A Review on Non-Invasive Localisation of Focal Epileptic Activity Using EEG Source Imaging*

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Summary

Over the past few decades, diverse brain imaging techniques have been applied in different areas of experimental psychology and neuroscience, and have begun to provide unprecedented windows on the functional and the structural anatomy of the human brain. Recent technological innovations have achieved to convert conventional electrophysiological methods (e.g. electroencephalogram or EEG) into modern functional brain imaging procedures (i.e. electric source imaging or ESI); allowing neuroscientists to measure the spatial and temporal dynamics of the brain.

In patients with drug-resistant epilepsy who are candidates for surgery, non-invasive functional imaging methods are helpful in guiding placement of surgical resections or invasive EEG recordings. ESI consists in a non-invasive recording of the electrical potential field on the scalp while using dense array EEG (up to 256 channels), which allows estimating intra-cerebral electric sources. Nowadays, ESI became an accessible technique mainly due to the increase in computational power and the appearance of user-friendly sophisticated analysis software. Despite the large amount of literature supporting the validity of ESI in terms of localization, the introduction of this technique into clinical routine has been rather slow. In this review we intend to tackle the theoretical aspects, practical procedures and ESI clinical studies; in addition, we will compare with other well established imaging tools used in presurgical evaluation of epilepsy workup.

Epileptologie 2012; 29: 80 – 88

Keywords: Multichannel EEG, EEG source imaging (ESI), long-term EEG monitoring, epilepsy surgery, presurgical evaluation

Nicht-invasive Lokalisierung von fokaler epileptischer Aktivität mittels elektrischer Bildgebung

In den letzten Jahrzehnten wurden mehrere Hirnbildgebungsverfahren in verschiedenen Bereichen der experimentellen Psychologie und Neurowissenschaften angewandt, die uns ein noch nie dagewesenes Fenster in die funktionelle und strukturelle Anatomie des menschlichen Gehirns gegeben haben. Technische Innovationen führten zu einer Umwandlung von konventionellen elektrophysiologischen Methoden (hier: Elektroenzephalogramm oder EEG) in moderne funktionelle Bildgebung (das heisst elektrische Quellenlokalisation oder ESI), die den Neurowissenschaftlern erlaubte, die räumliche und zeitliche Dynamik des Gehirns zu messen.

In Patienten mit Medikamenten-resistenter Epilepsie, die chirurgische Kandidaten sind, zeigten sich nicht-invasive funktionelle Bildgebungsverfahren sehr hilfreich, den Resektionsort oder den Ort der Platzierung der intrakraniellen Elektroden zu bestimmen. ESI besteht aus dem nicht-invasiven Aufnehmen des elektrischen Potenzialfelds auf dem Skalp mit hochauflösenden EEG (das heisst bis zu 256 Elektroden), was die Schätzung der intrazerebralen elektrischen Quelle erlaubt. Heutzutage ist ESI eine relativ zugängliche Technik, dank höherer Computerleistung und benutzerfreundlicher Analyse-Software. Trotz vieler Studien, die die Validität von ESI bezüglich Fokuslokalisation zeigen konnten, ist die klinische Einführung eher langsam. In dieser Zusammenschau umreissen wir die theoretischen und praktischen Aspekte sowie die klinischen ESI-Studien; ausserdem werden wir ESI mit anderen etablierten Bildgebungsverfahren, die in der prächirurgischen Evaluation angewandt werden, vergleichen.

Schlüsselwörter: EEG-Quellenlokalisation, Epilepsiechirurgie, Bildgebung

***Acknowledgements**
The Cartool software, used for the figures has been programmed by D. Brunet, from the Functional Brain Mapping Laboratory, Geneva, Switzerland, and is supported by the Centre for Biomedical Imaging (CIBM) of Geneva and Lausanne. We acknowledge the financial support of the Swiss National Science Foundation No. 33CM30-124089, 33CM30-124115, 320030-141165, 320030-122073 and the CIBM.

Localisation non invasive des réseaux épileptiques au moyen de l'imagerie de source électrique : état de l'art

Ces dernières années, les efforts dans la recherche neuroscientifique ont permis le développement de techniques modernes permettant l'exploration avancée du fonctionnement et de l'anatomie du cerveau. Des innovations technologiques récentes, ont réussi à convertir les méthodes neurophysiologiques conventionnelles (électroencéphalogramme) en techniques d'imagerie fonctionnelle (imagerie de source électrique). Cette évolution nous permet d'étudier l'activité cérébrale avec des résolutions spatiales et temporelles accrues.

Les techniques d'imagerie fonctionnelles non invasives sont utiles pour localiser la zone épileptogène chez des patients avec une épilepsie pharmaco-résistante et candidats à une résection chirurgicale de leur foyer épileptique. L'imagerie de source est basée sur des enregistrements électroencéphalographiques multicanaux (jusqu'à 256 électrodes), nous permettant d'obtenir une configuration topographique du champ électrique de surface et d'estimer les sources électriques sous-jacentes dans le cerveau individuel. Grâce à des améliorations sur le plan computationnel ainsi qu'au développement de logiciels plus abordables pour les utilisateurs, l'imagerie de source est devenue une technique accessible au monde médical clinique. Néanmoins, malgré une vaste littérature scientifique validant cette technique en termes de localisation, son utilisation en tant qu'examen de routine dans le domaine de l'épilepsie reste limitée.

Dans ce contexte, les aspects théoriques et pratiques de l'imagerie de source seront présentés. De plus, nous allons citer les différentes études cliniques qui ont utilisé cette technique, et nous allons la comparer avec des nouvelles méthodes d'imagerie fonctionnelle et structurelle.

Mots-clés : Imagerie de source EEG, chirurgie de l'épilepsie, EEG multicanaux

Introduction

Epilepsy is a neurological disorder with a reported overall incidence of 50/100,000 cases per year and a prevalence of 4-10/1000 persons in industrialized countries [1]. In most cases, seizure appearance can be controlled by antiepileptic medication. However, approximately 1/4 to 1/3 of epileptic patients suffer from medically-refractory seizures [2]. Insufficient control of epileptic seizures and drug toxicity burden (linked to multiple medication and elevated dose), are related to an increase in morbidity and, moreover, have a large impact on patient's quality of life and disease-related costs [3].

Epilepsy surgery in eligible candidates might substantially reduce or eliminate seizure appearance at a rate of ~60% [4]. The main aim of epilepsy surgery is to delimit the resection margins of the epileptogenic area with preservation of the so-called "eloquent cortex" (i.e. cortical region vital for a certain neurological function).

Presurgical workup comprises several non-invasive techniques such as long-term scalp video-electroencephalogram (EEG) monitoring, invasive subdural EEG recordings (sEEG), high-resolution magnetic resonance imaging (MRI), positron emission tomography (PET), ictal and interictal single photon emission computed tomography (SPECT), substraction of the two SPECT modalities coregistered to MRI (SISCOM) and quantitative MRI analysis which is recently gaining popularity [5]. The neurologist's capacity to determine the epileptogenic zone is based on sensitivities and specificities of the aforementioned methods. These techniques yield a ~50-80% correct localization of the epileptic area as validated by surgery and/or intracranial EEG, varying according to the presence or absence of visible structural lesion [6, 7]. Regarding more practical aspects, the use of brain imaging tools requires a certain degree of cooperation and understanding. Many patients either in pediatric age and/or with moderate-to-severe cognitive impairment might need sedation in order to accomplish these examinations, which imply an additional safety risk. In this sense, non-invasive and safer tools for mapping epileptic activity in the alert subject are needed.

These requirements are fulfilled by EEG source imaging (ESI), a technique based on non-invasive scalp EEG recorded with multiple electrodes, which allow estimating the underlying electric sources of the brain. This modern tool can be applied to study the dynamics of the epileptic network with high temporal resolution, enhancing our knowledge on the neurophysiological mechanisms of seizure disorders.

This review is intended to describe the current of the role of ESI in presurgical evaluation workup, ranging from its methodological background to the latest clinical studies, as well as its concordance with other brain imaging techniques.

EEG in presurgical evaluation of epilepsy

Despite current technological innovations, interictal and ictal EEG recorded continuously during several days (i.e. long term monitoring), by either scalp electrodes or subdural grids, remain the gold standard in presurgical evaluation of drug-resistant epileptic patients.

During the period while the subject is being monitored a large amount of EEG, during awake and sleep stages, are digitally recorded. Subsequently, analysis is performed on the basis of visual detection of the spatial distribution and amplitude maxima of different EEG abnormalities (i.e. sharp waves and spikes). In

terms of localization, this type of analysis can be considered quite valuable; however, it only provides partial information available on the EEG signal and, furthermore, it is operator-dependant [8].

Since the 50's, sEEG play an essential role in localization precision, allowing ictal recordings to be performed without skull attenuation [9]. Nevertheless, this tool is highly invasive, thus, implying a certain degree of post-operative risk [10]; and confined to near-by cortex since it records signals originated from a limited circumference of neighboring tissue [11].

In order to avoid these technical limitations and potential risks, several epilepsy centers are currently analyzing EEG signals with modern non-invasive signal processing tools. EEG Source Imaging (ESI) is a technique, based on the recording of the electrical potential field on the scalp using multichannel EEG, which allows for the 3D reconstruction of the electric active areas in the brain. Subsequently, we will explain how we carry out multichannel EEG data acquisition and pre-processing in our presurgical unit. In addition, we will expose the theoretical framework underlying ESI and its current clinical applications. Finally, we will contrast this technique with other non-invasive tools.

ESI of interictal epileptiform activity: practical procedures and underlying theoretical concepts

During the past few years, enormous progress has been made in the neuroscience laboratories concerning the recording analysis and interpretation of EEG. Nowadays, electrical signals are recorded from a large array of electrodes distributed all over the scalp (up to 256 channels). These methodological and practical improvements have encouraged the application of multichannel recordings and analysis, by means of ESI, in the epilepsy domain [12-14] (**Figure 1a**).

Interictal epileptiform activity (i.e. spikes) of similar localisation and morphology are visually detected and averaged and a potential map is obtained for each time point (**Figure 1b**). The EEG map at the 50% rising phase of the averaged interictal activity is selected for further source localization. It has been argued that the primary focus is more consistently localized whilst using the rising phase rather than interictal epileptogenic discharge peak, which already involves areas of propagation [15, 16].

Using spatial configuration of the scalp's potentials, with sophisticated inverse solution algorithms, allow estimating the underlying electric sources in the realistic brain [17] (**Figure 1c**); transforming the recording of these signals into a functional brain imaging method. These techniques have to face mathematical challenges referred to as the forward and the inverse problem.

The dilemma of determining the source locations which are responsible for the measured potentials at the EEG electrodes is known as the inverse problem [18]. For any set of measurements or recording sensors outside the head, there are infinite current sources in the brain that model the recorded data (for review see [19]). Two different groups of algorithms, which are capable of estimating the sources of scalp activity, have been described in the literature: simple dipole estimations (i.e. continuous dipole analysis [20]; multiple distributed current dipole [21]) and, more recently developed, three-dimensional current density distribution methods (for reviews see [22]).

All these techniques are based on a model of the propagation of electrical activity through different conductivity values of the interfaces such as brain, skull and scalp: the forward model, expressed as the lead field matrix [23-25]. The inversion of this matrix by means of sophisticated algorithms provides the so-called "source localization". This would mean that for each time point within the spike wave complex, inverse solution calculation is applied to calculate the location of the epileptic source within the solution space based on the voltage map of that precise time point. The high temporal resolution provided by this tool is considered key for visualization of spreading of epileptiform activity.

The forward model can be based on a normalized head or, more precisely, on the individual MRI (**Figure 1d**). In any case, both must previously undergo cortical grey matter segmentation (**Figure 1e**) in order to define the solution space (**Figure 1f**, areas within the brain where the epileptic source will be allowed to be located). We will discuss the benefits of applying single subject MRI together with ESI, as well as the technical limitations encountered, in the following section.

Methodological considerations of ESI

Conversely to single waveform analysis of EEG, ESI is based on spatial analysis of the potential maps; therefore, the quality of these maps will set the ground for further analysis. In this sense, it is vital that these scalp potential fields are properly acquired and analysed. Suitable recording of the potential field of the scalp, in terms of electrode number (spatial sampling) and positioning, is necessary in order to proceed with the analysis of the collected data. During the pre-processing period, artefact detection and suppression is crucial, in order to obtain a good signal-to-noise ratio. Once the data has been processed, source reconstruction can be carried out in a template brain of the Montreal Neurological Institute (MNI) or, more accurately, in the individual MRI.

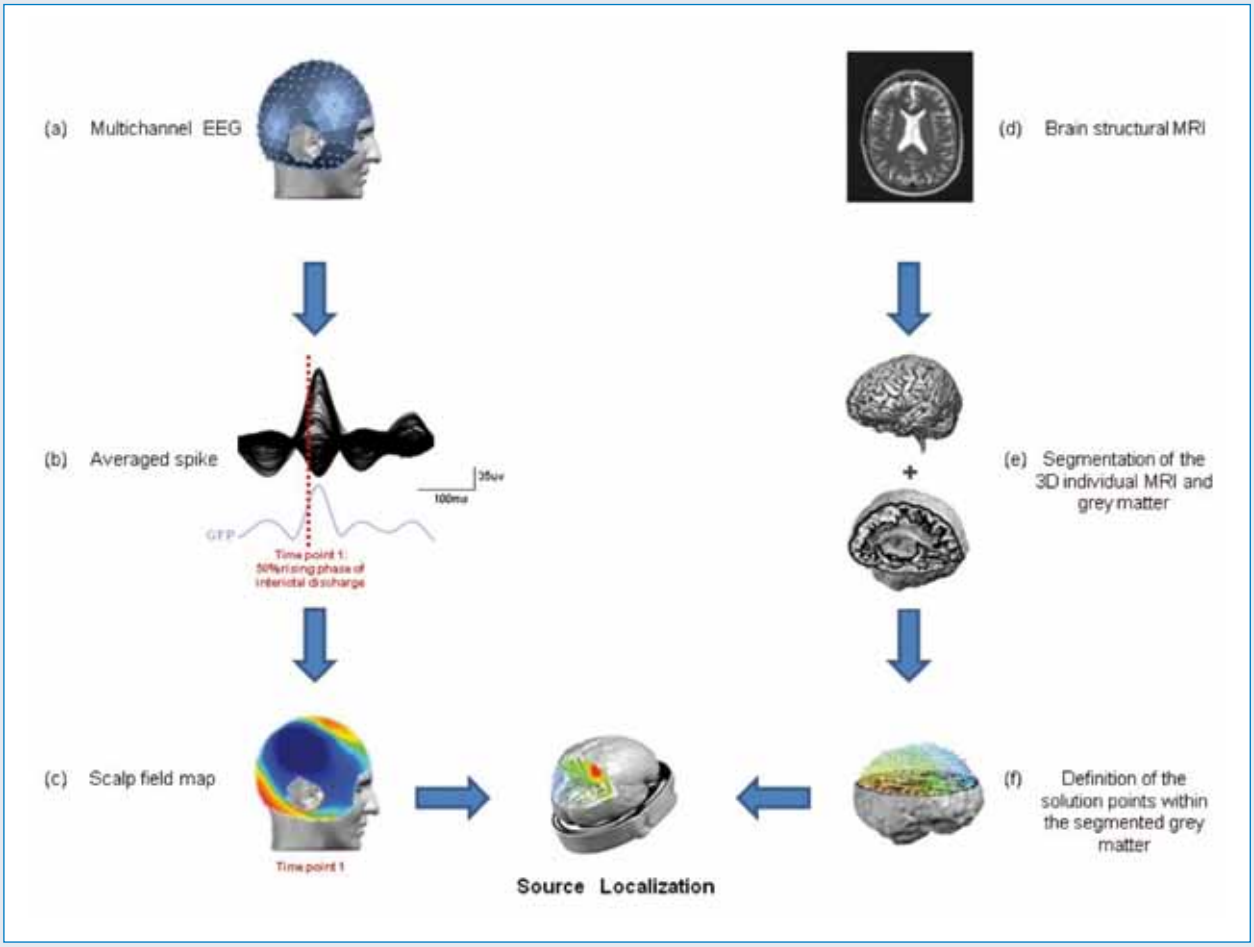

Figure 1: Principle of EEG Source Imaging
Source localization methods rely on mathematical models of the bio-electrical generators and the volume conductors within which they lie. On the one hand, the inverse problem relies in identifying the intracranial generators from the measured potentials (b, c) recorded from a large array of electrodes (a). On the other hand, the forward problem consists in modeling the scalp electromagnetic fields produced by a known source configuration. These models are based on the segmentation of the individual MRI and the grey matter (d, e). A regular grid of solution points in the gray matter is determined and the lead field matrix is computed using the known analytical solutions for a head model (f).

a) Spatial sampling

The optimum number of electrodes required for adequately sampling the potential field has been debated. Standard clinical EEG proposes a setup of some few electrodes (around 20) with a relatively large inter-electrode distance (around 6 cm). In the early 90s, several studies were carried out claiming that 3 cm is the minimum inter-electrode distance necessary for proper sampling of the underlying brain sources [26-28]. These findings were validated by a study in a group of 14 patients with refractory focal epilepsy which showed that source localization precision to a sub-lobar level is possible when using an electrode setup of more than 63 electrodes [16, 29]. Further increase from 64 to 128 channels showed less significant improvement.

Recent research took into account the different conduction properties and resistivity that exist between skull and brain, and claimed that the brain/skull conductivity ratio is higher than previously estimated [30-34]; therefore, a larger number of electrodes would help to solve this issue. In addition, different conduction properties between the pediatrics population and adults have been described [35, 36]. These new studies concluded that even more than 100 channels would be required to optimally sample the brain electric fields. A more recent study was performed using a more restrictive head model (finite difference model) and realistic values for brain/skull conductive characteristics; showing that improvement in terms of localization can be attained with up to 256 scalp electrodes [37].

b) Electrode position

Electrode position is an additional factor that should be taken into account while interpreting the potential field. In principle, the electrode array should cover the

entire scalp surface rather than a circumscribed sector, in order to attain a complete electric field showing all positive and negative potentials. For instance, since conventional 10/20 EEG system does not incorporate inferior electrodes, medio-temporal sources are often misplaced [38]. In case that only low resolution EEG is available, a complete coverage of the scalp should be ensured.

c) Artifact detection and elimination

While applying multiple electrodes covering the scalp surface, the risk of having bad contacts during the recording cannot be avoided. Once the data was collected, offline detection by either suppressing or "interpolating" bad electrodes from the neighboring electrodes using a spline interpolation algorithm can be performed [39]. In case an artifact is observed in multiple electrodes at the same time point, methods such as independent component analysis (ICA) can be applied. This method relies on the hypothesis that brain activity is the result of a superimposition of several independent activities [40].

d) Individual vs. Template MRI

Up to now, most choices have been reduced to the following question: do we intend to carry out an analysis on an individual or a group basis? On the one hand, selection of a template brain provides a direct interface between the subject's source and template space, permitting all sorts of group analysis [41]. Nevertheless, this would not be valid in patients having large brain abnormalities altering the skull/brain conductivity, in which an individual-based analysis would be required (**Figure 2**). On the other hand, a recent study revealed significant differences while comparing the localization yield of high-resolution source imaging while using individual MRI versus MNI [42]. This would mean that, from a surgical point of view, the epileptogenic zone will be more precisely delimited using individual MRI and that, in addition, further post-operative risks could be reduced.

ESI: estimating the epileptic focus

The clinical field in which EEG mapping has been used the most is probably in presurgical evaluation of patients presenting with medically intractable epilepsy. ESI, in combination with advanced inverse solution methods, has shown successful results even in epileptic patients with diverse clinical features (i.e. age, lesion size, localization).

ESI has already proven its worth in patients with lesional epilepsy. As shown in previous studies, this technique is capable to localize brain sources arising from extra-temporal up to deep mesio- and latero-temporal localizations [43, 44]. A study carried out in 30 post-operatively seizure-free paediatric patients of whom 13 had temporal lobe epilepsy, using 29 electrodes and the patient's individual MRI, reported a correct localization of 90% at a lobar level [38]. Conversely, the same success rate was not observed when including only temporal lobe epilepsy patients, due to an insufficient electrode coverage of the basal temporal areas (i.e. low resolution ESI) [45]. For temporal epilepsy, increased spatial sampling allowed successful localisation in those cases that showed discordant results with ESI performed on clinical recordings (for more details see "Methodological considerations of ESI"). More precisely, in a series of 152 epileptic patients, ESI based on high-resolution EEG (>64 electrodes) and individual MRI as a head model rendered the highest sensitivity of 84% (defined as % of seizure free patients with focus localization within the resected zone) and specificity of 88% (defined as % of patients with focus localization outside the operated area) as compared to standard EEG recordings (19-29 electrodes) which showed a sensitivity of 66% [42].

From a hypothetical perspective, because EEG is affected by conductivity changes, the use of ESI was felt to be limited when studying patients with large brain lesions. Previous simulation studies have addressed this question, but were incapable to answer whether in case of individual's data, accuracy of ESI is still satisfactory [46, 47]. A recent study showed that ESI is able to properly localize the epileptogenic zone in 12/14 patients with very large brain lesions (**Figure 2**) notwithstanding the conductivity changes [48]. Conversely to prior research, this group used a more precise head model and a reconstruction based on spherical deformation of the individual grey matter known as "SMAC" [23]. The same authors discussed the application of ESI in patients with no apparent brain lesion; being capable of appropriately localizing the epileptic focus in 8/10 cases [13]. The interest of this research lies on the fact that previous studies of postsurgical outcome in this group of patients showed that around half of them would not become seizure-free in spite of an exhaustive pre-surgical evaluation [49, 50]. In this regard, ESI would provide relevant information, concerning the epileptogenic focus in this particularly difficult group of patients in which MRI provides no significant information.

Despite these interesting findings, one concern regarding ESI for pre-surgical epilepsy evaluation is that the analysis solely relies on interictal changes rather than ictal activity. While interictal activity might provide beneficial information, it does not always seem to correspond with the seizure onset area [51, 52]. On the other hand, ictal EEG patterns are essential for determining the origin and spread of epileptic activity [53]. However, its application has been hampered due

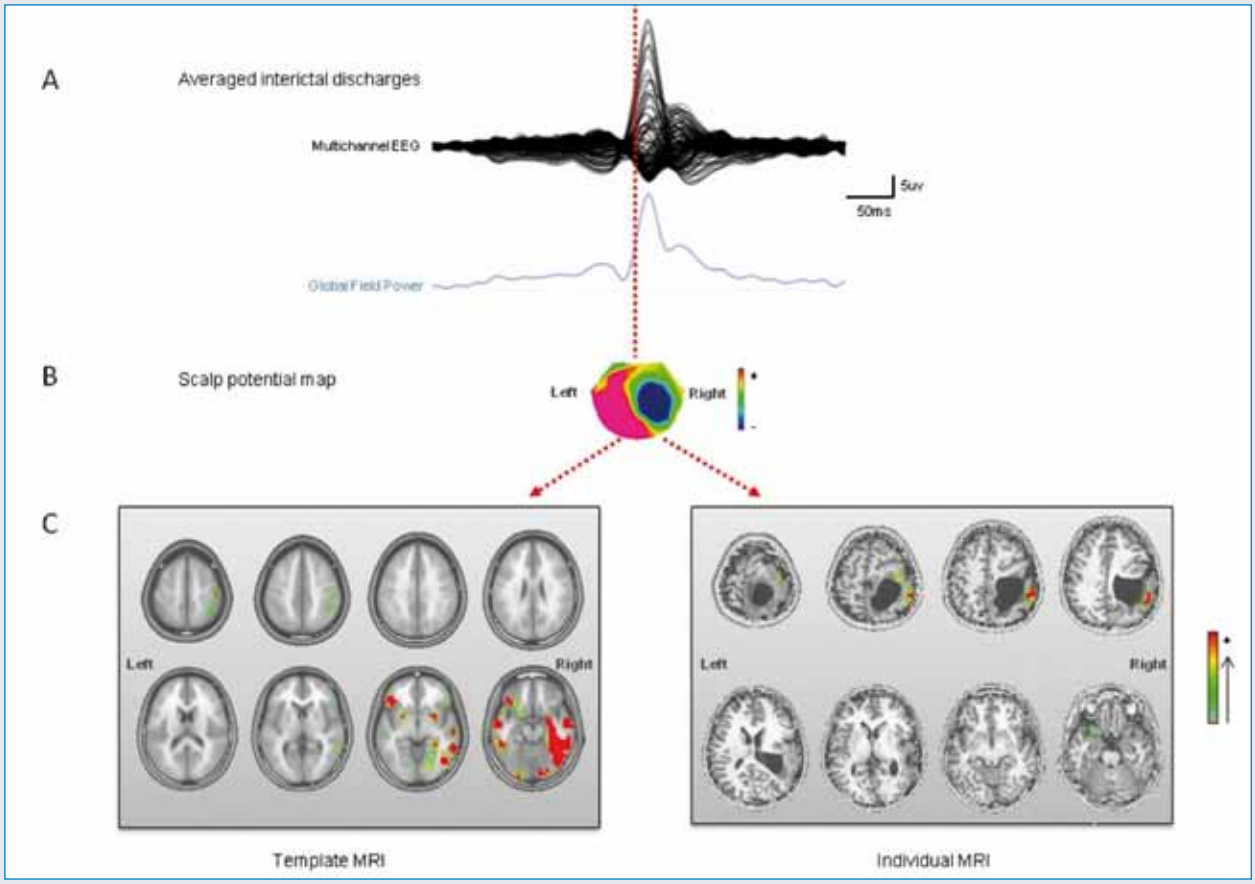

Figure 2: EEG Source Imaging for the localization of interictal epileptiform discharges in patients with large brain lesions
(A) Averaged interictal discharges recorded from 128 channel-EEG, displayed on a butterfly plot (overlaid traces) and referenced to the average reference. Global field power (GFP) curve is depicted in blue. The time point corresponding to the 50% rising phase of the average interictal discharge is plotted in a red-dotted line. (B) Scalp potential map corresponding to the aforementioned time point (red, positive voltage; blue, negative voltage). (C) Source localization with a linear distributed inverse solution in the template MRI (left) and the individual MRI (right) at a single time point of GFP peak. Maximal activity is seen on the right parietal lobe while using the individual MRI, whereas template MRI depicts a more distributed activation and maximal in the right temporal lobe, with activity even within the LCR-filled cavity.

to the large amount of artefact and the low signal-to-noise ratio. A number of ictal long-term monitoring (LTM) studies in adults have shown promising results that were concordant with clinical presentation and intracranial EEG recordings [54, 55]. Since high-resolution EEG long-term systems are available, the use of ESI in spike analysis is now possible and could be of great interest since it is thought to reflect the epileptogenic area. In the following segment we will discuss the advent of LTM recordings and spike analysis in the framework of presurgical epilepsy evaluation.

Long term monitoring (LTM) and ESI of ictal epileptiform activity

Since the early 80s, in-patient LTM recording of video-EEG is routinely applied in preoperative assessment of epilepsy using few numbers of electrodes (i.e. less than 30) [56]. Nowadays, recent software development allows dense array (up to 256 electrodes) video-EEG LTM to be recorded for numerous days. Since recordings are carried out during various hours (>24), LTM can easily capture multiple seizures, as opposed to other non-invasive techniques (i.e. SPECT, MEG). The main aim is to determine the lateralization or estimated localization of the seizure onset area. Nonetheless, in order to assess its worthiness, direct comparison with more well established techniques is needed.

In a LTM study using high resolution ESI (up to 256 channels), the surface ictal patterns of 10 medically intractable epileptic patients were compared to gold standard sEEG, and a high level of agreement between both techniques was obtained [55]. However, this study supplies restricted information (i.e. source localization) coming from only the selected spike at seizure onset, disregarding the temporal and spatial propagation of ictal activity. Rare scalp EEG studies have been focused in improving the analysis of seizure activity by applying diverse approaches ranging from full scalp frequency

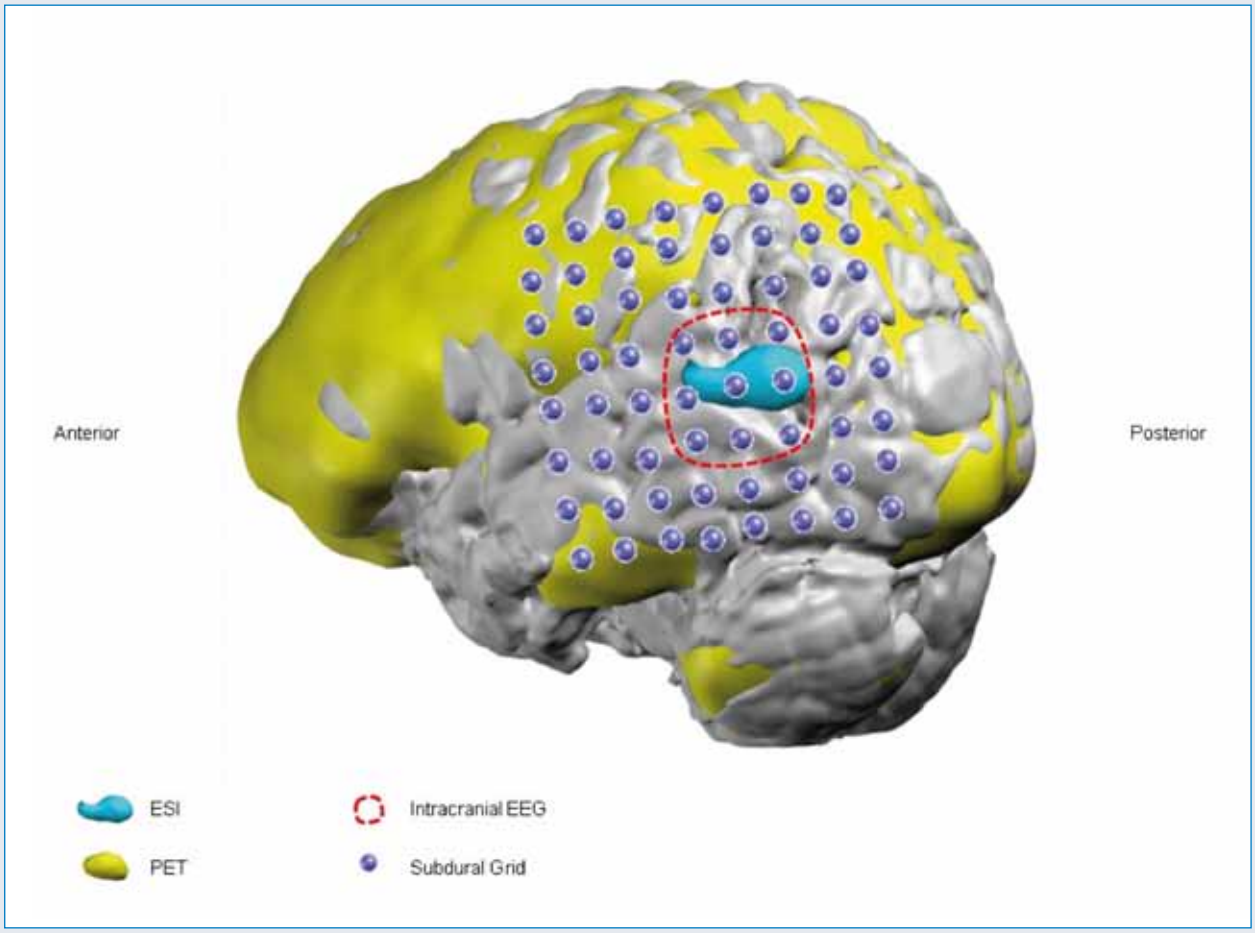

Figure 3: Multimodal imaging in a presurgical evaluation workup.
A 15-year-old female patient diagnosis with a tuberous sclerosis and a drug-resistant epilepsy who underwent interictal PET coregistered with the MRI (depicted in yellow) and ESI of interictal epileptiform discharges (depicted in pale blue) prior to intracranial electrode implantation. A large hypometabolism is seen concordant with the ESI maximum. Subsequently, the patient underwent subdural grid implantation which was also co-registered with the MRI. Intracranial EEG analysis showed a restricted area of ictal onset (illustrated with a red-dotted square). The ESI result of the patient shows a perfect correspondence with the subdural electrode recordings.

analysis described in terms of source space [57] or temporal evolution [58], to space-oriented temporal segmentation (i.e. functional microstates) on multichannel EEG data [12] in combination with different source-imaging algorithms. In a recent study, 8 drug-resistant epileptic patients were recorded with a LTM 76-channel EEG system and seizure onset zone was properly identified in 6/8 (2 cases presented false positive results) cases by means of independent component analysis [59].

The aforementioned studies aimed at localizing the seizure onset zone. On the other hand, other research groups have been trying to determine the so-called pre-ictal state (i.e. few minutes prior to seizure onset) by means of automated seizure detection algorithms (for a review see [60]). This would provide a new perspective into understanding the mechanisms of seizure generation. However, to our knowledge, no research has intended to characterize the underlying changes during pre-ictal period. Pattern recognition methods have been applied to investigate brief functional EEG changes by determining a series of periods of stable map configuration (brain functional "microstates") [61]; and 4 stable microstates were characterized in the spontaneous EEG of awake healthy adults [62-64]. It can be hypothesized that abnormal microstates patterns can be found a few minutes prior to seizure onset. In a multicentric scientific project (SNF 33CM30-124089, SPUM epilepsy), we are currently investigating the temporal and spatial properties of large-scale epileptic network. We apply multichannel (>64 electrodes) analysis of the resting EEG in the time domain, in a large population of extra-temporal and temporal lobe epilepsy patients to describe the behavior of the different microstate classes during the pre-ictal state.

Comparison with other non-invasive techniques

In addition to LTM EEG recording, presurgical workup includes the following techniques: high-resolution MRI, PET and SPECT. Nevertheless, when these methods are unable to precisely localize the epileptogenic focus, invasive recordings from surgically implanted electrodes might be required [65]. In these cases, accurate localization of the seizure zone with a priori hypothesis allows better preparation for intracranial electrode implantation.

From a clinical point of view, ESI is a very alluring non-invasive technique which provides a superior temporal resolution (**Figure 3**), in the millisecond range, as compared to those methods based on changes in metabolic or vascular correlates of neural activity [66, 67]. From a practical perspective, this type of examination does not require sedation, it can be performed at patient's bedside and it is, therefore, suitable in the pediatric population and cognitively impaired patients.

The abovementioned prospective study of Brodbeck et al. compared the results of ESI (low or high-resolution analyzed using either individual MRI or template head model) with other well defined imaging tools such as MRI, PET and SPECT in a group of 152 operated epileptic patients with a follow-up period of more than 1 year [42]. A total of 43 patients underwent all examinations; showing that high-resolution ESI using individual MRI rendered the highest sensitivity (80%) and, principally, specificity rate (88%), followed by MRI (71.4% and 50%), PET (62.9% and 37.5%) and SPECT (54.3% but a higher specificity as compared to MRI and PET of 62.5%).

Conclusion

ESI is a reliable non-invasive imaging tool that, due to technical progress, can be easily applied in a clinical setup and does not require highly experienced personnel. Commercially available EEG recordings allow short and comfortable sessions and, even, long-term monitoring acquisitions are possible. In addition, recent research has demonstrated the advantage of ESI, in terms of localization precision, over other non-invasive functional methods in a large prospective study.

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