

***Identification of the epileptogenic network using multimodal data fusion involving electrophysiology (MEG-EEG), simultaneous EEG-fMRI acquisition and near infrared spectroscopy (NIRS)***

Epilepsy is a neurological disorder that affects 0.5 to 1% of Canadians. The major form of treatment is long-term drug therapy to which approximately 30% of patients are unfortunately refractory. Surgical treatment may be considered in these cases of drug resistant epilepsy. The goal of the surgery is the resection of brain tissues that contribute to generate seizures, without causing any important functional loss.

In this context of presurgical investigation, identification and understanding of the underlying mechanisms involved during the generation and propagation of interictal epileptic discharges is a key issue, as interictal discharges are most often involved in similar networks to those recruited during a seizure. Moreover, it is more convenient to study interictal activity than seizures, as interictal discharges are more frequent and do not induce patient movement, so they can be investigated using **several non-invasive imaging techniques**. Standard presurgical investigation involves clinical ElectroEncephaloGraphy (EEG) and anatomical Magnetic Resonance Imaging (MRI) that are the reference non-invasive exploration techniques used to identify the epileptogenic focus. EEG provides information regarding neuronal activity at high temporal resolution (~1 ms) and is the gold standard measure of epileptic activity, but provides only weak spatial localization. High-resolution anatomical MRI enables many patients to have an underlying structural lesion disclosed, and therefore identification of a potential cause for the epilepsy. Whereas these lesions constitute a well defined target for surgery, the reason why selective lesionectomies may lead to seizure control or long-term failure is still an open question.

The overall objective of my research project proposal is to **characterize brain mechanisms underlying the generation of interictal discharges using the integration of multimodal data. To do so, I plan to evaluate the clinical value of combining three promising functional modalities to standard EEG acquisitions:**

- (1) **Simultaneous EEG - MagnetoEncephaloGraphy (MEG) acquisitions**, measuring directly on the scalp electric and magnetic components of signals generated by a population of pyramidal neurons synchronously active during an interictal discharge (temporal resolution: 1ms, high density covering the whole head surface: 275 sensors in MEG and 64 electrodes in EEG).
- (2) **Simultaneous EEG – functional MRI (fMRI) acquisitions**, measuring within the whole brain, hemodynamic responses that correlate with interictal discharges detected on scalp EEG (temporal resolution: 1s, spatial resolution: 3 mm). fMRI measures hemodynamic processes through the Blood Oxygenation Level Dependent (BOLD) signal, which results from local variations of deoxy-hemoglobin combined with regulations of regional blood flow and volume.
- (3) **Simultaneous EEG – Near Infrared Spectroscopy (NIRS) acquisitions**, measuring local change in oxy- and deoxy-hemoglobin at the time of discharges detected on scalp EEG, exploiting absorption properties of infra-red light within brain tissues using optic fibres placed on the surface of the head (temporal resolution: 1 ms, penetration: 2-3 cm from the surface of the head).

The high resolution anatomical MRI of each patient will provide the common spatial support to localize, analyze and fuse all these functional data, whereas EEG will be the common marker of epileptic activity used to ensure that similar phenomena are studied in the three sessions.

**Simultaneous acquisition of EEG-MEG data and source localization of interictal spikes**

The rationale of combining EEG and MEG recordings is to measure additional information about epileptic activity, not seen when measuring the EEG only. Indeed, MEG and EEG are sensitive to different aspects of neuronal activity. An epileptic spike will only be visible on scalp EEG if at least 6 cm<sup>2</sup> of cortex is activated. Magnetic fields being less interfered by the resistance of the skull and scalp than electric potentials, MEG is able to detect less extended generators, 4 cm<sup>2</sup> of cortex was suggested. MEG sensors are only sensitive to tangential sources, whereas EEG electrodes are sensitive to any source. MEG sources are then more sensitive to signals originated in the sulci, assumed to be at the origin of interictal discharges,

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whereas EEG will be more sensitive to generators located on gyri. Consequently, some spikes can then be seen in only in MEG and others only in EEG, and the use of both increases the sensitivity to epileptic activity. Even coincident EEG and MEG spikes can have different features and the simultaneous analysis of both can allow better detection of epileptiform abnormalities. Complementary properties of EEG and MEG data can be used to improve source localization and MEG can bring pertinent information regarding propagation of the activity during interictal discharges.

**Objectives:** My objective is to use redundancy and complementary aspects of MEG and EEG recordings of interictal spikes to provide an **accurate description in space and time of the generators of these events**, using spikes detected only in MEG, only in EEG or in both EEG and MEG. We will pay particular attention to additional information that MEG could bring to EEG regarding **additional sources and also propagation pathways during interictal discharges**.

### Simultaneous acquisition of EEG-fMRI data and concordance with source localization

**Rationale:** The paramagnetic property of the deoxy-hemoglobin (HbR) is at the origin of fMRI signal used to measure brain activity. Being paramagnetic, HbR perturbs local magnetic field resulting in a local signal loss. Local increase in neuronal activity requires energy, which result in a local increase in oxygen consumption. The response of the system, involving regulations of regional blood flow and blood volume (e.g., by vasodilatation), brings more oxy-hemoglobin (HbO) than needed. This effect results in a local decrease of HbR by dilution and then a local increase in the fMRI signal: this is the Blood Oxygenation Level Dependent (BOLD) signal. Simultaneous recordings of fMRI and intracortical neural signals have shown invasively correlations between BOLD signal changes and main generators of the EEG signals. These results support the existence of a coupling between generators of EEG-MEG signals and the hemodynamic response elicited by such activity. **Simultaneous EEG-fMRI acquisition** constitutes then a unique technique, which allows to study within the whole brain the hemodynamic changes correlated with interictal epileptic activity detected on the scalp EEG. EEG-fMRI concordance was mostly reported by comparing fMRI results with scalp topology of the discharges, but the results have rarely been compared with EEG source localization. Many phenomena linked to the generation and propagation of a spike may then be missed by scalp EEG. Propagated sources can already be involved at the time spikes are seen on the scalp, whereas one can measure a BOLD response as soon as it correlates with scalp EEG. Because of the inertia of the hemodynamic phenomena (few seconds), it is feasible to detect BOLD response corresponding to events that could occur slightly before or after the main spike seen on scalp EEG. For instance, distant BOLD responses located in sub-cortical or contralateral regions are not rare and may reflect such phenomena.

**Objectives:** Our objective is to explore **the underlying network of anatomical structures** involved within the whole brain at the time of epileptic discharges, and to assess what cortical regions identified within such a network are in concordance with **EEG and/or MEG sources**.

### Simultaneous acquisition of EEG-NIRS data and neurovascular coupling

**Rationale:** Near Infrared Spectroscopy is a new technique, which allows the measurement of hemodynamic changes associated with neural activity. The different light absorption spectra of oxy-haemoglobin (HbO) and deoxy-haemoglobin (HbR) within the near-infrared spectrum reflects concentration changes of these substances in living tissues. Near-infrared light of a wavelength between 680 and 1000 nm is directed through optic fibers to the head of the patient. This wavelength window is used because other wavelengths are mostly absorbed by human tissues, water and haemoglobin (Hb). The near-infrared light travels through the skull and diffuse inside the brain in a semi-spherical trajectory so that a fraction of light is recaptured by detectors located elsewhere on the scalp. Two wavelengths, one of 690 nm and one of 830 nm, are frequently used at the same time. The 690 nm light is more absorbed by HbR whereas the 830 wavelength is absorbed more by HbO. The amount of detected light provides information about the amount of absorption of the two wavelengths, which in turn indicates HbO and HbR concentration changes in targeted cerebral areas. These hemodynamic changes reflect cerebral activation, usually characterized by simultaneous

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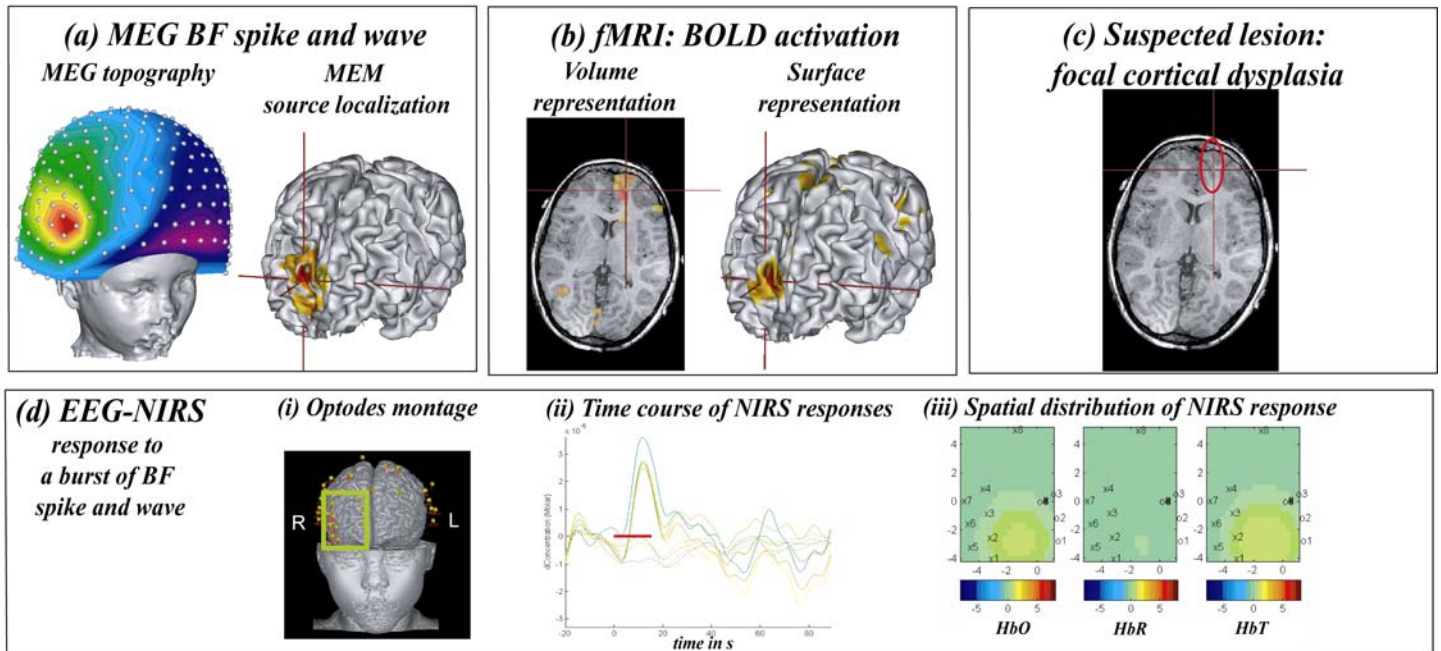
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increase of HbO and decrease of HbR in the same area. The BOLD signal results from a modifications in HbR concentration, but also from regulations of the regional cerebral blood flow and blood volume, whereas NIRS is the only technique able to distinguish HbR and HbO. Evidence of local modifications HbO and HbR during spike and wave discharges has recently been demonstrated.

**Objectives:** Our objective is to use NIRS to accurately characterize the neurovascular coupling in cortical regions selected as part of the epileptogenic network according to previous multimodal investigations (EEG, MEG, fMRI), whether corresponding fMRI responses were classified as concordant or discordant with EEG and/or MEG sources.

### A clinical example of multimodal concordance

## Converging evidence using multimodal data fusion



Converging evidence using multimodal data fusion. MEG sources, fMRI responses and NIRS response associated with bilateral frontal (BF) bursts of spike and wave in a patient with focal refractory epilepsy. For all figures a, b, and c the red cross corresponds to the same left frontal point on all images. (a) MEG sensors topography (gray dots = sensors positions) and MEG sources localized at the main peak of the average spike. (b) Simultaneous EEG-fMRI: significant BOLD activation ( $p < 0.05$  corrected) in response to bursts of bilateral frontal spike and waves detected on scalp EEG,  $t$ -maps of BOLD response superimposed on the 3D anatomical MRI (left) and projected onto the cortical surface (right). (c) Lesional zone: a focal cortical dysplasia could be suspected in the right fronto-mesial sulcus indicated using the red ellipse. This diagnosis was confirmed after surgery. (d) Simultaneous EEG-NIRS: oxy-hemoglobin (HbO), deoxy-hemoglobin (HbR) and total hemoglobin (HbT) responses to a single burst of BF spike and wave. (d,i) MEG and fMRI results were used to optimize the position of the optic fibers, in order to explore the lateral and mesial aspects of the right frontal lobe as shown in the optode montage (green rectangle). (d, ii) Time course of the response of HbO (plain lines) and HbR (dotted lines) occurring few seconds after a single burst of BF spike and wave detected using scalp EEG (horizontal red line). Each color line (plain for HbO, dotted for HbR) corresponds to a pair of source-detector indicated in the green rectangle of the montage. (d, iii) Spatial distribution (within the green rectangle of the montage) of the concentration of HbO, HbR and HbT at the peak of the response. This figure illustrates an example of excellent concordance between the three proposed modalities (EEG-MEG, EEG-fMRI and EEG-NIRS), showing as well the feasibility of the project. Each modality brings converging evidence for the others. The detected right fronto-mesial region was resected 6 months ago, and the patient is seizure free since then.