

# EEG, fMRI and Their Combination in the Study of Epilepsy

Electroencephalography (EEG) and Functional Magnetic Resonance Imaging (fMRI) are two important techniques for the study of the human brain, healthy or diseased. For example, EEG is of primary importance in the clinical evaluation of patients with epilepsy, by allowing the visualisation of very brief (order of ms) electrophysiological abnormalities during seizures and between seizures, such as interictal spikes (focal epileptic spikes).<sup>1</sup> EEG can therefore provide specific markers of epilepsy containing some localising information in relation to an underlying brain abnormality responsible for the epilepsy. EEG is also capable of recording patterns linked to specific external (visual, sensorial, etc) stimuli, in the form of evoked responses. Salient features of the scalp EEG, such as spikes or rhythms, reflect increased synchronisation of cortical activity at various spatial scales, ranging from sub-lobar to the entire brain. Simulations and experimental data have shown that such EEG features must involve a patch of cortex with an area of at least 10cm<sup>2</sup>. Crucially, scalp EEG is most sensitive to superficial cortical activity with limited or no sensitivity to events taking place deeper in the brain such as on the medial aspect of the temporal lobe, which are only detectable via propagation to more superficial cortex.

Some localising information on the generators of EEG features can be derived qualitatively from visual inspection of the recordings by experienced observers, mainly based on consideration of the feature's amplitude in relation to the various channels particularly for discharges such as focal epileptic spikes. In patients with drug-resistant epilepsy who may benefit from surgery EEG recordings combined with careful examination of

the clinical manifestations observed during seizures (such as recorded on video-EEG telemetry) are capable of providing very useful information, but at the lobar level. Focal spikes being much more common than seizures, a great effort has been made to use these for localisation purposes. Although in general spikes may originate from outside the epileptic focus itself (their generator is called the irritative zone), in many cases there is considerable overlap. In theory, spike generator localisation can be improved on using computational EEG source reconstruction methods based on assumptions on the form of the EEG generators.<sup>2</sup> The simplest and commonest assumption is that EEG generators can be represented as electrical dipoles, consisting of combined positive and negative sources. Although widely used in research this type of localisation has had limited impact on clinical practice in large part due to uncertainties in the modelling assumptions.

## Functional MRI

Therefore, EEG-based localisation remains limited in accuracy and clinical utility. On the other hand functional MRI, in the form of activation maps derived from series of scans, is a powerful tool for visualising changes linked to epochs of specific brain activity contrasted to a control state.<sup>3</sup> Two great advantages of fMRI are its more or less equal sensitivity irrespective of location in the brain and sampling down to a few mm. Although fMRI-based localisation does not suffer from the same type of uncertainties as EEG-based localisation as highlighted above, it is limited by other factors such as poor temporal resolution (of the order of seconds) and is subject to numerous artefacts (particularly at high field strengths such as 3T and above). Perhaps more impor-



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Born in the city of Québec in Canada, Louis Lemieux obtained a PhD in Physics at the Université de Montréal in 1990. He joined the Institute of Neurology (which became part of University College London in 1997) at Queen Square, London, the same year to work in the Epilepsy Research Group (Drs David Fish and Simon Shorvon) on multi-modal imaging applied to Epilepsy. In 1995 the Group established an MRI Unit entirely dedicated to research in Epilepsy located on the site of the National Society for Epilepsy in Chalfont St Peter, Buckinghamshire. Professor Lemieux's interests focus on the application of functional MRI to the study of paroxysmal activity and longitudinal quantitative MR imaging.

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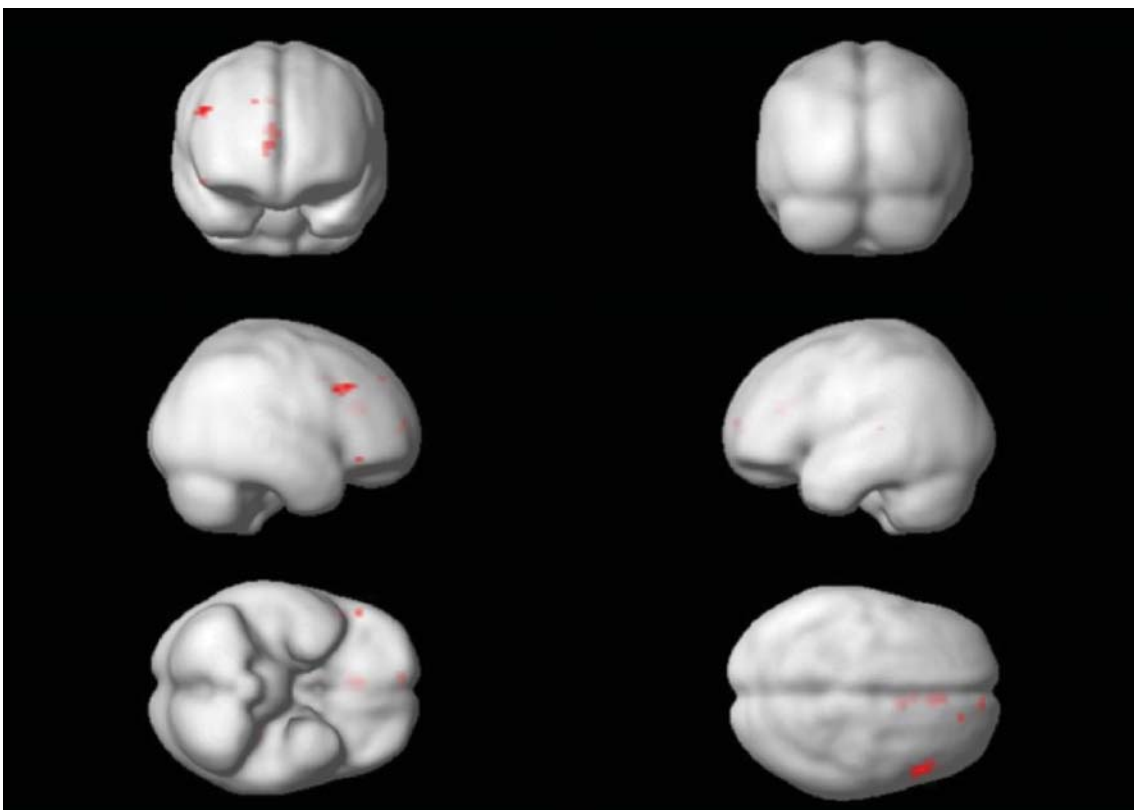


Figure: Spike-related activation pattern (BOLD increase, in red) derived from combined EEG-fMRI experiment, associated with frequent focal spikes originating in the right frontal lobe in a patient with drug-resistant epilepsy. There are clusters in the mesial and lateral aspect of the frontal lobe.

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tantly, fMRI reflects neuronal activity only indirectly, in the form of signals related to the haemodynamic changes that are associated with neuronal activity. The most commonly used form of fMRI signal is the Blood Oxygen-Level Dependent (BOLD) effect. The spatio-temporal relationship between the BOLD signal and neuronal activity in general remains the subject of intense investigation.<sup>4</sup> One of the main features of the BOLD signal is that it develops (grows and resolves) over a period of 15-20 seconds following a brief external stimulus. In some circumstances, the BOLD signal decreases following an event; this is thought to reflect mainly local decreases in blood flow and neuronal activity. This means that fMRI activation maps, although often extremely revealing and compelling, can present the investigator with an interpretation challenge. This may also reflect the fact that fMRI is novel compared to EEG, about which much remains to be understood. An important aspect of fMRI, quite distinct from most EEG, is its reliance on correlation with an independent factor, such as external stimulus or task, i.e. precisely timed queues, for acquisition and interpretation. Therefore most fMRI is acquired and analysed in a fashion similar to evoked potential EEG experiments rather than free-running as in most routine EEG.

### The combination of EEG and fMRI and its application in the study of Epilepsy

A question that arose in the early 1990s was whether paroxysmal activity of the type encountered in patients with epilepsy, such as seizures and focal spikes, could be imaged using fMRI. In view of the way fMRI is analysed, this requires data to be collected in two states, normal background (control state) and paroxysmal ('active' state), such that each scan in the time series can be labelled as either. Therefore imaging seizures may be possible based on behavioural manifestations in some cases. However, in most cases it is neither practical (because of the rarity of ictal events on one hand and the image artefacts caused by head movement on the other) nor safe to aim to image seizures in an MR scanner, although there have been a few attempts at imaging focal seizures.<sup>5</sup> In generalised epilepsy, absence seizures (which are usually devoid of motion) are interesting candidates for imaging. Interictal events, such as focal spikes, occur much more commonly but by definition are devoid of clinical manifestations. Therefore, imaging this type of activity requires the recording of EEG during the fMRI acquisition; this type of experiment is called EEG-correlated fMRI or EEG-fMRI. This EEG-fMRI represents a technical challenge because of interactions between the MR scanner and EEG recording equipment, which can result in degradation of image and EEG data quality, and because of patient safety concerns. These have been largely addressed over the last 10 years, although combined EEG-fMRI experiments remain some of the most technically challenging in the field of neuroimaging.

In a typical EEG-fMRI experiment, as performed in our centre, EEG electrodes in a cap are attached to the patient's scalp and to a specially designed MR-compatible EEG recording system, and the patient is asked to keep their eyes closed and to relax during the 20 to 40 minute scan. One of the main features of this type of EEG recording system is that the lack of ferrous components to avoid mechanical forces turning it into a dangerous projectile and minimise image quality degradation, and the very high sampling signal rate (and synchronization link to the scanner) necessary to get rid of the artefacts caused in the EEG by the scanning process.

No experimental task or stimulus is therefore imposed; this type of experiment is called resting-state fMRI. As noted previously, the experimental state at any given time is determined based on the simultaneously recorded EEG. Scans acquired during or following an EEG event

of interest (focal spike, spike-wave complex or run of events) are compared to those acquired during periods of background activity and activation maps obtained following the application of statistical tests to assess the likelihood of genuine correlation at any given location in the brain.

The application of EEG-fMRI in epilepsy remains largely exploratory, focusing on investigating the technique's ability to reveal activations in relation to various types of EEG abnormalities and syndromes (see Figure). The technique has now been applied in hundreds of patients with focal epilepsy in many centres throughout the world. The main findings are: fMRI provides localising information (i.e. statistically significant regional BOLD changes) in roughly 60% of cases in which focal spikes are captured; regions of positive BOLD changes tend to co-localise with the presumed focus; regions of negative BOLD changes tend to be more remote from the presumed focus; activation of the ipsilateral hippocampus and deactivation of the precuneus commonly observed in relation to temporal spikes; a time course of BOLD signal increase similar to that observed following brief external stimuli or tasks in healthy subjects.<sup>6</sup> Although much more work needs to be done to assess the technique's potential added clinical value, effectively taking the technique into a more clinical hypothesis-driven phase, there are already signs that EEG-fMRI can provide additional information in the pre-surgical evaluation of patients with drug-resistant epilepsy.<sup>7</sup> An interesting potential role for EEG-fMRI is that of providing implantation targets for intra-cranial EEG investigation.

In the generalised epilepsies, absence seizures and interictal generalised spike-wave discharges have been shown to be characterised by thalamic activation and widespread (though rather variable) cortical deactivation, including a set of regions comprising the precuneus, labelled 'default mode network' which is altered in relation to variations in brain state away from restful wakefulness.<sup>8</sup> These new and unique observations highlight EEG-fMRI's great potential as a scientific tool.

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