Non-Invasive Work-up in Presurgical Evaluation of Extratemporal Lobe Epilepsy

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Summary

Surgery of extratemporal epilepsy is still a challenge, due to difficulties to define precisely the epileptogenic zone and the presence of vital cortex, such as motor, sensory, visual or language cortex. Both may be perceived as too close, preventing the complete resection of the epileptic focus and thus, leading to a less favorable result of extratemporal lobe epilepsy surgery as compared to temporal lobe epilepsy surgery. In most cases, invasive monitoring with implanted electrodes is required. However, pre-operative comprehensive localization of the focus as well as essential cortex can be done also with non-invasive tools. Here, we discuss the most advanced techniques, readily applied in extratemporal surgical epilepsy, i.e. electric source imaging (ESI) of the focus and evoked potentials, simultaneous EEG-fMRI recordings, and co-registration of the different imaging modalities with the individual patient’s MRI.

Key words: Extratemporal lobe epilepsy, presurgical evaluation, localisation, EEG source imaging, EEG-fMRI

Zusammenfassung


Schlüsselwörter: Extratemporale Epilepsie, prächirurgische Abklärung, Lokalisation, elektrische Quellenanalyse, EEG-fMRI

Bilan non-invasif dans l’évaluation préchirurgicale de l’épilepsie extra-temporale


Mots clés : Epilepsie extratemporale, évaluation préchirurgicale, localisation, imagerie de source électrique, IRMf-EEG

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Introduction

An essential task in the surgical treatment of epilepsy is the definition of resection margins that allows the removal of the epileptogenic zone as complete as possible while avoiding neurological deficits. To achieve this goal, the pre-surgical work-up includes precise localization of the epileptogenic cortex and of the functionally surrounding eloquent cortical areas. While this requires often invasive evaluation with intracranial electrodes, recent research showed that a large amount of work-up can be done with non-invasive tools.

It has to be kept in mind, that even with intracranial monitoring, the chances to become seizure-free when suffering from extratemporal lobe epilepsy are still less likely than in temporal lobe epilepsy. Most studies report 50-70% of extratemporal patients with post-operative complete seizure control, and if the MRI is normal, only around 40% can be expected to become seizure-free after surgical intervention [1].

The risks and benefits of invasive monitoring have to be carefully balanced against each other. Up to 10% of all patients with intracranial monitoring experience more or less significant complications. Reported risk factors are the following: greater number of intracranial electrodes, longer duration of monitoring, older age at implantation, left hemisphere implantation, and experience of the neurological and neurosurgical team. In the Cleveland clinic experience, in the first 10 years of their activity, 42% of all implanted patients had complications, which deceased to 19% after >10 years of teamwork [2]. Most frequent problems are bleeding (subdural, epidural or intracerebral hematomas) and infections, requiring constant clinical monitoring by an experienced staff. Moreover, intracranial electrodes cover only a small amount of surrounding tissue (in the order of several cm³) [3], which means that the placement of electrodes needs careful elaboration of hypothesis of possible seizure origins. If the intracranial electrodes are not correctly placed, the yield of this costly and physically demanding exam is markedly reduced.

As indicated above, not only the focus but also the vital cortex needs to be localized before an eventual resection. Again, this may require intracranial electrode placement, with consecutive electrical stimulation (or electro-corticography, ECOG), but ECOG alone as gold standard for functional localization has been also questioned [4, 5].

Given the significant impact of proper localization of the focus and adjacent eloquent cortex on the surgical results, considerable research on the development of more sophisticated imaging methods has been done during the last years, to be applied before surgery and/or implantation and in particular for patients with extratemporal lobe epilepsy.

We will briefly characterize the most promising approaches, including electric source imaging (ESI) with high density EEG, evoked potentials for localization of essential cortex, simultaneous EEG-fMRI recordings, and finally, the co-registration of the results from different imaging modalities.

Electric source imaging (ESI)

In contrast to fMRI, PET and SPECT, ESI directly measures neuronal activity [6, 7]. It is based on the recording of the electric potential field on the scalp using electroencephalography (EEG), and similar to any other imaging technique, its yield is higher with "sensors", or scalp electrodes allowing a more extensive coverage of the brain [8]. The high temporal resolution (milliseconds) allows tracing the flow of neuronal activity in the whole brain in real time. This is important for a disease like epilepsy where fast propagation is regularly encountered during interictal and ictal activity. Magnetoencephalogram (MEG) relies on the same electrophysiological phenomena, i.e. temporally synchronized and spatially aligned postsynaptic potentials, however, EEG – when recorded with a sufficient high number of electrodes – has a higher sensitivity than MEG because it "sees" neuronal activity independent of the dipole orientation and it is more susceptible for deeper sources [9]. Given that MEGs require a larger financial investment and maintenance, and that it is difficult to carry out ictal recordings with MEG, we are focusing here only EEG/ESI.

Our own studies showed that >100 electrodes are necessary to perform ESI with good to excellent precision. ESI is reliable and provides valid results only if basal temporal, frontal and occipital regions are covered [10]. Due to lower conductivity than previously estimated, in particular in young children or newborns (thinner skull), >250 electrodes are theoretically necessary to obtain correctly localizing results [11, 12]. Fortunately, this requirement is now met by several recent systems, which are commercially available and allow recordings of up to 256 electrodes [6, 13], probably more in the near future. Fast application of electrode caps with large number of electrodes is now readily possible, making high density EEG well feasible in clinical routine.

Most of the clinical ESI studies analyzed interictal spike activity. Simultaneous intracranial and scalp recordings showed that the analysis of scalp spikes provides more reliable localizing information about the epileptogenic zone than the analysis of ictal activity [14]. This is principally due to less extensive propagation of interictal vs ictal discharges. However, even during a single spike, substantial propagation may already occur, leading to incorrect results. Only certain segments of the spike, in particular during the “rising phase”, provide good localizing information [15].
We evaluated the clinical yield and localization precision in a group of 32 patients with focal epilepsy, recorded with 128 electrodes [16]. A correct localization on the lobar level was found in 93.7% of the cases. In the 24 patients who were successfully operated, the maximal ESI source lied within the resected area in 79%.

**Localization of eloquent cortex with evoked potentials and ESI**

Functional MRI (fMRI) has become the most established tool of non-invasive imaging of vital cortex and provides good localizing results of primary sensory and motor cortex. While EEG source imaging is primarily used for the localization of epileptogenic foci [17 - 20], its use in the localization of eloquent cortex in presurgical planning is less frequent. High resolution MEG systems have been on the market longer and were therefore explored for this purpose, particularly for the localization of sensory and motor cortex. These studies showed good correlation between sensory and motor evoked fields and ECOG [21, 22], providing a valuable alternative in patients who have difficulties to undergo fMRI (e.g. very young or retarded patients with difficulties to stay motionless for > 30 min). Similar good localization has been achieved with ESI applied to somatosensory evoked potentials [23], which is supported by own experiences with ESI based on > 60 EEG channel recordings.

A recent study activity in children compared the yield of EEG and MEG for localizing the somatosensory cortex. Good localization precision in all subjects with structurally normal cortex was found for both techniques in the healthy control group [24]. However, EEG source localization was found to be superior to MEG in patients with central structural lesions, due to more radial orientation of the dipoles which are less well detected by MEG.

Thus, EEG source imaging can be an alternative to

![Image of ESI application](image1.png)

*Figure 1. Electric source imaging (ESI) in a 15 year old girl with tuberous sclerosis and channels for numerous tubers in both hemispheres, including a large tuber in the left posterior temporal lobe. Top left: overlapped spike average recorded from 204 electrodes. Top right: result of ESI applied to this map, co-registered to the girl's brain showing a left posterior temporal source. Bottom right: superposition with the patient's implanted 8 x 8 electrode grid. The intracranial EEG result (green) was very well corresponding to the ESI result (red). Bottom left: language fMRI is strongly suggestive of right hemisphere language lateralization, confirmed by the intra-arterial amytal test (Wada-test). The patient was operated (removal of tuber and dysplastic lesion in the left temporo-parietal cortex) and is seizure-free since > 2 years. No language changes were encountered post-operatively.*
localize functional cortex in the presurgical planning. This conclusion was based on a study with 122 channel MEG and only 33 channel EEG, i.e. a setting rather unfavorable for EEG. It may be speculated that ESI is even more precise if more EEG channels are used [25]. Since this is now easily obtained in clinical routine [26], high resolution ESI of somatosensory evoked activity (or in the future, also motor evoked potentials) should be considered for non-invasive pre-surgical functional localization of the somatosensory cortex, particularly in patients with cortical malformations extending to central areas.

Localization of associative cortex, like language, is more problematic. Most fMRI studies content themselves in reporting the “lateralizing index”, i.e. how many voxels “light up” in the left vs right hemisphere. It has been repeatedly shown that language lateralization with fMRI is as reliable as with WADA testing and more reliable than speech arrest following ECOG [27, 28]. However, the use of fMRI for language localization is less promising. Concordance between intraoperative speech mapping using ECOG and fMRI is rather modest [29]. While some areas were identified by both techniques, several areas identified by ECOG (e.g. Wernicke’s area) were not seen in the fMRI. On the other hand, there are areas which are identified by the fMRI, but it is not clear if these areas are necessary or sufficient [30]. The use of MEG or EEG source imaging for localization of language cortex is rather sparse, but research on the use of these techniques in clinical evaluation of language function is becoming more and more promising (for a review see Salmelin [31]). It is obvious that the combined spatiotemporal information that MRI and EEG source imaging provide is an important asset when it comes to the specificity of the different areas that are involved in higher cognitive functions. Studies are urgently needed to establish the yield of magnetic or electric source imaging in localization of language areas in the individual patient.

Combined EEG-fMRI

The combination of simultaneously acquired EEG-fMRI has recently become possible thanks to MRI-compatible EEG systems [32]. Subsequently, powerful artifact removal algorithms for the EEG-signals have been developed that now allow to recover the EEG despite the high amplitude MR-artifacts during scanning [33, 34].

EEG-fMRI combination has become of particular interest for the localization of epileptogenic foci. Several groups have repeatedly shown the possibility to detect spike-related activity in the fMRI when the BOLD response is correlated with the epileptic discharges recorded in the simultaneous EEG. In the first EEG-fMRI recordings, Warach et al. studied interictal activity in two patients, one of them with generalized epilepsy that showed, surprisingly, a focal response [35]. However, further work-up was not done and so the clinical significance of this finding remained unclear. Other studies followed, and most of them in patients with chronic extratemporal lobe epilepsy. In particular for this group, EEG-fMRI appeared as a promising localizing tool which would provide better localizing information [36-39]. In many cases, blood oxygenation level dependent (BOLD) signal increases concordant with the lesion were found, i.e. EEG-fMRI is able to provide localizing information on the generators of the discharges [40, 41]. In some cases, the concordance of the “real” focus could be confirmed.
with intracerebral recordings [37, 42].

However, the overall clinical yield of the EEG-fMRI alone is relatively low: less than 1/3 of all patients could be analyzed [47, 43]. This is due to the lack of visible interictal epileptic discharges (IED) in the scanner, movement artifacts, or for unknown reasons – lack of significant BOLD response. Another important limitation of the EEG-fMRI for the localization of epileptic discharges is the low temporal resolution of the fMRI which is in the order of several seconds. Interictal epileptic discharges usually propagate within millisecond-range to remote or even contralateral brain areas [44]. These secondary activations consume also oxygen and may show up as additional, or sometimes, even the most predominant areas of activation. Our group was the first to successfully combine ESI and fMRI [40]. In a more recent study [45] patients with benign childhood epilepsy with centrotemporal (rolandic) spikes were analyzed with fMRI and ESI. In all patients, the electric source was localized in the rolandic face or hand region as expected. The fMRI analysis provided results in only 4 of the 11 patients (36 %), but showed also additional areas in the central cortex, the sylvian fissure and the insula. Most of these areas (but not all) corresponded to the propagated electrical activity as identified by the ESI.

It is also not yet clear to which extent the BOLD response is related to abnormal neuronal activity and of functional significance for the patient. For example, extensive BOLD changes related to brief focal electrographic seizures have been described in a patient with right temporo-parietal gray matter nodular heterotopia [46]. Brief focal seizures resulted in major widespread BOLD activations. Moreover, there is still an ongoing discussion if the BOLD increase or decrease provides a better presentation of the “true” epileptogenic focus. The reasons for negative BOLD response related to interictal epileptogenic activity are not yet clear: a steal phenomenon secondary to the increased blood flow, abnormal coupling between neuronal activity and blood flow in the pathological area, or decreased or inhibited synaptic activity are discussed as possible explanations (for a discussion see Gotman, 2008 [47]).

Thus, EEG-fMRI has become an interesting additional diagnostic tool in patients with chronic partial epilepsy, but needs to be complemented by other imaging tools, or by ECOG. It is now well known in clinical practice that the propagation behavior of single spikes is quite variable, even in patients known for unifocal epilepsy. Very powerful correction algorithms are currently

Figure 3: 45 year old patient with large glioblastoma of the left frontal and temporal region. fMRI indicated correctly the right hand motor and sensory cortex, which is superior from the lesion. The sagittal plane shown at the right indicates that this vital cortex is at distance from the lesion, albeit close.
available, so that artifact-reduced high density EEG (more than 64 channels) can be retrieved inside the magnet [48], so that ESI and fMRI can be obtained in a single session and increasing the yield of both [49, 50].

There is a clear correlation between extent of resection and outcome in terms of seizure control. Provided a careful elaboration of the indication and good surgical planning, higher rates of seizure-free patients could be obtained [51, 52]. The sparing of functionally relevant brain areas is important as to not reduce the gain of epilepsy control in exchange to the loss relevant neurological functions. Therefore, one aims at so-called tailored resections, which should take into account not only the individual pathological findings, but the patients higher cortical functions (motor, verbal, visuospatial etc.) as well which should not be affected by the surgery.

Detailed presurgical analysis of all imaging data and neuropsychological findings plus their co-registration is thus very important for successful individualized treatment and surgical planning. This requires considerable coordinated efforts of various subspecialties and information technology at an increasing scale in order to interpret the complex results from signal and source analysis together [53]. If more modalities concord on a single focus, the chances to benefit from surgery are significantly higher than if this is not the case [54]. From a surgical point of view it is quite clear that the results from pre-resective diagnostics, which includes the information obtained via intracranial electrode, should be brought as close as possible to the surgeon, so that he may orientate himself reliably and quickly. This is most important in extratemporal lobe epilepsy, where no clear anatomical boundaries are present and provide "natural" limits of the resection (as it is the case in temporal lobe epilepsy surgery).

Co-registration of different image modalities

Figure 4: 20 year old patient with non-lesional right frontal epilepsy. In the first row: EEG-triggered fMRI revealing several areas of increased BOLD signal, notably superior frontal, frontal polar and insular (patient's right side is on the right side of the image). ESI analysis (below) suggested that in particular the superior frontal and fronto-polar areas correspond to the epileptogenic zone (images 1-3 from the left).

Conclusion

Extratemporal lobe epilepsy requires careful evaluation of the site of the epileptic focus as well as precise mapping of all vital functions in the individual patient. Only the complete resection of the epileptogenic focus results in complete seizure control, and is an aim which needs to be pursued also in extratemporal lobe epilepsy surgery.

While studies in distinct healthy controls can be inspiring in terms of technical aspects, the presurgical team has to make a prediction in a single patient with
Despite advances in non-invasive functional brain mapping, pre-operative mapping of functional and dysfunctional cortex in extratemporal lobe epilepsy still relies largely on invasive procedures intracranial electrodes. This costly and lengthy procedure is associated to a significant morbidity and mortality. As indicated above, there is no procedure, not even invasive EEG and ECOG, which can be considered as gold standard for all clinical questions. If the invasive procedure can be at least abbreviated or even abandoned due to well-localizing pre-operative non-invasive results, more patients could be operated with better outcomes.

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