

Dependency of the paroxistic activity duration on its localization through its analysis using a simultaneous combination of EEG-fMRI:First Results

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Abstract. Acquisition of electroencephalogram (EEG) during functional Magnetic Resonance Imaging (fMRI) provides, non-invasively, the simultaneous capture of cerebral haemodynamic response as well as the registered electric cerebral activity on the scalp. And, consequently, the union of these techniques gives the chance to study the existent correlation between abnormal epileptogenic shapes (spikes, spike-and-wave) and its related haemodynamic response.

The main aim of our purpose is to define an approximation of the correlation between the EEG signal and the fMRI applied to the localization of the epileptogenic focus. In order to reach our objectives, firstly, we have to obtain a proper sincronization of recording systems EEG/fMRI and the activation of a filtering system allowing to remove all the noisy artifacts produced by the Magnetic Resonance equipment. Subsequently, the identification of epileptogenic shapes in the EEG filtered signals by marking their timings and periods, to analyse the fMRI signal when these events appeared. The last step consists on checking the concordance between the suspected focus of epileptogenic activity extracted from EEG information and the activation areas in the fMRI image. Additionally, the most important proposal consists on dividing the paroxistic activity as a function of its duration and analyses its haemodynamic response separately. Our results showed that the areas of BOLD activation were different depending on the duration of paroxistic activity in a patient suspected to be suffering from generalized epilepsy.

Keywords: EEG, fMRI, BOLD, epilepsy, duration of paroxistic activity

1. Introduction

Combination of EEG [Niedermeyer et al. 2004] and fMRI [Moonen et al. 1999] data provides an ideal combination of the excellent spatial resolution of fMRI with the millisecond temporal resolution of EEG (Debener et al. 2006). The concurrent utilization of both methods has only been established in the last few years. This is due mainly because of several technical challenges when combining both methods. The most important problems arise from the physical phenomenon of electromagnetic induction [Lemieux et al. 1997] that introduces noise artifacts in registered EEG signal inside MR scanner. In fact, one of major efforts has been devoted to the development of proper artifact removal techniques.

One of the most interesting applications of this combination of techniques is the study of the interictal activity in patients with epilepsy [Petra et al. 2006] This work differs from most applications of fMRI because the stimuli is internally generated, in a random and infrequent way and with a limited duration (rarely more than 10 seconds). Among the results obtained from different authors, it is found that activation of a neuronal zone was more significantly recognized when more epileptogenic waveforms appeared after the instant when BOLD function began to be integrated [Bagshaw et al. 2005]. Some other authors have showed that some epilepsy diagnosed as focal, presented also other focus in its haemodynamic response [Kobayashi et al. 2005; Federico et al. 2005; Detre et al. 2005]. Furthermore, positive haemodynamic response in scattered regions and the thalamus have been found in patients with IGE (Idiopathic Generalized Epilepsy) [Hamandi et al. 2006; Laufs et al. 2006; Jann et al. 2008]. In previously mentioned studies, only positive BOLD was analyzed but some others that

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considered also negative BOLD [Hamandi et al. 2007; Tana et al. 2008] discovered some concordances difficult to explain.

Epileptiform activity could be categorized by using its morphology, its occurrences, its clinical consequences, and also, using its duration. Some authors have analyzed the haemodynamic response observed when clustering interictal epileptiform discharges by distinguishing them from its morphology and field [Liston et al. 2006]. Another study evaluated the influence of the duration of epileptogenic events into the models of haemodynamic response function of paroxysmic brain activity obtaining that, in general, it is better to include this parameter in the statistical analysis [Bagshaw et al. 2005].

2. Material and Methods

Patient

The patient recruited from the Department of Neurology of Jimenez Diaz Foundation Hospital was selected because of his visible frequent interictal activity recorded with routine surface EEG. The patient was clinically evaluated by a board certified neurologist with subspecialization in epileptology. According to the evaluation, the patient was suspected to suffer from IGE (Idiopathic Generalized Epilepsy), based on clinical semiology and previous EEG findings. The analysis of structural high-resolution MRI of the patient did not show any lesion.

In different previous studies, EEG and Video-EEG, the patient was diagnosed to suffer from absent, tonic, mioclonic and tonic-clonic crisis. From the evaluation of Epilepsy Unit, the localization of crisis was localized in frontal lobe.

Written informed consent was obtained in accordance with the regulations of the Department of Neurology of Jimenez Diaz Foundation Hospital of Madrid. The study has been approved by the local ethical committee.

Data acquisition

EEG data were recorded using a Brain Amp MR EEG amplifier, Brain Vision Recorder (Version 1.03) software and a BrainCap electrode cap (Brainproducts, Munich, Germany) with 30 Ag/AgCl electrodes positioned over the scalp according to the international 10-20 system with impedances of 5K Ω , and two polygraphic electrodes with impedances of 15 K Ω , for electrocardiography (ECG) and electrooculography (EOG). The 30 cm long ECG lead was positioned at the chest of the patient. The BrainAmp system allows the use of a sampling rate of 5 KHz and incorporates hardware filters that limit the frequency range of the recorded signal to 0,016-250 Hz by default, although we limited high frequency to 70 Hz to reduce artifacts at high frequencies, it also included a Notch Filter at 50 Hz. The cap provided a reference electrode positioned between Fz and Cz, which were situated along the central line of the head at the top, near the crown. This equipment was totally compatible with MR scanner so patient with the electrode cap was put inside the scanner and the EEG amplifier just next to it. The amplifier was connected by an optic fiber with the computer running the signal acquisition software (Brain Vision Recorder) which was situated in the control room. Moreover, the trigger signal sent by the MR scanner was connected to the computer to mark the beginning of each volume acquisition of MR.

MRI data were collected using a General Electric Signa 3.0 T MR scanner (General Electric Healthcare, Farfield, CT) using a whole-body radiofrequency (RF) coil for signal excitation. For the structural image, a high-resolution 3D T1-weighted Gradient Echo-SPGR (1-mm slice thickness, 260x260 matrix, Preparation Time= 650 ms, TE = 4,2 ms, TR = 9,2 ms, flip angle 12°, complete volume 156 slices) Functional data was acquired using a continuous multislice EPI sequence (3-mm slice thickness, 96x96 matrix, TE = 50 ms, TR = 3 s, flip angle 90°, complete frame 36 slices). Additionally, all patients underwent a structural MR imaging protocol, including diffusion tensor imaging using EPI sequences, axial FLAIR images and T2-weighted Gradient Echo for the detection of structural brain lesions. Note that TR of all MR sequences was always a multiple of the EEG scanner clock period, thus reducing the impact of gradient artifact in EEG signal [Mandelkow et al. 2006]

EEG preprocessing

EEGs recorded during the MRI sessions were post-processed using Vision Analyzer software (Version 1.05, Brain Products, Munich, Germany) EEG data recorded in the MR scanner is contaminated with two main artifacts which are much larger in magnitude than the electrical brain activity of interest. The largest artifact is produced by the temporally varying magnetic field gradients used in fMRI, which generate voltages in the conducting tissues of the human body and the wires of the EEG recording system. This artifact is called as gradient artifact [Anami et al. 2003] which can be more

than a few mV in magnitude, as we can see in Fig. 1, making the EEG signal unrecognisable. The second artifact is caused by the movement of the cardiac cycle at frequencies of approximately 10 Hz and below. This artifact is called pulse artifact or ballistocardiograph [Allen et al. 1998]

To remove these artifacts we applied the average artifact subtraction method (AAS) described previously [Allen et al. 1998; Allen et al. 2000] which removed most of the MR pulse artifact. Subsequently, down-sampling to 500 Hz was performed and a high pass filter at 50 Hz and ocular correction were also applied. Then, Pulse Artifact correction was performed using Independent Component Analysis (ICA) [Srivastava et al., 2005]. Fig. 1 shows EEG signal before and after artifact correction.

The paroxysmic activity was visually identified by an expert observer and the time of the beginning and end of their occurrences noted (Figure 1).

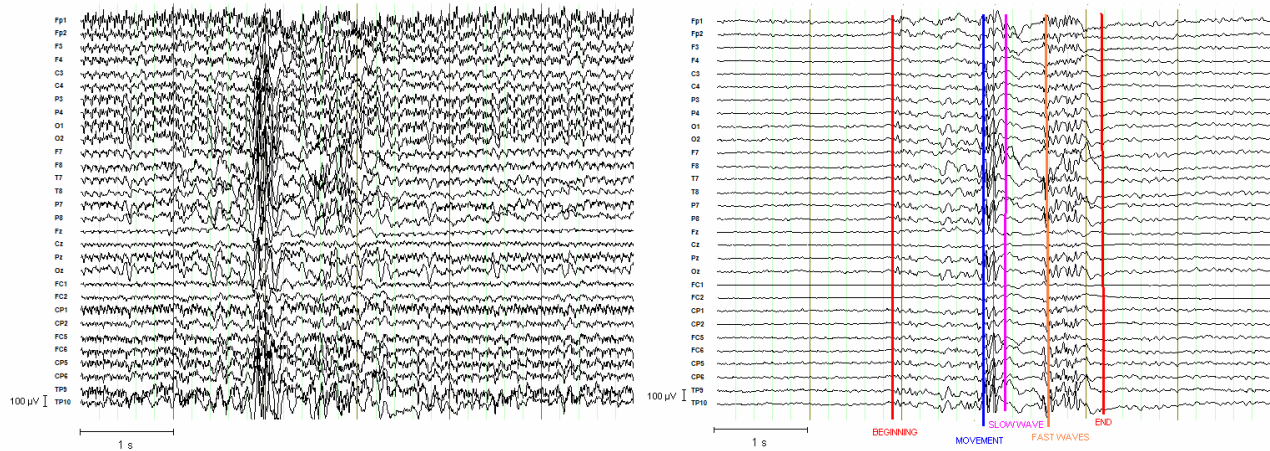


Figure 1: Example of paroxysmic activity of 2 seconds registered by EEG before (left) and after (right) elimination of gradient and pulse artifact. It can be seen in the right figure how we can distinguish different events caused by the seizure: its beginning, a facial movement followed by an slow wave, finishing with a burst of fast waves.

MRI preprocessing

Analysis of the MRI data was performed using Statistical Parametric Mapping as implemented in the SPM 8Beta analysis software package. The EPI images were realigned and unwarped, resulting in motion-corrected images and corresponding translation and rotation realignment. After that, images were normalized to Montreal phantom and smoothed using an 8 mm FWHM (Full-width at Half Maximum).

Functional images were formed by the convolution of delta functions at the times of paroxysmic events marked previously in EEG with a canonical HRF (Haemodynamic Response Function) and its temporal derivative (TD). A T test was performed across the HRF in order to search for any significant correlated BOLD activation.

3. Results

The fMRI response obtained after analyzing all the events previously marked in the EEG can be seen in Fig. 2, so all this epileptogenic activity is joined to make the analysis. The maximum BOLD activation was clearly detected in the frontal left lobe ($p < 0,01$). However, an activation in the occipital lobe ($p < 0,05$) and a central activation ($p < 0,05$) including the Corpus Callosum also appeared to have a haemodynamic response to epileptogenic discharges. From these results, we couldn't establish that those focuses found corresponded with the localization of the epilepsy discharges.

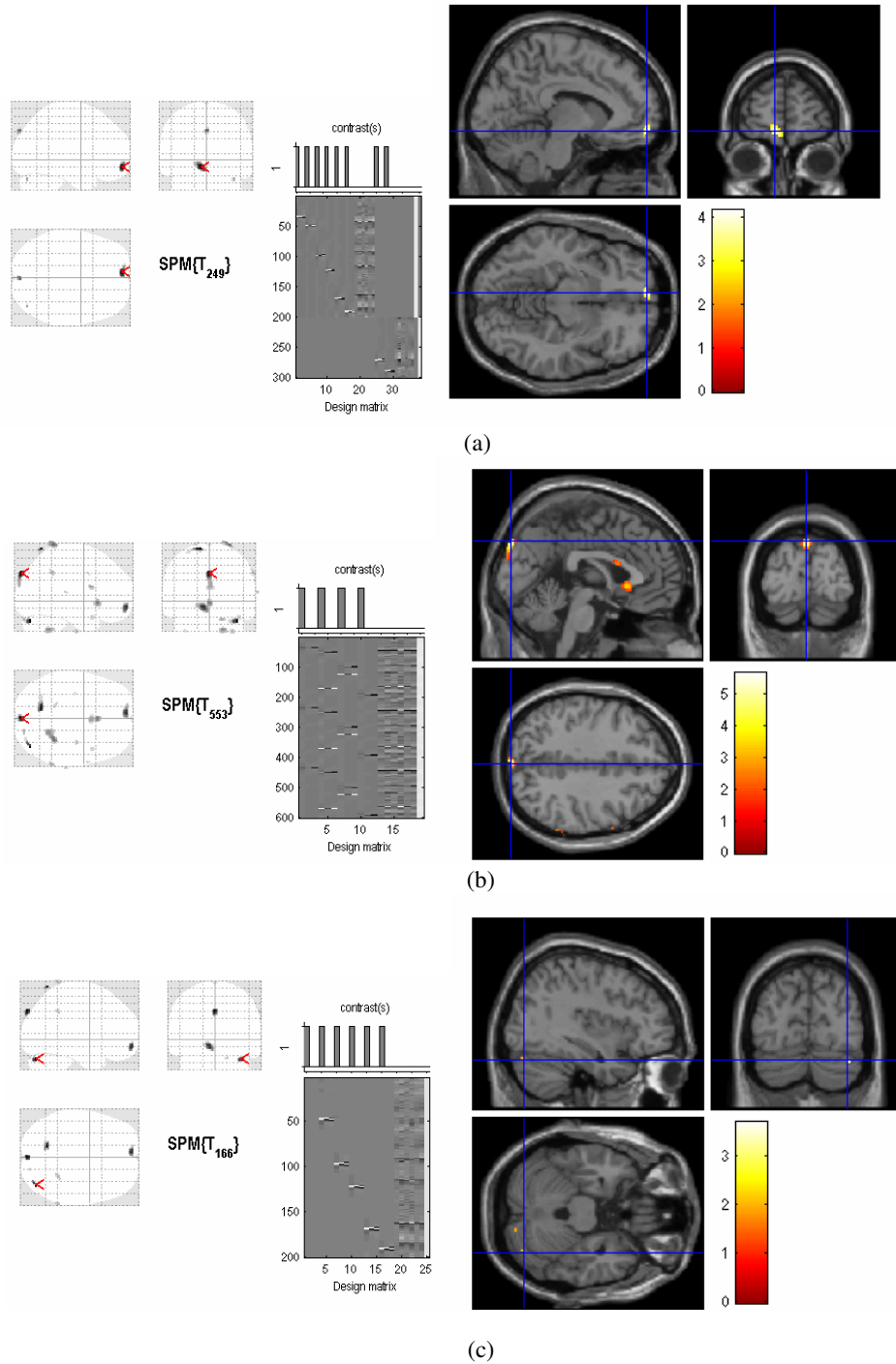


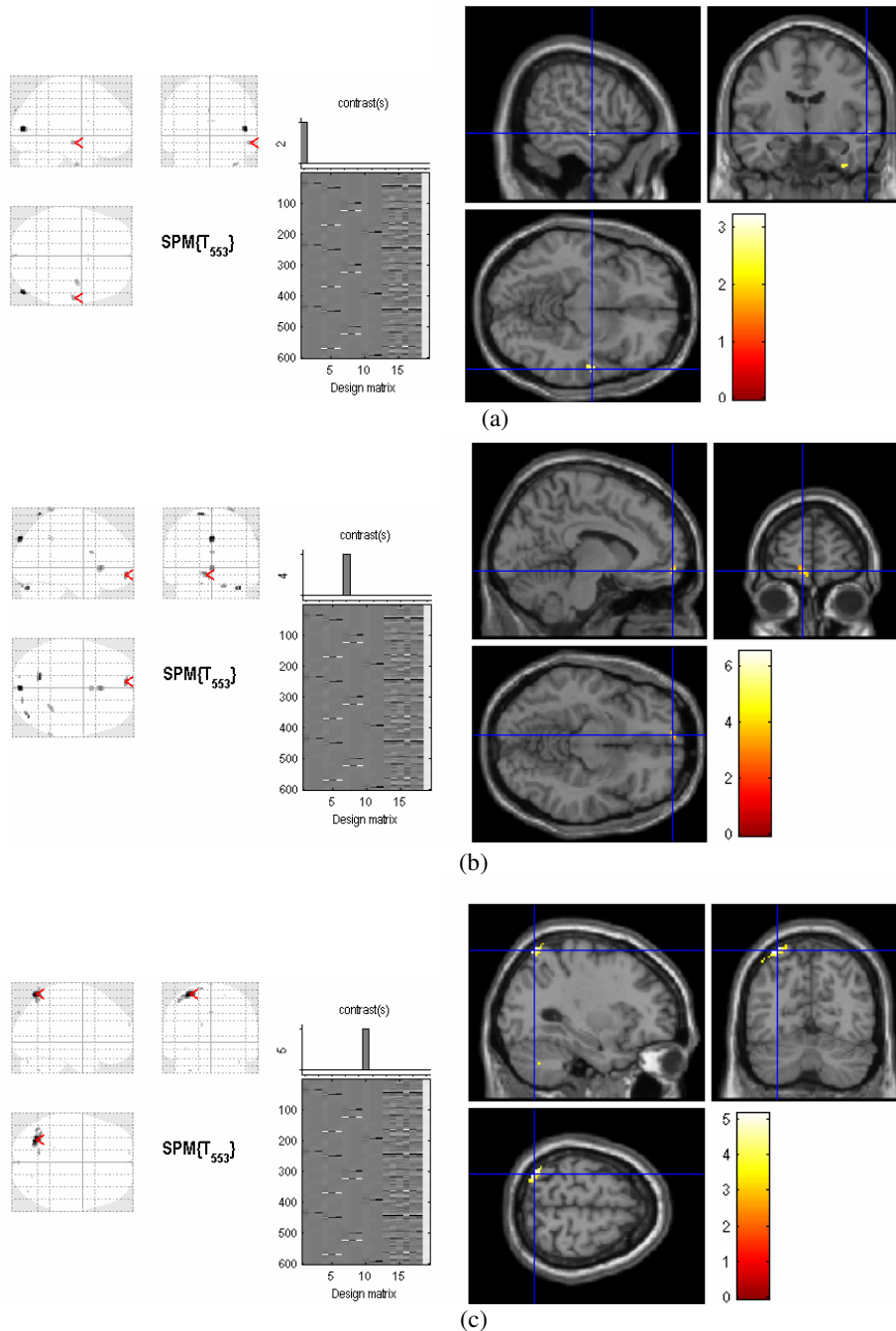
Figure 2: The fMRI response obtained after analyzing all the events previously marked in the EEG can be seen in Figure a-c this epileptogenic activity is joined to make the analysis. (a) The maximum BOLD activation was clearly detected in the frontal left lobe ($p < 0.01$). However, (b) an activation in the occipital lobe ($p < 0.05$) and (c) a central activation ($p < 0.05$) including the Corpus Callosum also appeared to have a haemodynamic response to epileptogenic discharges.

Clustering

As the previous results were not conclusive, EEG data was examined by an expert observer (marking the beginning and the end of epileptogenic activity in EEG), and we realized that paroxistic activity lasted always the same periods of time. In order to have more information we decided to divide the analysis of haemodynamic response to the epileptogenic seizure according to its duration. Four

different categories of paroxistic activity were visually defined by the EEG reviewers: 1.5 seconds (Group a), 2 seconds (Group b), 3 seconds (Group c) and 4 seconds (Group d).

Fig. 3 shows the Statistical maps obtained when the different groups were analysed. For Group a, results showed that BOLD activation appeared in the Temporal lobe. Group b results presented the strongest activation which is in concordance with the results in Fig. 2 when all kind of seizures were used to analyse fMRI signal. In Group c, BOLD activation could be seen in the Parietal lobe while as, Group d presented BOLD activation in both laterals of the Parahippocampal area and also in the Temporal right lobe. This last result was very interesting because one of the first clinical evaluations of the patient diagnosed bilateral crisis of epilepsy. This suspected diagnostic was then replaced to indicate the localization of crisis in frontal lobe as results of Group B revealed.



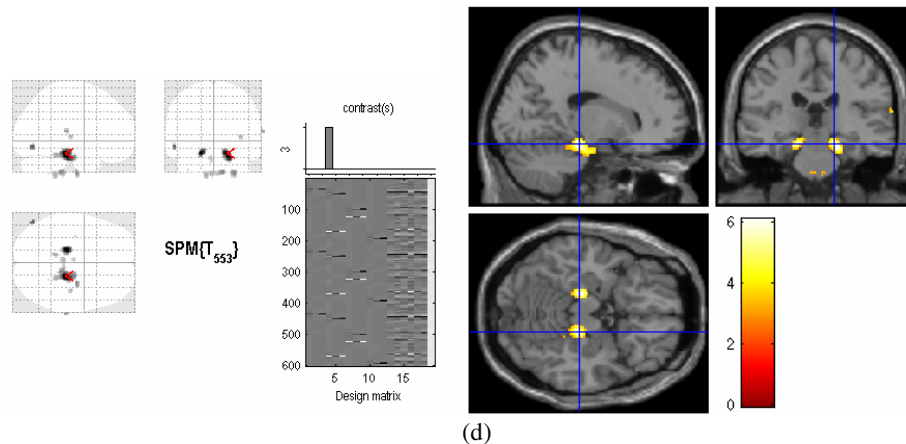


Figure 3: Statistical maps generated when paroxysmic activity was analyzed dividing the events by its time duration: 1,5 seconds(a), 2 seconds(b), 3 seconds(c) and 4 seconds(d). (a)BOLD activation in Temporal right lobe; (b) BOLD activation detected in Frontal left lobe; (c)BOLD activation in Parietal left lobe and (d)BOLD activation in both laterals of thalamus and also in Temporal right lobe.

These results do not only confirm the previous clinical diagnostic established by the expert neurologists but also introduce a new concept for analysis: the localization of the paroxysmic activity depending on the duration of the crisis. This fact will be probably decisive for the localization of epileptic focus in the future in the clinical practice.

4. Discussion

After having analyzed the haemodynamic response that corresponds to a paroxysmic activity with different timings of the crisis duration, we consider it as an interesting parameter for further study in the EEG-fMRI recordings in epilepsy, because as we can see in Fig. 3, the localization of epileptic focus changes when clusters of crisis with different duration were analyzed separately. Therefore, two of these localizations correspond with previous clinical diagnostics: 1) Last diagnostic of the patient indicated a suspicion of a frontal lobe seizures as the analysis of crisis of 2 seconds showed (which was correlated with the maximum activation when all crisis werxe analyzed jointly), 2) On the other hand, the localization found for 4 seconds crisis matched with the first clinical evaluations of the patient diagnosed of bilateral crisis of epilepsy.

The influence of the duration of the crisis is supported by previous basic neurophysiological studies where trial changes in the modulation of an epileptogenic signal has proved that neuronal hyperpolarization by cation screening or applied fields decreased the burst frequency but did not affect the burst amplitude or **duration** [Bikson et al. 1999; Lea et al. 2003]

Moreover, studies made by using Diffusion-weighted and perfusion MRI in complex partial status epilepticus, have indicated that the **duration** of an ictal activity may be a critical factor responsible for the changes detected by PI and DWI [Szabo et al. 2005].

However the current results need to be compared with a greater group of epileptic patients in order to establish valid and reliable conclusions about this possible new concept to analysis developed.

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