Localisation of Focal Epileptic Activity in Children Using High Density EEG Source Imaging*

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Summary

In children suffering from epilepsy, a better understanding of the brain networks involved in epileptic activity is of great clinical and scientific importance. Non-invasive mapping of the epileptic focus can be performed with EEG source imaging (ESI), a technique based on scalp EEG recordings to estimate the localisation of the intra-cerebral electric sources. Recent technological development now allow recording high density EEG with only a short preparation and recording time (ca. 30 minutes in total) making this technique particularly suitable for clinical use in children, even when awake or very young. In children suffering from medically refractory focal epilepsy, ESI is often highly concordant with the epileptogenic zone and can be used in epilepsy surgery to improve the chance of post-operative seizure freedom, provided a sufficient number of electrodes is used, as routinely performed in our centre. More globally, the mapping of onset and propagation of epileptic discharges helps better understanding the pathophysiology of certain epileptic conditions and the potentially associated neurological and cognitive dysfunction. In this article, we present the methodological background and clinical studies of ESI and concordance with other imaging techniques in pediatric epilepsy.

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Keywords: EEG source imaging, pediatric epilepsy, surgery

Lokalisierung von fokaler epileptischer Aktivität bei Kindern mit Hilfe des „High Density EEG Source Imaging“

Ein besseres Verständnis der zugrunde liegenden Netzwerke im Gehirn von epilepsiekranken Kindern ist von grosser klinischer und wissenschaftlicher Bedeutung. Die nicht-invasive Kartierung des epileptogenen Fokus kann mit der EEG-Quellenlokalisation (EEG Source Imaging, ESI) durchgeführt werden, einer Technik, die auf Skalp-EEG-Ableitungen basiert und die Lokalisation der intrazerebralen elektrischen Quellen erlaubt. Neueste technische Entwicklungen erlauben die Ableitung eines hochauflösenden EEGs mit einer kurzen Vorbereitungs- und Ableitezeit (ca. 30 Min. insgesamt), was die Technik besonders für Kinder, auch für sehr kleine Kinder, interessant macht. Bei Kindern mit pharmakoresistenter fokaler Epilepsie ist ESI oft hochkonkordant mit der iktalen epileptogenen Zone und kann zur Vorbereitung von epilepsiechirurgischen Eingriffen benutzt werden, um die Chance post-operativer Anfallsfreiheit zu erhöhen, vorausgesetzt eine ausreichende Zahl von Elektroden wird appliziert, wie es routinemässig in unserem Zentrum durchgeführt wird. Global gesehen ermöglicht die Kartierung des Beginns und der Propagation von epileptogenen Entladungen, die zugrundeliegende Pathophysiologie von bestimmten Epilepsie-Erkrankungen besser zu verstehen mit ihren eventuell assoziierten neurologischen und kognitiven Dysfunktionen. In diesem Artikel präsentieren wir den methodologischen Hintergrund sowie klinische Studien zu ESI und Konkordanz mit anderen Bildgebungsverfahren in pädiatrischer Epilepsie.

Schlüsselwörter: EEG-Quellenlokalisation, pädiatrische Epilepsie, Chirurgie

Localisation des sources d’une activité épileptique focale chez les enfants par imagerie EEG

Chez les enfants souffrant d’épilepsie, une meilleure compréhension des réseaux cérébraux impliqués dans l’activité épileptique est d’une grande importance clinique et scientifique. L’imagerie non-invasive du foyer épileptique peut être réalisée avec l’imagerie de source EEG (EEG Source Imaging, ESI), une technique basée sur l’EEG de scalp pour estimer la localisation des sources électriques intracérébrales. Les développements technologiques récents permettent désormais d’utiliser l’EEG haute densité avec un temps de préparation

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et d'enregistrement courts qui rendent cette technique particulièrement adaptée à l'utilisation clinique chez les enfants, même lorsqu'ils sont éveillés ou très jeunes. Chez les enfants avec épilepsie pharmaco-résistante, l'ESI est souvent hautement concordante avec la zone épileptogène et peut guider la chirurgie de l'épilepsie afin d'augmenter les chances de supprimer les crises après l'opération, pour autant qu'un nombre suffisant d'électrodes soit utilisé, comme c'est systématiquement le cas dans notre centre. Plus globalement, la localisation des zones d'initiation et de propagation des décharges épileptiques aide à mieux comprendre la pathophysiologie de certaines conditions épileptiques et les dysfonctions neurologiques et cognitives associées. Dans cet article, nous présentons les bases méthodologiques de l'ESI, les études cliniques et la concordance avec d'autres techniques d'imagerie dans l'épilepsie pédiatrique.

Mots-clés : Imagerie de source EEG, épilepsie pédiatrique, chirurgie

Background

Around 1 - 2% of children are affected by recurring seizures. Poor control of epilepsy is associated with important morbidity as well as devastating effects on psychomotor development and quality of life. In children with medically-refractory seizures, epilepsy surgery can lead to seizure freedom in patients carefully selected by presurgical evaluation. The goal of epilepsy surgery is to alleviate seizures and there is a wide consensus that achieving seizure control is also beneficial with respect to neurological and cognitive development although dedicated confirmatory studies are still lacking [1]. The use of some of the imaging tools in children is often limited by the level of collaboration and sedation is frequently required for imaging (structural MRI, PET, SPECT) causing increased risk and logistical needs so that non-invasive tools for mapping epileptic activity in awake children are needed. These requirements can be met by EEG source imaging (ESI), a technique based on scalp EEG recordings to estimate the localisation of the intra-cerebral electric sources that allows recording times and conditions suitable for children and yield robust localisation in presurgical evaluation. More generally, ESI can be applied to study the dynamics of epileptic network with very high temporal resolution to increase our understanding in the mechanisms underlying varying seizure disorders.

This article gives an overview of the integration of ESI in the presurgical evaluation in pediatric epilepsy, from methodological background to clinical studies and concordance with other imaging tools.

Presurgical epilepsy evaluation: EEG recordings and ESI

Interictal and ictal EEG are the most important diagnostic tools in the presurgical evaluation of children with medically intractable focal epilepsy. Multichannel video-EEG recordings can be performed continuously for several days (LTM = long term monitoring of EEG), and seizures as well as interictal epileptiform discharges are recorded. The examination of the EEG during interictal discharges before, during, and after seizures has traditionally been performed through visual inspection of the traces. This kind of analysis certainly has a considerable localizing value in the hands of an experienced epileptologist, but it has been argued that traditional trace analysis of the EEG only provides a fraction of the information that is available in the signal [2]. Almost all clinical EEG laboratories have now moved from paper-EEG to digitally recorded EEG, and advanced analysis of the signals with modern signal processing tools have thus become possible. EEG Source Imaging (ESI) is a technique, which allows for the 3-dimensional reconstruction of the electric active areas in the brain based on the surface recorded EEG.

EEG Source Imaging (ESI) of interictal epileptiform activity: principles

During the past 15 years different EEG source imaging (ESI) techniques have been used for the purpose of localizing the focus of interictal epileptiform activity with a very high temporal resolution corresponding to the sampling rate of the EEG. The oldest are "equivalent current dipole" localization methods, where a single or several current dipole(s) are used to model the source of the EEG recorded at the scalp [3-14]. Distributed inverse solution techniques [13, 15-24] represent better models of extended neuroelectric sources, as found in epileptic activity, but require further mathematical assumptions for the localisation. All these techniques are based on a model of the propagation of electrical activity through the head (brain and other tissues): the forward model, expressed as the lead field matrix. The inversion of this matrix using sophisticated algorithms provides the source localisation. The forward model can be based on a normalized head or on the MRI of individual patients, the latter offering a definite advantage when the epileptic activity occurs in the context of large brain lesions.

ESI: principle of the analysis procedure

Figure 1 shows the analysis procedure that is applied in the context of our presurgical evaluation workup. Similar analysis with variations is carried out in other centres using ESI. The analysis is first divided into

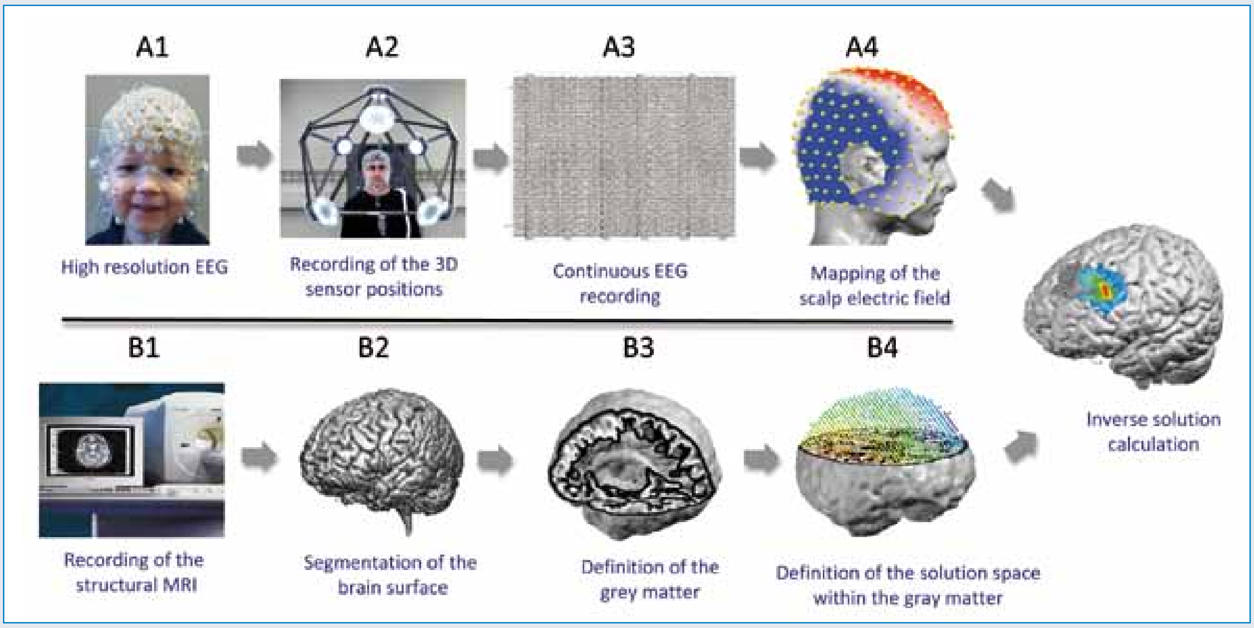

Figure 1: Principle of EEG Source Imaging
A) EEG recording and analysis: (A1): Distribution of the electrodes on the scalp (in this case 256 electrodes). (A2): The exact position of the electrodes on the head can be determined with the use of a photogrammetry system (Electrical Geodesic Inc). (A3): EEG recording and visual identification of interictal spikes. (A4): Averaging of similar epileptic spikes leading to a potential map for each timepoint during the epileptiform discharge.
B) Head model: (B1): structural MRI. (B2): Brain segmentation into different tissue classes. (B3): The grey matter is identified. (B4): The solution space is defined based on the gray matter definition. White matter, ventricles and large cavities within the brain are excluded from the solution space.
C) Inverse solution: For each timepoint within the spike wave complex, a mathematic algorithm (inverse solution calculation) is used to estimate the location of the epileptic source within the solution space (B4) based on the voltage map of that timepoint (A4).

the averaging of the interictal epileptic spike (A1 - 4: upper row) and the segmentation of the cortical grey matter from the anatomical MRI to define the solution space (B1 - 4: lower row). The inverse solution is then performed to localise the generators of the spike in the solution space.

(A1): Distribution of the electrodes on the scalp (in this case 256 electrodes). For short recordings (less than 2 hours) a saline sponge net is used, and this net only needs to be soaked in salt water and applied on the head without any need to glue the electrodes. The application time for this net is approximately 10 - 20 minutes. For recordings exceeding 2 hours another type of net is used, where the electrodes need to be attached with usual EEG paste. The application time for this net is somewhat longer, but normally no more than 30 - 45 minutes for 256 electrodes.
(A2): The exact position of the electrodes on the head can be determined with the use of a photogrammetry system (Electrical Geodesic Inc). The time required for this analysis is approximately 10 minutes.
(A3): EEG is recorded with 128 or 256 electrodes. Interictal spikes are identified through visual inspection of the traces using a standard bipolar montage.
(A4): An average of spikes with similar morphology and spatial distribution is performed, and a potential map is obtained for each timepoint during the epileptiform discharge. Given the high sampling rate of EEG (the number of times per second the EEG activity is measured) separate potential maps can be obtained with only a few milliseconds time difference. This high temporal resolution is especially important for the visualization of propagation of epileptiform activity.
(B1): A structural MRI recording is performed.
(B2): The brain is segmented into different tissue classes.
(B3): The grey matter is identified.
(B4): The solution space (the areas within the brain where the epileptic source will be allowed to be located) is defined based on the gray matter definition. White matter, ventricles and large cavities within the brain are excluded from the solution space.
(C): For each timepoint within the spike wave complex, a mathematic algorithm (inverse solution calculation) is used to estimate the location of the epileptic source within the solution space (B4) based on the voltage map of that timepoint (A4).

Methodological considerations

ESI studies, even performed using a standard clinical electrode setup with only 30 electrodes, have confirmed that inverse solutions can indeed provide an adequate definition of the epileptogenic zone (see clinical studies below). However, several theoretical studies indicate that a more dense sampling of the scalp electric fields should lead to a better accuracy of the source localizations [25 - 28]. These studies, using both simulations and real data, have indicated that inter electrode distances of around 2 - 3 cm (corresponding to at least 100 electrodes on an adult head) would be needed. Moreover, it is important not only that a sufficient number of electrodes are used, but also that the electrodes provide an adequate coverage of all areas of the brain. The consequences of insufficient coverage of the lower temporal areas in a patient with a temporal lobe focus are illustrated in **Figure 2**. In more recent investigations, different conduction properties between skull and brain have been assumed than previously [29-33], and it has also been taken into account that these conduction properties are different in children than in adults [34, 35]. These new studies concluded that even more than 100 channels would be required to optimally sample the brain electric fields. In a more clinically oriented study [36], significantly improved localization accuracy of interictal epileptiform activity was demonstrated when increasing from 32 to 64 recording channels. Further increase from 64 to 128 channels showed less significant improvement. This study has recently been repeated using a more accurate head model (Finite Difference Model), and with more realistic values for brain/skull conductivity differences [37]. The results of this study indicate that improvement in localization accuracy will occur up to at least 256 electrodes. Other clinical studies using either 64 channel [19, 38 - 40] or 128 - 256 channel EEG systems [36, 41 - 45], also demonstrate the high spatial precision that can be obtained with high-density EEG for the purpose of epileptic focus localization.

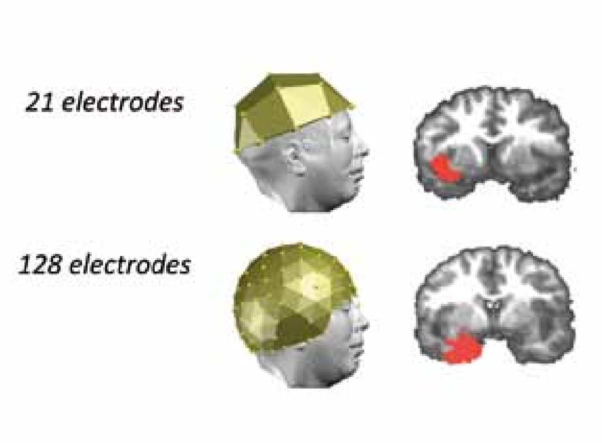

Figure 2: Example of the consequences of insufficient electrode coverage
The patient had an epileptic focus in the left temporal lobe confirmed by seizure freedom after temporal lobe resection. Top row: Due to the insufficient coverage of lower temporal areas with the 21 electrode setup, the epileptic source localizes outside the temporal lobe above the sylvian fissure. Bottom row: The 128 electrode setup more adequately covers the lower temporal areas, and with this setup the source is correctly located to the mesial temporal area.

LTM-recordings in presurgical epilepsy evaluations have traditionally been performed with a limited number of electrodes (up to 30), and until recently, high density EEG for the purpose of ESI had to be recorded in a separate session. Recent software development now allow LTM recording of video-EEG with up to 256 electrodes for several days, enhancing the role of ESI in presurgical evaluation.

Clinical studies of ESI in focal epilepsy in children

There are only few ESI studies focusing on children with focal epilepsy although several studies included both children and adults. The major electroclinical differences to consider between children and adults with respect to ESI is that spikes are usually more frequent in children but that these also often show multifocal irritative zone related to etiologies commonly encountered in children with epilepsy (e.g. tuberous sclerosis, extensive or multifocal cortical dysplasia). In a study including children and adults, high density EEG and ESI allowed lobar localisation in 94% of patients and good concordance with resection area was found in 79% post-operatively seizure-free patients [42]. A retrospective study in children showed very good accuracy of low density ESI performed on the spikes identified on low density clinical long-term monitoring (19 - 29 electrodes) [43]. ESI accurately localized the epileptic focus in 90% of the patients as validated by the spatial concordance with the resection area in these post-operatively seizure-free patients. ESI results were particularly good for extra-temporal epilepsy (100% concordance). For temporal epilepsy, additional high density EEG recordings allowed successful localisation in those cases who showed discordant results with ESI performed on clinical recordings.

Ictal recordings, now increasingly acquired with a large number of channels, can be used for ESI but methodology still needs to be refined as artefacts and evolution of the discharge are major confounds. Some studies in adults have found encouraging localizing results that were concordant with intracranial EEG recordings [46, 47].

Comparison with other non-invasive techniques

In addition to LTM with interictal and ictal EEG, modern presurgical evaluations also include high-resolution MRI, neuropsychological exams, and centre specific combinations of PET, ictal SPECT, simultaneous EEG and functional MRI (see below) and quantitative analysis of structural MRI to precisely delineate the epileptogenic focus. When the different tests are not sufficient to adequately delineate the epileptic focus, invasive recordings from surgically implanted electrodes subdurally or intracerebrally may be needed [48]. In these cases, precise estimation on localisation of the epileptic focus with a priori hypothesis is important to guide the placement of intracranial electrodes. Through multimodal co-registration it is possible to display the results of the different non-invasive imaging results superimposed to the patients individual structural MRI and thus get a better estimation of the location of the epileptic focus.

One major advantage of ESI over other non-invasive techniques in the presurgical work-up of patients with epilepsy is a direct recording of neuro-electrical activity with a very high temporal resolution, which is particularly relevant to describe epileptic activity. Moreover, the technique can be applied on bedside recordings even in very young children.

In presurgical epilepsy evaluation, the concordance of several imaging modalities lends stronger support to the obtained localisation. The pediatric ESI study of Sperli et al. mentioned above [43] compared the results of ESI and isotopic techniques, namely interictal 18Fluoro-Deoxy-Glucose Positron Emission Tomography (FDG-PET) and ictal/interictal Single Photon Emission Computed Tomography (SPECT) and SISCOM (substraction of Ictal SPECT coregistered to MRI). ESI (90%) was more accurate than interictal FDG-PET (82%) or ictal SPECT (70%) in localizing focal epileptic activity. Further studies involving both adults and children showed that ESI associated with individual brain anatomy was very reliable when the MRI was normal and when the MRI showed large brain lesions [45, 49].

Although the comparison between Magneto-Encephalography (MEG) and EEG Source Imaging is conceptually very interesting because each technique captures a different component of the neuro-electromagnetic activity of the brain, studies comparing these techniques are generally flawed as simultaneous EEG is recorded with a limited number of electrodes compared to MEG, thus biasing the precision of the localisation in favour of MEG. However, several advantages of ESI over MEG (ESI is possible on readily available clinical EEG recordings; lower cost and smaller space requirement of high density EEG systems; motion allowed during EEG recording; EEG compatibility with simultaneous MRI or PET recordings) make it a particularly interesting tool in pediatric epilepsy surgery.

Combination with simultaneous EEG and functional MRI (EEG-fMRI)

Simultaneous EEG and fMRI recordings with dedicated equipment can be safely performed and yield EEG and fMRI recordings of high quality. In patients with epilepsy, this technique allows mapping whole-brain haemodynamic changes correlated to epileptic activity identified on scalp EEG and can reliably localise focal epileptic activity [50]. Simultaneous ESI and mapping of haemodynamic changes related to interictal epileptic discharges recorded during fMRI acquisition can be performed and recent studies in adults and children [51, 52] have shown that the two methods are very complimentary for exploring epileptic networks. fMRI reveals a complex network of focal haemodynamic changes related to epileptic activity with millimetric spatial resolution, while ESI allows to identify which of these regions are involved in spike onset vs propagation. Such combination brings valuable non-invasive localizing information in presurgical evaluation. Such approach, although with ESI and EEG-fMRI performed in separate recording sessions, has also been applied to benign rolandic epilepsy, an idiopathic focal epilepsy syndrome with motor partial or secondary generalized seizures. Initiation of the spike in the face or hand motor area with propagation to the sylvian fissure and insula was shown.

In another recent study, simultaneous ESI and fMRI was used to investigate children suffering from Continuous Spikes and Waves during Slow Sleep, an epileptic encephalopathy associated with severe cognitive dysfunctions [53]. Despite heterogenous etiologies in 12 children ESI showed a common involvement of perisylvian, insular and cingulated regions irrespective of the site of spike onset and alteration of physiological brain networks (resting state networks) providing insight into the pathophysiology of this condition.

In the Geneva-Lausanne joint epilepsy surgery program, we have a long experience in high density EEG and ESI. Patients routinely benefit from high density EEG recordings (256 channels) for the purpose of ESI and from EEG-fMRI, both providing clinically useful information for guiding surgical resection or implantation of intracranial electrodes. These surgical cases also offer validation of the results by intracranial EEG or post-operative follow-up. The recent possibility of long-term high density video-EEG recordings offers new possibilities for obtaining ESI in patients in whom interictal spikes are rare or limited to sleep and also allows high density ictal recordings. In a translational scientific project (SNF 33CM30-124089, SPUM epilepsy), we are currently investigating temporal and spatial properties of large-scale epileptic networks. We combine high density ESI, EEG-fMRI (up to 256 MRI compatible channels) and tractography based on Diffusion Tensor MRI to explore the relationship between functional networks and structural connections via white matter tracts. Besides mapping epileptic activity, we are also using ESI and fMRI to localise eloquent cortex for language, somato-sensory and memory functions in surgical candidates (FNS 320030-122073).

Figure 3 shows multimodal non-invasive imaging in a child suffering from tuberous sclerosis who was recently investigated in our centre. The results of ESI, EEG-fMRI, PET and SPECT were concordant with the most epileptogenic tuber as confirmed by subsequent intracranial EEG and the child is post-operatively seizure-free (>12 months follow-up).

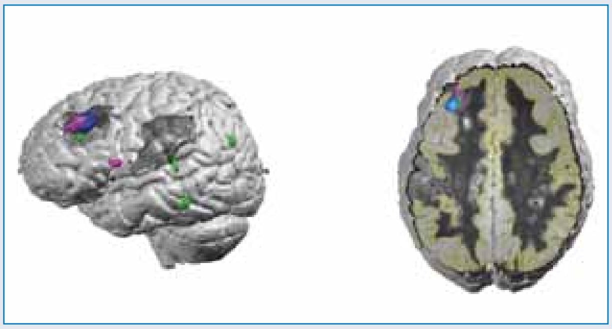

Figure 3: 3D reconstruction (left) and FLAIR axial view (right) of multimodal non-invasive imaging in a patient with tuberous sclerosis and symptomatic left fronto-parietal epilepsy

Intracranial EEG recording revealed seizure onset in the frontal lobe and the parietal tubers. Both were removed, resulting in seizure freedom (>12 months follow-up): blue = ESI, pink = EEG-fMRI, green = SISCOM, yellow = PET. Several tubers can be seen on the FLAIR image, notably colocalised with the PET hypometabolism, ESI and EEG-fMRI results. The area of surgical resection (left frontal and left parietal tuber) has been added in black to the 3D reconstruction.

Conclusion

ESI is a reliable non-invasive imaging tool allowing some motion of the patient during the recording. This aspect and the frequent presence of a very active interictal epileptic focus in pediatric epilepsy make this technique particularly suitable for children with epilepsy.

Modern equipments allow high density EEG recordings during short and comfortable sessions and long term acquisition is also possible. Clinical studies and combination with PET, SPECT and EEG-fMRI showed that ESI yields very reliable localisation in presurgical patients and increases our understanding of certain epileptic syndromes.

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