Combination of Electroencephalographic and Magnetic Resonance Imaging to Characterize Epileptic Networks

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Summary

The aim of the presurgical evaluation of focal epilepsy is to localize the epileptic focus as precise as possible and to reliably delineate it from eloquent cortex. While the gold-standard to achieve this goal is the recording from and the stimulation of electrodes directly implanted in the brain, attempts are undertaken to improve the non-invasive phase of the pre-surgical evaluation by new functional imaging methods. This review article describes two of these newly emerging techniques, electric source imaging (ESI) based on high-density EEG, and functional magnetic resonance imaging informed by simultaneously recorded EEG (EEG-fMRI). While both methods have demonstrated their utility in focus localization, they have their limitations due to low spatial (EEG) or low temporal (fMRI) precision. To overcome these limitations, we propose to combine the two methods by performing source analysis of the EEG recorded in the scanner and using these results to guide the interpretation of the fMRI.

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Key words: Electroencephalography (EEG), functional magnetic resonance imaging (fMRI), source localization, epilepsy

Kombination von EEG und funktionellem MRT zur Charakterisierung epileptischer Netzwerke

Ziel der prächirurgischen Abklärung von Patienten mit fokaler Epilepsie ist es, den epileptischen Herd so genau wie möglich zu lokalisieren und abzuklären, ob neurologisch wichtige Funktionen betroffen sind oder in der Nähe liegen. Der Goldstandard für diese Abklärung sind die Ableitungen und die Stimulation von direkt im Gehirn implantierten Elektroden. Es werden aber vermehrt Studien durchgeführt, die neue, nichtinvasive bildgebende Verfahren zur Fokus-Lokalisation evaluieren. Dieser Artikel beschreibt zwei dieser Methoden, die Quellenlokalisation basierend auf hochauflösendem EEG (ESI) und die kombinierte Registrierung von EEG und funktioneller Magnetresonanztomographie (EEG-fMRI). Wir zeigen, dass beide Methoden durchaus zu einer Verbesserung der Lokalisation epileptischer Areale beitragen, und dass sie als Standardmethoden in der prächirurgischen Diagnostik in Betracht gezogen werden sollten. Eine besondere Rolle spielt dabei die direkte Kombination von ESI und EEG-fMRI, da damit die unterschiedliche zeitliche und räumliche Auflösung der beiden Methoden optimal ausgenutzt wird und dadurch sowohl Beginn als auch Ausbreitung der Aktivität in epileptischen Netzwerken abgebildet werden kann.

Schlüsselwörter: Elektroenzephalographie (EEG), funktionelle Magnetresonanztomographie (fMRT), Epilepsie

Combinaison de l'EEG et de l'IRM fonctionnelle pour la caractérisation des réseaux épileptiques

Le but de l'évaluation préchirurgicale des épilepsies focales est de localiser le foyer épileptique aussi précisément que possible et de le délimiter du cortex éloquent de façon fiable. Le „gold-standard" pour atteindre cet objectif est l'enregistrement direct du cerveau avec des électrodes implantées et la stimulation électrique de ces mêmes régions au moyen des électrodes implantées. Toutefois, des efforts importants sont entrepris pour améliorer l'évaluation non-invasive avec des nouvelles techniques d'imagerie fonctionnelle. Cet article décrit deux de ces techniques émergentes, l'imagerie de source électrique (electric source imaging, ESI) et l'imagerie par résonance magnétique fonctionnelle guidée par l'enregistrement simultané de l'EEG (EEG-fMRI). Ces deux méthodes ont prouvé leur utilité pour localiser le foyer épileptique mais sont limitées par leur basse résolution spatiale (EEG) ou temporelle (fMRI). Pour surmonter ces désavantages, nous proposons de combiner ces deux méthodes en réalisant l'imagerie de source de l'EEG enregistré dans l'IRM et d'utiliser ces résultats pour guider l'analyse de l'IRM. Cette combinaison permet de visualiser précisément l'initiation et la propagation de l'activité neuronale dans des réseaux épileptiques.

Mots clés : Electroencéphalographie (EEG), imagerie par résonance magnétique fonctionnelle (IRMf), épilepsie

Introduction

While the EEG is doubtlessly the most important tool in the diagnosis of epilepsy and the determination of the epileptic syndrome, it is usually not considered as a method that allows to localize the epileptic focus more precisely than on a lobar level. The reason is that each EEG electrode reflects activity from multiple regions to different extends due to volume conduction, and thus does not only measure the neuronal activity directly underlying it. However, by not only looking at the local activity at a certain electrode but looking at the simultaneous activity of many electrodes distributed all over the head, we can actually estimate the sources in the brain that produced the scalp potential at any given moment in time. The precision of this source localization improves by increasing the number of electrodes and by incorporating realistic models of the head derived from structural images of the patient's brain in the calculations. Using such techniques, EEG has become a mature functional brain imaging method with the unique advantage of excellent temporal resolution. The importance of temporal resolution is particularly evident in the localization of epileptic activity, because it very quickly (within a few milliseconds) spreads within large-scale, whole-brain networks (**Figure 1**).

Despite impressive improvements of EEG source localization in the last years, there are natural limits concerning the spatial precision, particularly if areas further away from the scalp surface are involved. High spatial precision is better achieved by functional magnetic resonance imaging (fMRI), a method measuring local blood oxygenation level dependent (BOLD) changes due to neuronal activity. Given the high spatial resolution, the request to apply this method to the localization of epileptic foci emerged. However, fMRI alone is challenging because seizures are difficult to record due to movement artifacts, and interictal activity can only be detected by the EEG. Therefore, attempts have to be undertaken to record EEG within the MRI scanner in order to determine the time point of interictal events and search for BOLD changes that are correlated with these events. This EEG-informed fMRI technique has been used by several groups in the last years and provided very useful information about the large-scale networks that are involved in the epileptic activity of a given patient.

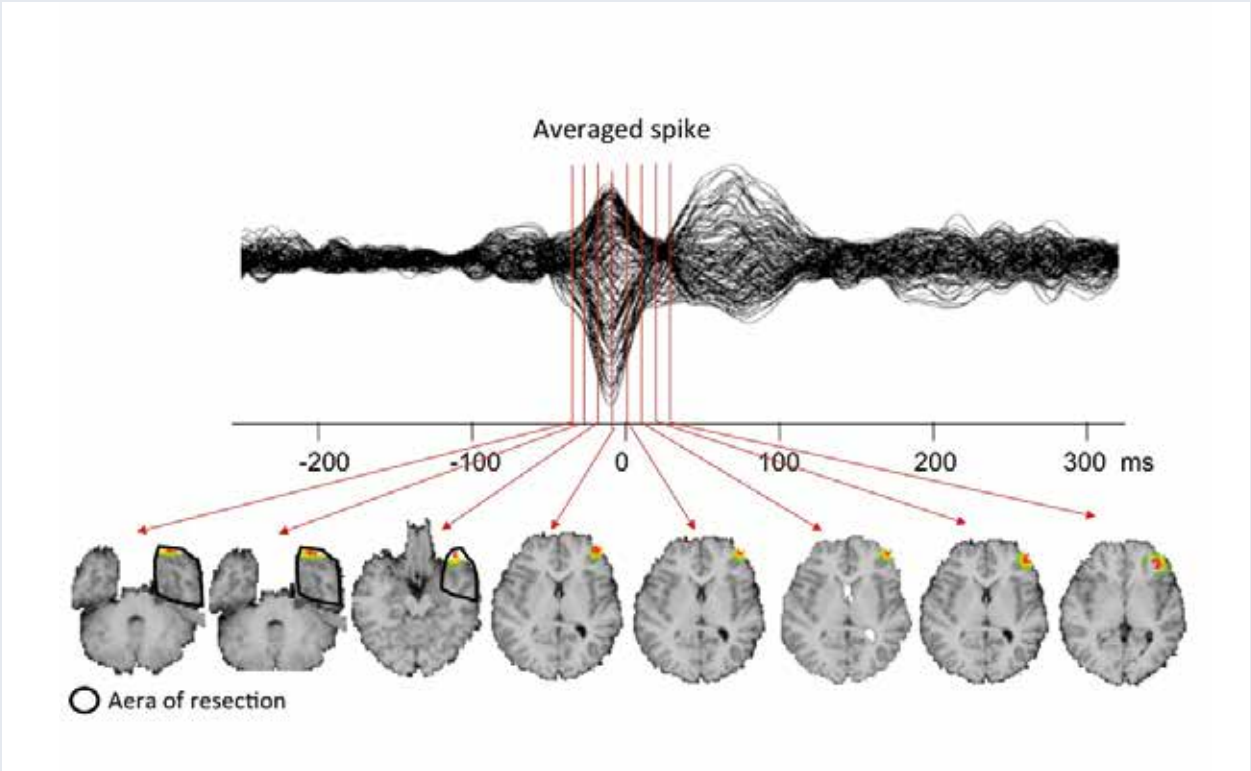

Figure 1: Evidence for fast propagation of interictal activity within the brain by electric source imaging (ESI). The top row shows overlaid traces of an averaged interictal spike recorded from 128 electrodes. Below, the ESI result using the individual MRI as head model is shown for different time points during the spike (in 10 msec steps). The encircled area illustrates the region that was subsequently resected. The example illustrates that the source maximum is initially (at the beginning of the spike) well localized within the resected area but then quickly propagates and is already outside of the epileptogenic zone at the peak of the spike. It underlines the importance of the fast temporal resolution of electric source imaging. Data from Lantz et al. [1].

However, the spike-related BOLD responses are often widespread and do not only involve one brain area that could be considered as the focus. The reason for these multiple responses is the spread of epileptic activity within the epileptic network during ictal, but also interictal events. fMRI results are thus often difficult to interpret if no additional information about the focus location is available. We propose to get this additional information from source-analysis of the EEG in the scanner. Thereby, the temporal resolution of the EEG source imaging allows to disentangle initiation from propagation of the activity and to pinpoint to the area of interest for the fMRI interpretation. If the fMRI indeed shows BOLD responses in this area, it will be of higher spatial precision than the EEG source imaging and could therefore guide the eventual surgical intervention more precisely. In the following chapters, I give an overview of these imaging techniques and their application in epilepsy.

Electric Source Imaging (ESI)

An increasing number of studies demonstrated that EEG analysis with source modeling methods provides valuable information about the localization of the epileptic focus. While simple equivalent dipole fitting already gave good source estimations [2, 3], an important step towards achieving a real 3-dimensional imaging of the electrical activity in the brain was provided by the distributed inverse solution algorithms [4-7] that are able to visualize the current density distribution in the entire brain at each moment in time (the so-called electric source imaging, ESI; for reviews see [8, 9]).

Sperli and colleagues [10] used this ESI technique to analyze interictal discharges of 30 operated and seizure-free children recorded with the standard clinical EEG of less than 30 channels. They reported correct localization on a lobar level in 90% of the cases, whereas the traditionally used nuclear imaging methods PET and SPECT revealed only 82% and 70% correct localization, respectively. Michel et al. [11] applied ESI to spikes recorded with 128-channel EEG in 24 patients who were subsequently successfully operated. They found that the source maximum was located within the resected zone in 79% of the patients. Zumsteg and colleagues [12] 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 result that has also been demonstrated by Lantz et al. [13] in simultaneous EEG and intracranial EEG recordings.

It has been assumed that ESI might have problems in patients with large lesions due to changes in the electrical conductivity within the brain. This does not seem to be the case: Despite large cerebral lesions, ESI correctly localized spike activity within the resected zone in 12 of 14 patients in the study by Brodbeck and colleagues [14]. The same authors also investigated patients without any lesion visible in the MRI [15]. Non-lesional epilepsy is known to be most challenging for focus localization. They found that ESI based on high density EEG (more than 128 channels) correctly localized the maximal activity of the spikes in the subsequently resected zone that rendered the patients seizure-free.

Given these promising studies Plummer and colleagues [16] concluded in a recent comprehensive review that ESI deserves a place in the routine work-up of patients with localization-related epilepsy, but that a prospective validation study conducted on larger clinical groups is still required. Recently, such a prospective study was reported by Brodbeck et al. [17]. 152 patients who were operated and had a sufficiently long post-surgical follow-up to define the outcome of the surgery with respect to their epilepsy were included in the study. This allowed to evaluate the sensitivity and specificity of ESI. The results showed that ESI had a sensitivity of 84% and a specificity of 88% if the EEG was recorded with a large number of electrodes (128-256 channels) and if the individual magnetic resonance image was used as head model. These values were superior to those of structural MRI (76% sensitivity, 53% specificity), PET (69% sensitivity, 44% specificity) and ictal/interictal SPECT (58% sensitivity, 47% specificity). However, the sensitivity and specificity of ESI decreased to 57% and 59%, respectively, with low number of electrodes (32 channels) and a template head model, emphasizing the importance of high-density recordings and realistic head models.

While there is now more and more convincing evidence on the yield of the analysis of interictal spikes [18], there is a constant criticism that the true identification of the seizure onset zone requires the analysis of ictal and not only interictal activity [19]. In contrast to other imaging techniques such as MEG and fMRI that are sensitive to movement artifacts, EEG can be used to record seizures. However, the challenge in the analysis of ictal EEG is the determination of the exact time point of the onset of the seizure, which is required in order to correctly localize the seizure onset zone. In many patients, seizures start with clinical changes without any visible changes in the scalp EEG. Once the seizure is also evident on the EEG, propagation already started and complex patterns of different frequencies arise and may change over a short period of time. Several methods have been tested to capture EEG onset before they are obvious by visual inspection. Blanke et al. [20] and Lantz et al. [21] applied phase-corrected frequency analysis to determine which area started first with the most prominent initial ictal frequency. In Lantz et al. [21], the source reconstruction of the predominant frequency was concordant with the intracranial findings

in 7 of 9 cases. However, this type of simple frequency analysis is not able to catch very fast propagation because the time-resolution of the FFT is low. Time-frequency analysis might be more promising in this respect. Recently, Yang et al. [22] used independent component analysis in the time-frequency domain to determine maps that represented the rhythmic discharges at seizure onset. While this method is very promising, it only works in patients in whom the seizure onset is characterized by continuous synchronized rhythmic discharges. Lantz et al. [23] proposed a frequency-independent method based on topographic pattern recognition algorithms. Using k-means cluster analysis, map topographies that were most dominant during seizure onset were determined. Source reconstruction of these maps yielded results which were consistent with the results from invasive recordings. Further studies with high-density EEG applied to a larger number of patients are needed to establish the most reliable method to localize seizure onset with ESI.

EEG-guided functional Magnetic Resonance Imaging (EEG-fMRI)

The most established functional imaging method is functional resonance imaging (fMRI) and it was thus natural that researchers tried to use this method to localize the epileptic focus. However, since EEG is the only way to determine interictal epileptic activity, the recording of EEG in the scanner was required. Such MR-compatible EEG systems have been developed in 1993 by John Ives and colleagues [24]. Several groups have used these systems to perform spike-triggered fMRI analysis [25-27]. In these initial studies, BOLD acquisition was initiated by spikes observed in the ongoing EEG. During the BOLD acquisition, the EEG was lost, but since the hemodynamic response peaks several seconds after the related neuronal activity, the destroyed EEG during the scanning was not a major problem. Nevertheless, recording sessions were long, the timing was variable, and an experienced epileptologist needed to be present during the recording to identify epileptic discharges. Soon after, algorithms were developed that allowed to eliminate the main artifacts during the BOLD acquisition, namely the gradient and the ballistocardiac artifacts [28, 29]. With these algorithms in hand, continuous BOLD acquisition could be performed and the EEG could offline be inspected for epileptic discharges. These marked spikes could then be used as regressors for the convolution with the hemodynamic response function. Commercial systems were quickly available and used by several groups who repeatedly showed the possibility to detect spike-related activity in the EEG-fMRI (for reviews see [30-33]).

EEG-fMRI is particularly interesting to investigate the eventual participation of deep brain structures in the generation or propagation of epileptic activity, because they are difficult to identify by the EEG source imaging methods described above. Such deep generators have been identified in patients with malformations of cortical development [34], as well as in patients with different types of generalized epilepsy [35-38].

Multiple studies have demonstrated that BOLD signal changes do not only occur in regions tightly coupled with the region generating the spikes in temporal lobe epilepsy, but also in regions remote from the presumed focus [39], where no spikes, but sometimes EEG spectral changes are observed [40]. These findings support the concept of functional networks activated by the epileptic discharge [31]. Interestingly, these remote changes are not always increases in BOLD signals but sometimes also BOLD decreases [41, 42]. The reasons for negative BOLD response related to interictal activity are not yet clear and could be related to steal phenomenon secondary to the increased blood flow, to abnormal coupling between neuronal activity and blood flow in the pathological area, or to decreased or inhibited synaptic activity (for a discussion see [30]). When located in the spike area, negative BOLD appears to have the same localization value as the positive BOLD [43].

A problem for EEG-fMRI studies poses the fact that many patients do not display any epileptic discharges during the short period during which they can remain in the scanner. As the epileptic discharges are needed to build the regressor, data of patients without spikes in the scanner are generally lost. Recently, a method has been developed that can save some of these data and provide meaningful results [44]. The principal idea of the method is to use the EEG recorded during long-term clinical monitoring outside the scanner to search for spikes and construct a spike-specific scalp potential map. Then, the correlation of this map with the EEG in the scanner is computed for each time frame. The time course of this correlation coefficient can then be used as regressor for fMRI analysis to map hemodynamic changes related to these epilepsy-specific maps (**Figure 2**). In the study of Grouiller et al. [45], this algorithm provided concordant results with intracranial electroencephalography or with the resection area in 14 of the 18 patients (78%) whose data was not usable with the conventional method. This approach, developed in collaboration with groups from Geneva, London and Kiel, significantly increases the yield of simultaneous EEG-fMRI to localize the epileptic focus non-invasively.

The major limitation of EEG-fMRI for the localization of epileptic discharges is the low temporal resolution of the fMRI, which makes it virtually impossible to separate discharges coming from the primary focus from activity generated in propagation areas in the epileptic network. It is therefore rather the rule than the exception to find multiple areas of BOLD changes, and it needs additional tools to determine their functional-anatomical relationship. Already in our first report of EEG-fMRI in epilepsy, we proposed to use EEG source imaging as additional information to guide the inter-

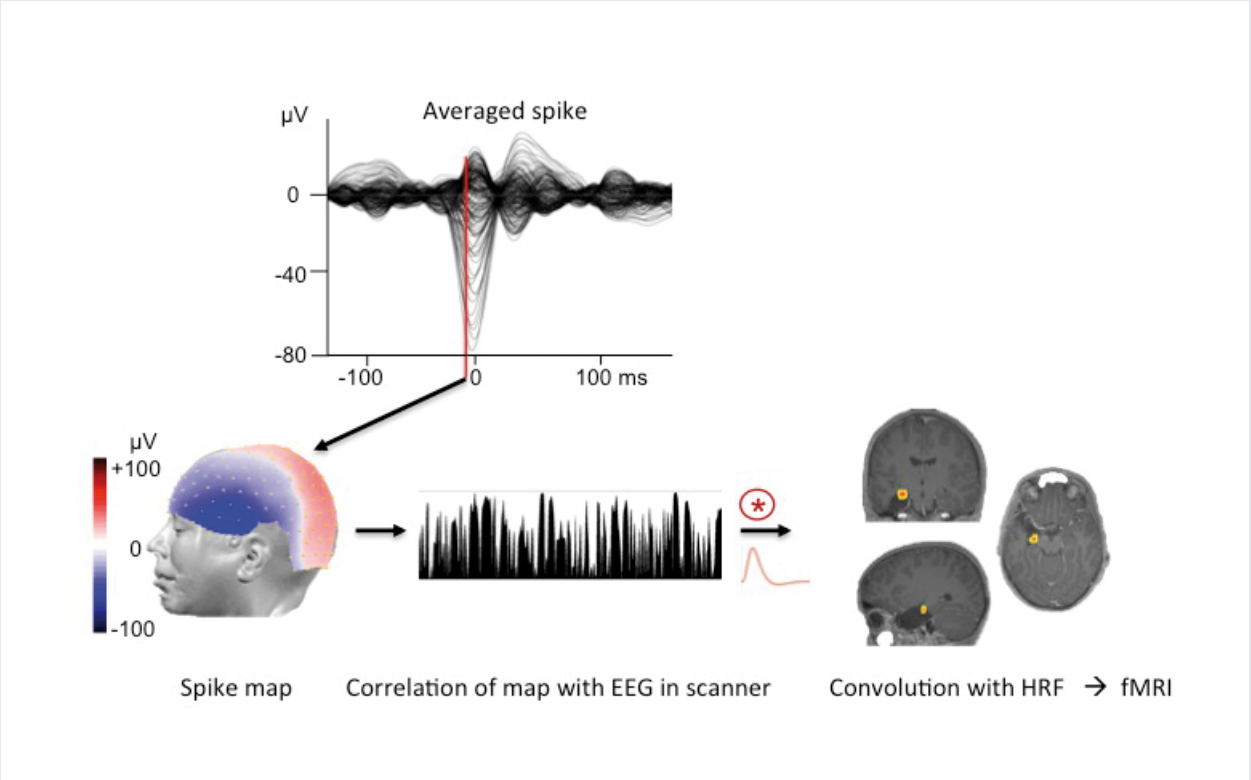

Figure 2: EEG-informed functional MRI using the method described in Groullier et al. [45] . Spikes are detected in EEG recordings outside the scanner and averaged. The scalp potential map at half-rise of the spike is determined and the spatial correlation of this map with each single map of the EEG recorded inside the scanner is calculated. The higher the correlation the more the EEG resembles the one seen during the spikes. The correlation is then down sampled and convolved with the hemodynamic response function in order to determine voxels with significant BOLD response related to the presence of the spike map. In this example, maximal BOLD is found in the left mesial temporal lobe. The patient suffered from a left hippocampus sclerosis that was surgically removed and rendered the patient seizure-free. The fMRI result is co-registered with the post-surgical MRI. Data from Grouiller et al. (45).

pretation of the fMRI results [25]. Several studies then demonstrated the use of such multimodal analysis [46-50] but they usually used the EEG recorded outside the scanner to compare with the BOLD response, assuming that the spatiotemporal behavior of the spikes are the same in- and outside the magnet. It is well known in clinical practice that the propagation behavior of single spikes is quite variable, even in patients known for stable unifocal epilepsy. Very powerful correction algorithms are currently available, so that artifact-reduced high density EEG (up to 256 channels) can be retrieved inside the magnet [51, 52]. Therefore, EEG source analysis can now be performed on the EEG in the scanner and directly be correlated with the hemodynamic response function [53], assuring that the same spikes are used for both, ESI and fMRI.

A systematic study using this method has been performed by Vuillemoz et al. [54]. They found that in 10 of the 12 recordings, ESI at the beginning of the spikes was anatomically close to one BOLD cluster. Interestingly, ESI was closest to the positive BOLD cluster with maximal statistical significance in 4/12 cases and closest to negative BOLD responses in another 4/12 cases. ESI at later time frame showed propagation to remote sources co-localised with other BOLD clusters in half of the cases. It was concluded that simultaneous ESI and EEG-fMRI analysis are more powerful to distinguish areas of BOLD response related to initiation of IED from propagation areas than fMRI alone. Very similar findings were reported in the study by Groening et al. [55].

Based on these studies Vulliemoz et al. [56] investigated in 10 patients whether the estimated EEG source activity improved models of the BOLD changes in EEG-fMRI data. ESI was performed on intra-fMRI averaged spikes to identify the irritative zone. The continuous activity of this estimated spike source over the entire recording was then used for fMRI analysis and the results were compared to the conventional spike-related model. The continuous ESI model explained significant additional BOLD variance in regions concordant with results from video-EEG, structural MRI or, when available, intracranial EEG in 10 of 15 interictal epileptic discharges.

These studies clearly show that the source analysis of the EEG in the scanner, is extremely valuable to guide the interpretation of the fMRI. This ESI-guided fMRI interpretation allows to fully exploit the high spatial precision of the fMRI in the frame-

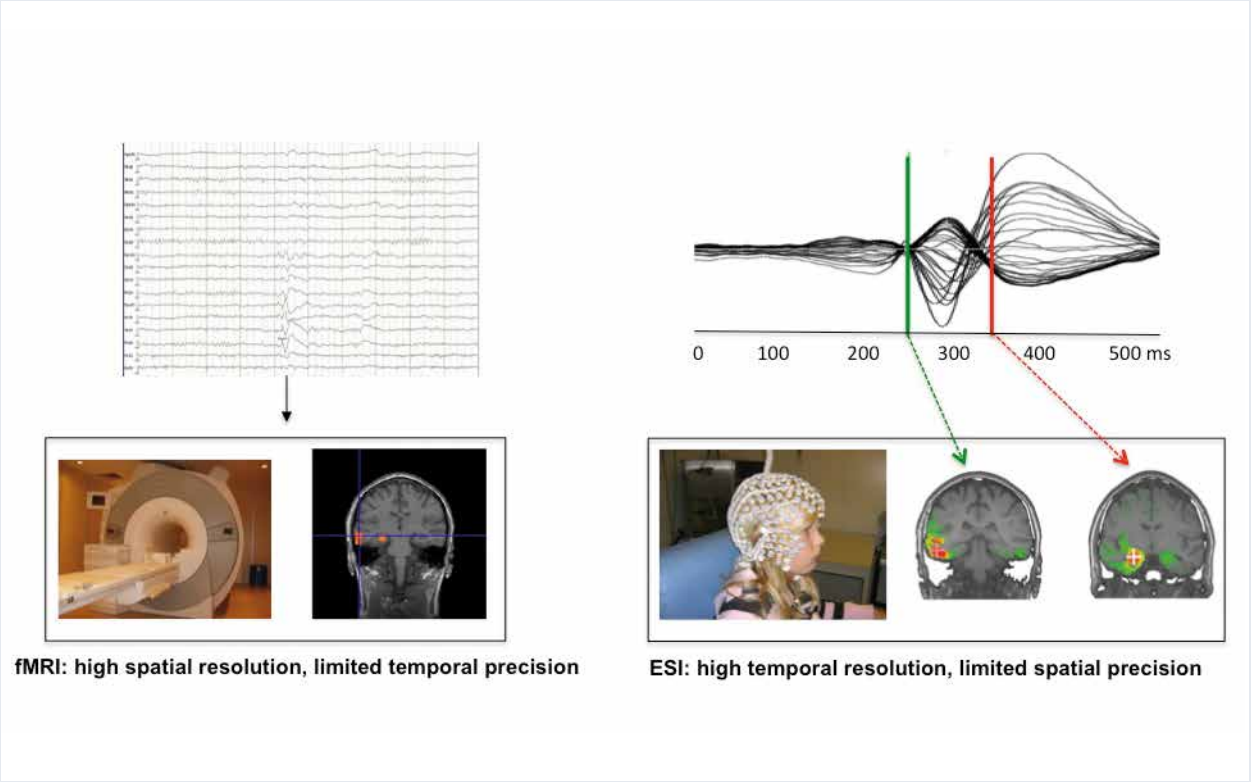

Figure 3: Combination of functional magnetic resonance imaging (fMRI) and electric source imaging (ESI). Left: EEG is continuously recorded in the scanner. Offline, the EEG is filtered and artifacts are removed. BOLD responses correlated with the appearance of spikes in the EEG are then calculated. In this case two significant regions were found in the left lateral and mesial temporal lobe. Right: Averaged spikes of the same recording in the scanner is analyzed with ESI. It reveals activation in the left lateral temporal lobe at the very beginning of the spike and then propagation to the mesial temporal lobe later during the spike-wave complex, strongly pointing to the lateral temporal lobe as epileptic focus. This information can then be used to select the fMRI voxels of interest in the lateral temporal lobe and look more carefully for structural or metabolic abnormalities in this area. Data from Vulliemoz et al. [54].

work of epilepsy surgery by pre-selecting the most relevant area of interest with ESI and then identifying the significant BOLD-voxels within this area. can teach us much about the functional properties of epileptic networks in focal as well as in generalized epilepsy.

Conclusion

This review intended to show that the presurgical evaluation of patients with pharmaco-resistent epilepsy can profit from new non-invasive imaging methods that are very powerful in localizing the epileptic focus: EEG-based electric source imaging and EEG-guided functional magnetic resonance imaging. Prospective studies on sufficiently large patient groups have clearly demonstrated the high sensitivity and specificity of these methods, particularly if modern technology (high-density EEG and high field fMRI) are used. Most powerful is in our opinion the direct combination of these two methods, as this combines in an optimal way the advantages of the two methods with respect to temporal and spatial resolution. There is no doubt that these methods should enter routine clinical use in presurgical epilepsy centers. They do not only help to localize the epileptic focus non-invasively, they also

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