solved to address the inverse.[6,9]

The forward problem accounts for the conduction of electrical signals towards the scalp via the use of a spherical shell or realistic head model. The spherical shell model is a simpler model using a sphere to represent the skull and the brain, ignoring more complex factors that might affect the spread of electrical activity towards the scalp. Realistic head models are based on the individual MRI scans of each patient and are preferred for their increased complexity and specificity. Popular techniques include the boundary element method, the finite element method, and the finite difference method.[6,10] These methods vary technically but have all shown to provide more accurate localization results than spherical models.[16,17]

The inverse problem further restricts the possibility of solutions by using a set of models. Single dipole, multiple dipole, and distributed source models are most prevalent within clinical ESI. Dipole models draw from the assumption that recorded potentials derive from either a single source or multiple sources in the brain. Dipoles are fitted using different computer algorithms to a location in the brain that is calculated to most likely be the epileptogenic focus. A single dipole or dipole cluster indicates where the epileptogenic zone is likely to be. In contrast, distributed source models assume that each potential can be derived from thousands of sources across the brain. This model creates an overlapping map across the cortex of where the epileptogenic zone is most likely to be found.[6,10]

CLINICAL RESEARCH IN ESI

In order to examine the efficacy of ESI, studies compare ESI results to a desired outcome, or a gold standard, in diagnostic imaging.[18] Intracranial EEG (iEEG) localization and post-operative success are two commonly used standards in ESI research. iEEG is an invasive test that measures the spikes recorded from electrodes inserted directly over or into the brain. iEEG recordings can localize both the irritative and ictal onset zone, demonstrating greater spatial resolution than EEG.[2] One study retrospectively compared iEEG localization of the irritative and epileptogenic zone to ESI in 38 patients. ESI accurately localized the irritative zone to within 15 mm of iEEG analysis and was within the resection margins for 80% of seizure-free patients, demonstrating strong overlap with the epileptogenic region.[19] However, it should be noted that iEEG is an imperfect diagnostic standard and can run the risk of infection or hemorrhage.[8,20] In rare situations, the epileptogenic zone can be missed entirely if this region is located deeper within the brain.[6,21]

Comparisons to post-operative outcomes provide clinically relevant information regarding the efficacy of ESI. Seizure freedom following surgery indicates definitive proof of the epileptogenic zone. Correct localization is observed if the ESI result is within the resected region for seizure-free patients or the ESI result is outside of the resected region in patients with persistent seizures. Conversely, a false ESI localization is indicated by ESI results outside of the resected region in seizure-free patients or results within the resected region of unsuccessful surgeries. Several studies have looked at the effectiveness of ictal and interictal ESI when compared to the resected zone.[22-24] A prospective study, conducted by Brodbeck et al., examined the specificity and sensitivity of ESI in a cohort of 152 patients.[3] The use of interictal HD-ESI in combination with individual MRI head models compared favourably with established diagnostic tools. These included structural MRI, ictal single-photon emission-computerized tomography (SPECT), and positron emission tomography (PET) results. In fact, ESI was found to be more accurate than both SPECT and PET.[3] Additional studies conducted have further depicted the strong predictive value of HD-ESI and its strong concordance to other diagnostic measures.[22-24] Magnetoencephalography (MEG) is another important non-invasive modality worth mentioning. MEG is a resource-intensive test measuring the magnetic fields produced by electrical activity in the brain. MEG results are considered an accurate measure of the epileptogenic zone, acting as a strong predictor of post-operative seizure freedom.[25,26] While less accurate than MEG, the majority of ESI epileptogenic zone localizations were concordant with iEEG findings and clinical localizations.[27,28]

Most of these studies highlight the use of ESI with interictal waveforms to determine the irritative zone. This is in large part due to the difficulty in analyzing ictal patterns and the presence of artifacts disrupting EEG signals. Despite the preference for interictal ESI, there is some debate surrounding its overlap with the epileptogenic region.[29,30] This has led to a growing body of research towards the use of ESI in ictal onset zone localization. Studies have demonstrated the accuracy of both LD- and HD-ictal ESI with post-operative outcomes.[11,23,29] When combined with a functional connectivity analysis, a tool used to determine the spread of seizures and connectivity of pathological networks in the brain, there is a significant improvement to ictal source localization.[14,24] Comparative studies of ictal to interictal ESI depict similar accuracy in source localization and present both approaches as viable diagnostic methods.[30,31] The evidence points to the positive predictive value of both ictal and interictal ESI and their ability to provide clinically relevant information.

USE OF ESI IN PEDIATRIC EPILEPSY

Despite evidence indicating the reliability of ESI in adults, there are few studies assessing the predictive value in a pediatric population. Two papers examining the interictal ESI analysis of LD-EEG recordings in children saw correct localization of the epileptogenic zone in a majority of patients. ESI localizations compared favourably with PET and ictal SPECT and, in fact, displayed a higher accuracy in MRI-negative cases, which are arguably more difficult to diagnose. Using large cohorts of 30 to 60 patients, these studies demonstrate the specificity of ESI and the feasibility of LD-EEG recordings in ESI analysis.[12,13] Additional comparisons of interictal ESI to MEG in a pediatric population observed a strong correlation between HD-ESI localization and the resected region, suggesting that HD-ESI might provide similar accuracy to MEG data.[32]

LIMITATIONS OF ESI

There are a few underlying concerns regarding ESI research, preventing its widespread utilization within clinical epileptology. Particularly, there appears to be a lack of standardization across clinical research.

A recent systematic review assessed the clinical validity of papers relating to ESI and MEG source imaging (MSI). They determined studies were a reliable indicator of epileptogenic source localization if they utilized HD-ESI, included more than ten patients, and utilized post-surgical outcomes of at least ten months after operation as the reference standard. From 51 studies assessing MEG or ESI, 11 met the aforementioned criteria.

Additionally, they observed a lack of standardization with the use of inverse and forward models and what is considered an accurate ESI localization.[33] The authors address a need for standardization across clinical studies and to explore the efficacy of source localization in long-term prospective studies.[32]

Regarding pediatrics, a great deal of the literature surrounding ESI focuses on the localization of HD-EEG recordings utilizing 128 to 256 electrodes.[10] As previously mentioned, this method of recording is impractical for children and presents itself as a major detractor toward the implication of ESI in epileptogenic centers. Additional studies related to LD-ESI can work to address this concern and to warrant the widespread use of ESI in clinical settings.

CONCLUSION

Within children, there is an apparent need for non-invasive measures that effectively localize the epileptogenic zone. In conjunction with other diagnostic measures, ESI can work to guide the use of invasive modalities and improve the general understanding of the epileptogenic zone in patients. There is already a large body of evidence supporting the inclusion of source localization within the pre-surgical workup of children. ESI exhibits strong concordance with other established imaging techniques, namely SPECT, PET, and MRI scans, demonstrating high localization values. Taking advantage of readily accessible information in EEG recordings, ESI presents itself as an efficient method of predicting sources of abnormal neuronal activity in epilepsy. However, there is a lack of research for pediatric populations and for comparisons of ESI localization values to different epilepsy subtypes. Future studies must continue to examine the localization of both the irritative and ictal onset zone and create a clinical standard for conducting ESI.

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