

Non-invasive mapping of epileptic networks

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Key points

Epileptic activity involves a network of cortical and sub-cortical brain regions

Focal seizures and focal epilepsy are classically considered to be related to the abnormal neuro-electrical activity of a focal epileptogenic region: a distinct patch of cortex generating epileptic activity with subsequent propagation to other regions of the brain. That hypothesis has been crucial for the semiological understanding of focal symptoms and signs related to the onset and propagation of those seizures, and their correlation with the localisation of radiologically visible brain lesions or electroencephalographic abnormalities. Moreover, that hypothesis drives decision-making in candidates for epilepsy surgery as well as the development of imaging techniques that aim to localise epileptic activity for the purpose of surgery. However, there is growing evidence from recent advances in neuro-imaging that focal seizures and focal epilepsies are in fact caused by the abnormal function of a network of cortical and sub-cortical brain structures rather than by a single epileptogenic region. The abnormal neuronal activity of these connected regions, and the abnormal interactions between them (called “functional connectivity”) are responsible for the occurrence of interictal and ictal epileptic activity. This paradigm shift is reflected in the report of the commission by the International League Against Epilepsy for the new scheme of terminology of seizures and epilepsies [1]. This report proposes that the term “*focal*” indicates that the seizures arise primarily within networks limited to one hemisphere. These may be discrete or more widely distributed” [1]. For generalised seizures and generalised epilepsies, studies have also shown that they involve bilateral sub-cortical and cortical regions rather than the entire brain so that the current view is to not consider them as “*generalised*” but as “*originating within and rapidly engaging, bilaterally distributed networks*” [1]. Some of the brain regions in epileptic networks are sites of seizure initiation or propagation while other regions are more remotely involved, with their activity modulating or modulated by the occurrence of epileptic activity.

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This article presents non-invasive neuro-imaging techniques that map brain regions associated with the occurrence of epileptic activity and therefore can be used for mapping the epileptic networks. For obvious practical reasons (patient safety, recording duration), these techniques are based on the recording of interictal activity rather than seizures but there is now increasing evidence that interictal spikes can be a good estimator of the localisation of regions involved in the generation of seizures. Compared with other neuro-imaging applications, the field of epilepsy imaging greatly benefits from the unique presence of invasive validation of the localisation techniques in some patients by means of intracranial electroencephalography and/or post-operative follow-up (concordance between the electrical source and the resection zone). These validation studies could guide the application of these techniques in other disorders of the nervous system as well as in basic cognitive neurosciences.

Epileptic networks: clinical implications and epilepsy surgery

A good characterisation of epileptic brain networks is crucial for refining the classification of seizures and epilepsies. This is of great importance for designing epidemiological and pharmacological studies that will assess disease prognosis and optimal treatment strategies. From a more fundamental perspective, improved knowledge about the abnormal network properties could help to gain a better understanding of the initiation, propagation and termination of seizures within these networks. Last but not least, the mapping of the epileptic networks is of critical importance for the 30% of patients with epilepsy who suffer from pharmaco-resistant epilepsy and are evaluated for the possibility of epilepsy surgery. In well-selected candidates, resective surgery can lead to seizure freedom in 70–80% of cases with temporal lobe epilepsy and more than 50% of cases in extra-temporal lobe epilepsy. The epileptogenic zone is defined as the region of the brain that needs to be removed to obtain seizure freedom. The pre-surgical evaluation consists of estimating the localisation and extent of this region, and its relationship to the cortical and sub-cortical structures involved in important brain functions (e.g., vision, language, memory, and motor functions) in order to assess and minimise the risk of post-operative deficits. The estimation of the localisation and extent of this epileptogenic zone is based on the mapping of the irritative zone (generating interictal spikes), the seizure onset zone and the symptomatogenic zone (producing the

ictal symptoms and signs). To identify these components of the epileptic network in clinical practice, ictal video-EEG recordings, structural magnetic resonance imaging and neuropsychological evaluation remain the cornerstones of the work-up, while nuclear medicine techniques such as interictal PET (Positron Emission Tomography) and ictal SPECT (Single Photon Emission Computed Tomography) are also frequently used additional techniques. However, additional imaging techniques are needed. Combining the concept of the epileptogenic zone and the network approach, seizure freedom could be reached without the necessity to remove the entire network. Indeed, resection of a node or interruption of a critical connection of the network could sufficiently alter the network to suppress its epileptogenicity.

The identification of nodes which are important for seizure generation and propagation could also play a key role in the development of neuromodulation techniques in which deep brain electrical stimulation targets relay nodes of the epileptic networks in patients who cannot benefit from epilepsy surgery. The clinical effect of high-frequency electrical brain stimulation is probably due to alterations of the pathological neuronal activity and enhancement of inhibitory synaptic transmission within the epileptic network, as suggested by stimulation studies in movement disorders. Long-term significant reduction in seizure frequency has been reported for the stimulation of the amygdalo-hippocampal complex in temporal lobe epilepsy and for the stimulation of the anterior nucleus of the thalamus in focal epilepsies. Vagal nerve stimulation is another form of neuromodulation in which the stimulation of the vagal nerve has a modulation effect on the epileptic activity, probably by remotely modulating key structures of the epileptic network. While promising, these techniques so far remain limited to patients who cannot benefit from resective surgery, and complete seizure freedom is only rarely achieved. However, they may represent future options for reducing post-operative deficits and offer non-pharmacological options for patients with difficult-to-treat focal, but also generalised epilepsies.

Electric Source Imaging (ESI) based on high-density electroencephalography (EEG) localises focal epileptic activity with excellent clinical accuracy

EEG recordings can be displayed not only as multi-channel “waves” of scalp potential but also as voltage maps on the scalp that provide information about the large-scale brain dynamics with an ideal temporal resolution. Sophisticated mathematical algorithms can estimate the distribution of the electric source within the grey matter that give rise to these maps, millisecond by millisecond. Therefore, this technique is a very useful tool for directly estimating the source of focal epilepsy [2]. Several clinical studies have shown the reliability of the techniques in a wide spectrum of patients, adults and children with non-lesional epilepsy or large lesions. Recently, we reported the largest study of ESI in 152 patients who had subsequent resective surgery (invasive validation) for pharmaco-resistant epilepsy [3]. ESI applied to epileptic spikes had an excellent sensitivity and specificity that sur-

passed more classical localisation techniques, such as the presence of a lesion on structural MRI or focal abnormalities on isotopic imaging (interictal PET and ictal SPECT). Such accuracy was only obtained when using high-density EEG recordings (128 or 256 electrodes) and the individual patient’s brain anatomy, that notably allows to correctly estimate the inferior and medial temporal brain activity. However, even with a low density of electrodes, the sensitivity and specificity was comparable to that of interictal PET and ictal SPECT. The ease of use of EEG compared to Magneto-encephalography (bed-side test, some motion allowed, no sedation needed, possible in young children or cognitively impaired patients) makes it a very useful tool for localising the epileptic focus. The recent availability of long-term high-density systems will allow researchers to capture larger numbers of seizures and to develop new strategies for ictal EEG analysis. New techniques for estimating connectivity between brain regions based on scalp EEG (or MEG) are also being developed to analyse brain networks with high temporal resolution.

Simultaneous EEG and functional Magnetic Resonance Imaging (EEG-fMRI) map regions involved in epileptic activity at a whole brain scale

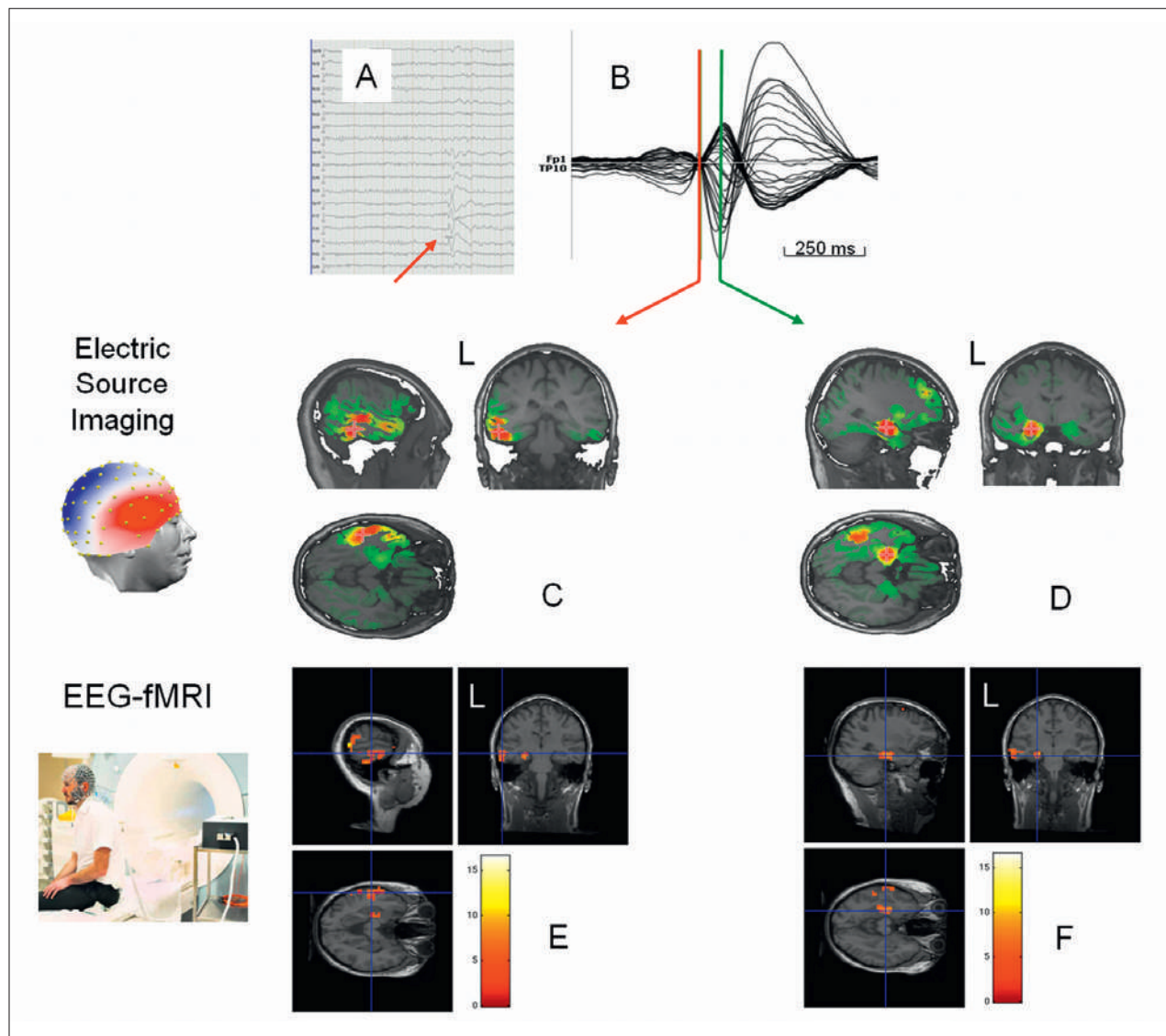
Combining the equipment required for fMRI and EEG recordings can seem very inappropriate and even prone to hazard: the varying magnetic field can induce electrical currents in the EEG system leading to large signal artefacts and also heating, and the EEG cables and electrodes distort the magnetic field and therefore data quality. However, technical developments have enabled safe recordings of scalp EEG (and even intracranial EEG) simultaneous to fMRI with good data quality after artefact correction. The analysis then reveals brain regions where there are haemodynamic changes (measured by fMRI) correlated to epileptic activity (detected on EEG) [2]. This whole-brain mapping tool has improved the characterisation of brain structures and regions associated with epileptic activity by often revealing multifocal regions involved in epileptic activity suggestive of the networks described above [4].

Several EEG-fMRI studies have improved our understanding of various epileptic syndromes. In particular, they provide hypotheses for the occurrence of transient alterations of cognition and consciousness associated with epileptic activity. In *generalised epilepsies* such as absence seizures and generalised tonic-clonic seizures, studies show an “activation” of both thalami as well as a widespread “deactivation” of the cortex correlated to epileptic activity. In *temporal lobe epilepsy*, seizures are often associated with impaired awareness and EEG-fMRI studies suggest a functional relationship between the activation of the hippocampus and the deactivation of a network comprising the lateral fronto-parietal cortex and the precuneus. These brain structures form the so-called “*Default Mode Network*”, a set of brain structures displaying more activity during quiet wakefulness compared to task-related activity or impaired consciousness. Therefore, a reduced activity in this network in relation with epileptic activity could explain the altered awareness experienced during seizures. An alternative

Figure 1

Multimodal combination of Electric Source Imaging (ESI) and simultaneous EEG and fMRI recordings to map epileptic activity in the human brain in a patient with left temporal epilepsy. Both techniques give important information and their combination further enhances spatial and temporal resolution.

- A EEG recorded during fMRI scanning showing left temporal epileptic spikes (arrow, after correction for gradient- and pulse-related artefacts).
- B Average of left temporal spikes.
- C ESI at the onset of the spike (red arrow) showing maximal source in left lateral temporal lobe (red cross).
- D ESI at later time during epileptic spikes (green arrow) showing propagation to medial temporal structures (red cross).
- E, F EEG-fMRI showing lateral and medial haemodynamic changes related to epileptic spikes that are concordant with ESI results. Therefore, EEG-fMRI improves the spatial resolution of ESI and offers whole-brain mapping including deep brain regions while ESI allows disentangling regions related to onset versus propagation of epileptic spikes.



hypothesis, related to a network inhibition of the diencephalic-cortical circuits mediated by the medial temporal structures has also been proposed [5].

For clinical applications, EEG-fMRI has been used to localise focal epileptic activity in patients who are candidates for epilepsy surgery. Several studies validated by intracranial EEG or post-operative follow-up show a good concordance of haemodynamic changes with the seizure onset zone and the epileptogenic zone. In one study of patients with focal cortical dysplasia, we have shown that EEG-fMRI yielded valuable information for the prediction of post-operative outcome. Focal spike-related haemodynamic changes in

these patients suggested a good prognosis when concordant with the intracranial EEG compared to more diffuse or multifocal haemodynamic changes associated with a poor prognosis. We and others have proposed several methodological developments to improve the sensitivity and specificity of the technique, notably by using more information from the EEG than just the occurrence of spike, especially via combination with ESI. The convincing results of these studies, some with strong invasive validation, give further support for the use of EEG-fMRI as a pre-surgical tool in epilepsy surgery candidates [6].

Multimodal combination of brain imaging techniques enhances our understanding of brain networks

The combination of functional techniques using different measurements can yield further improvements in spatial and temporal resolution, meaning an increase in sensitivity and specificity. The power of such multimodal combination is shown in figure 1, which illustrates ESI and EEG-fMRI techniques as well as their combination. ESI performed during fMRI recordings allows distinguishing between haemodynamic changes related to spike onset versus propagation thereby enhancing the temporal resolution of fMRI. Other techniques based on advanced EEG analysis of EEG-fMRI studies allow localising focal epileptic activity even in the absence of epileptic spikes [6]. Studies of functional relationships between brain regions based on fMRI, intracranial EEG, MEG (Magnetoencephalography recording magnetic rather than electric fields on the scalp) and now scalp EEG are currently integrating the network approach in the analysis. Combining maps of functional networks with knowledge of the structural connections revealed by diffusion MRI-based tractography may allow the identification of direct and indirect connections within these networks.

In summary, epileptic activity in the brain is increasingly considered as the dysfunction of a neuronal network rather than a single pinpoint source. Careful, specialised evaluation of patients with difficult-to-treat epilepsy is highly recommended as well-selected patients can benefit from epilepsy surgery leading to seizure freedom. Surgical success and a

reduced risk of surgical complications can be enhanced by the concordance of multimodal non-invasive brain imaging techniques that aim to better understand and map the epileptic network and the eloquent cortex. The combination of these techniques and future developments will improve our understanding of the dynamics of brain functions with a high spatial and temporal resolution. Invasive validation of these techniques in the field of epilepsy imaging can benefit large area of neuro-imaging research for clinical and basic neuroscience.

Key words: epileptic networks; electric source imaging; simultaneous EEG and functional MRI; abnormal functional and structural connectivity; epilepsy surgery

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