Investigation of seizure propagation using EEG-fMRI and dynamic causal modelling

P. Figueiredo[1], and A. Leal[2]
[1]Instituto Superior Técnico, Lisbon, Portugal, [2]Department of Neurophysiology, Hospital Júlio de Matos, Lisbon, Portugal

Introduction:
The simultaneous acquisition of the electron-encephalogram (EEG) with functional magnetic resonance imaging (fMRI) can be used to localize epileptic brain networks through the identification of the haemodynamic correlates of (inter-)ictal electrical discharges. Although focal seizures are thought to originate from a small brain region, knowing the directionality of discharge propagation through complex epileptic networks is of much clinical importance [1]. One of the challenges of EEG-fMRI techniques in epilepsy is therefore the investigation of the spatio-temporal dynamics of the Blood Oxygenation Level Dependent (BOLD) signal, in order to identify the epileptic focus and the direction of information transfer within a network of functionally connected brain areas. It has recently been shown that it is possible to estimate effective connectivity among hidden neural variables from BOLD-fMRI time series, through Dynamic Causal Modelling (DCM) approaches [2]. In contrast to data-driven functional connectivity methods, such as Granger causality, which test for statistical dependencies among the observed BOLD signals, DCM implements biophysical models of these signals as a function of the hidden neural variables that generate them. For this reason, the former techniques may fail if the haemodynamic response varies across brain regions. Here, we have employed DCM to test a number of competing models of discharge propagation within a network of functionally connected brain areas identified from EEG-fMRI data of ictal activity, in a patient with epilepsy associated with a hypothalamic hamartoma (HH) [3].

Methods:
The study of the HH patient has been previously reported [3]. Simultaneous EEG-fMRI measurements were performed on a 1.5 T Cvi/NVi GE scanner and included: (1) a 3D T1-weighted SPGR acquisition with 0.94x0.94x0.60 mm^3 resolution and (2) six BOLD-fMRI acquisitions consisting of 150 GE-EPI volumes, with TR=2.275 sec and 3.75x3.75x5.00 m^3 resolution, yielding an acquisition time of ~5 min 40 sec per acquisition. Light anesthesia with 1% Sevoflurane was applied by mask throughout the scanning session, as established by the local protocol for small children and uncooperative patients. The EEG was recorded using a 37-channel DC amplifier through an MR compatible system (MagLink, Neuroscan, Charlotte, USA), sampled at 1000 Hz with low-pass filtered at 70 Hz. The EEG artifacts induced during EPI were removed using the Scan 4.3.3 software and the cleaned signal was visually inspected to detect rhythmical spike activity typical of seizure events. In one of the six fMRI acquisitions, 5 events of left occipital spikes were detected, involving the left temporal and parietal lobes, as well as the frontal lobes on both hemispheres: this dataset is the one analysed here. Pre-processing of BOLD-fMRI data was performed using FSL (www.fmrib.ox.uk/fsl) and included: motion correction, slice time correction, spatial smoothing with an 8 mm Gaussian kernel and high-pass temporal filtering with a 100 ms frequency cutoff. A general linear model (GLM) analysis was then conducted using SPM5 (www.fil.ion.ucl.ac.uk/spm), by employing a design matrix defined by the convolution of the periods of ictal activity recorded on the EEG with a standard gamma haemodynamic response function (HRF). Clusters of significant BOLD signal changes related with the ictal activity were identified and used to define Volumes of Interest (VOI) for subsequent DCM specification and estimation, using SPM5 (www.fil.ion.ucl.ac.uk/spm).

Results:
Standard GLM analysis of seizure activity-related BOLD signal changes revealed a well-defined network of brain regions (Fig.1), including: the HH on the left hemisphere (**HH**), the left hippocampus (**Hip**); the left occipital cortex (**Occ**) and the left dorso-lateral frontal cortex and cingulate gyrus (**Fro**). A spherical VOI was defined for each cluster, centered on its Z peak position and with a 6 mm radius. Six DCM's were then specified to describe the connectivity among the four VOI's, according to anatomical criteria used to formulate hypothesis concerning the direction of seizure propagation (Fig.2). It was assumed that the HH was the seizure focus and hence the neural driver of the network. The negative free energy obtained by estimating each of the six models revealed that **Model 4** is the most plausible (Fig.3). The neuronal and haemodynamic kernels estimated for **Model 4** are in agreement with the architecture of the model, with HH responses preceding those of the hippocampus and occipital cortex, which in turn precede the response of the frontal lobe (Fig.4). These results support the hypothesis of propagation of seizure activity from the HH through the left fornix to the temporal and occipital lobes, and later through the cingulated fasciculus to the left frontal lobe.

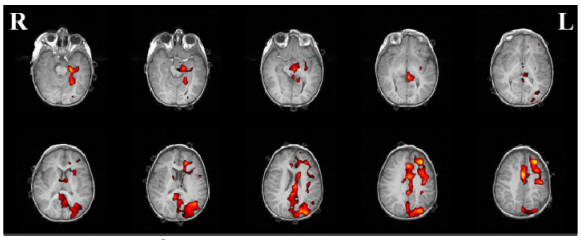

Figure 1. Z maps of seizure-related BOLD activity, overlaid on T_1 image.

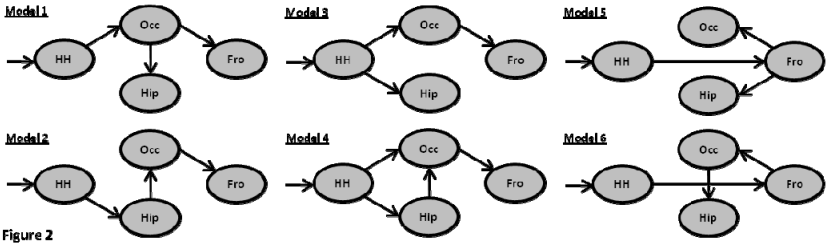

Figure 2

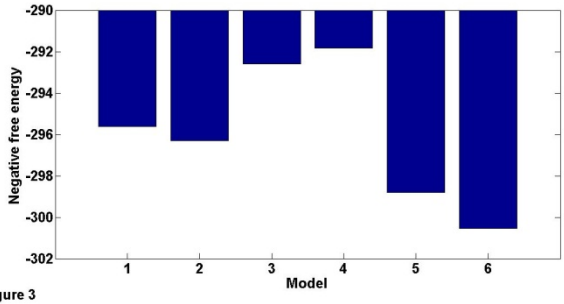

Figure 3

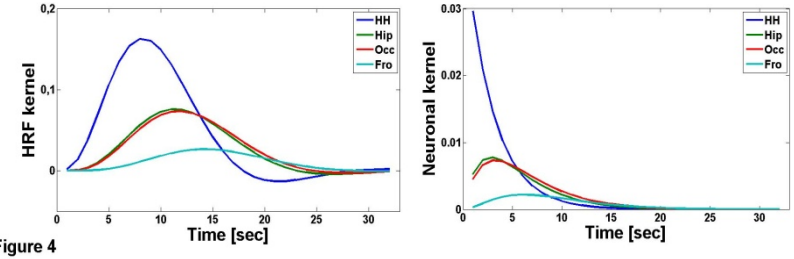

Figure 4

Conclusion:
Our results demonstrated the feasibility and utility of employing dynamical causal models to investigate effective connectivity in epileptic networks identified using EEG-fMRI. It is in this way possible to study the origin and propagation pathway of seizure activity, which may be of critical importance when deciding the surgical approach for epilepsy treatment.

References:
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