Effects of Inaccurate Identification of Interictal Epileptiform Discharges in Concurrent EEG-fMRI

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Abstract: Concurrent continuous EEG-fMRI is a novel multimodal technique that is finding its way into clinical practice in epilepsy. EEG timeseries are used to identify the timing of interictal epileptiform discharges (IEDs) which is then included in a GLM analysis in fMRI to localize the epileptic onset zone. Nevertheless, there are still some concerns about its reliability concerning BOLD changes correlated with IEDs. Even though IEDs are identified by an experienced neurologist-epilptologist, the reliability and concordance of the mark-ups is depending on many factors including the level of fatigue, the amount of time that he spent or, in some cases, even the screen that is being used for the display of timeseries. This investigation is aiming to unravel the effect of misidentification or inaccuracy in the mark-ups of IEDs in the fMRI statistical parametric maps. Concurrent EEG-fMRI was conducted in six subjects with various types of epilepsy. IEDs were identified by an experienced neurologist-epilptologist. Analysis of EEG was performed with EEGLAB and analysis of fMRI was conducted in FSL. Preliminary results revealed lower statistical significance for missing events or larger period of IEDs than the actual ones and the introduction of false positives and false negatives in statistical parametric maps when random events were included in the GLM on top of the IEDs. Our results suggest that mark-ups in EEG for simultaneous EEG-fMRI should be done with caution from an experienced and restful neurologist as it affects the fMRI results in various and unpredicted ways.

1. Introduction

Epilepsy is a neurological disease originating from the spontaneous and synchronous discharges of a neuronal group, also known as epileptic focus. The golden standard for the diagnosis and eventually the treatment of epilepsy is the electroencephalography (EEG). Interictal epileptiform discharges (IED) appear in the EEG of epilepsy patients as waveforms that vary according to the location and discharges of epileptic focus [1].

EEG offers a very high time resolution allowing time intervals between two measurements as little as 0.2μs. Although, it suffers from a very low space resolution, usually, having 32 or 64 measurements from the entire head. Electrical source imaging (ESI) has been proposed to handle this drawback. By solving the inverse problem, ESI was shown to map the epileptic onset zone (EOZ) making accurate predictions of the surgical outcome [2] [3]. Though, it has been shown in virtual EEG data that if there...
are more than one sources in the brain that generate the EEG timeseries then all algorithms that solves the inverse problem failed to predict the exact locations of these sources [4] [5].

On the other hand, functional magnetic resonance imaging (fMRI) lacks the time resolution of EEG, having a time interval of 2 to 3 seconds, but it is capable of a space resolution of a few millimeters with a whole head coverage, including structures deep in the brain, such as hippocampus, that EEG is not sensitive to. FMRI has contributed in the notion that epilepsy is a network disease, involving distant areas of the brain, rather than a single focus whose discharges affect the rest of the brain [6] [7].

Scientists have tried to merge these two modalities in order to take advantage of the high time resolution of EEG and the high space resolution of fMRI. Though, recording EEG inside an MRI environment introduces a number of novel artefacts caused by the effect of the rapid changes of the gradient field necessary for the fMRI acquisition and the slight movement of the subject including the small pulsatile movements induced by the cardiac rhythms. Although these artefacts can be reduced by a number of algorithms [8] [9], EEG measurements still suffers from their effects or even effects that the algorithms themselves introduce [10], making the timeseries uninterpretable. For these reasons, neurologists spend a lot of time identifying the IEDs in the recordings of EEG-fMRI and sometimes it is difficult to distinguish between artifact and IED. Furthermore, because the link between BOLD signal and IEDs is yet to be discovered, there is no golden standard for the timing the events should be marked. On top of that, the recordings are 3600 seconds and IEDs are usually less than 500ms making it easy for the neurologist to miss an event.

In this paper, we study the effect of inaccurate mark ups of IEDs in the fMRI statistical parametric maps with respect to these scenarios. More specifically, we investigated the changes in the statistical maps of fMRI when 1) we change the duration of the events by adding 500ms and 1s before and after the event as it was marked by the neurologist, 2) we include fewer events that the real ones and 3) we randomly add events on top of the real. We believe that this analysis should unravel the effects of different or inaccurate mark ups in the statistical parametric maps of the fMRI.

2. Methods

2.1 EEG-fMRI Acquisition

The acquisition was performed in St’Lukes Radiology Department, Thessaloniki, Greece in the past 6 months. All patients underwent the same acquisition protocol. At first the EEG cap (BrainAmp, 32 channels) was placed correctly and the resistance of electrodes was checked. Then the subject was placed in a MRI Siemens Avanto 1.5T where a whole brain fMRI with simultaneous recording from electrodes was performed for one hour or half an hour depending on the frequency of IEDs each subject revealed. EEG were acquired at 5kHz. fMRI was performed using a single shot gradient echo planar imaging sequence with GRAPPA acceleration (TR=2.8sec, TE=27ms, flip angle= 80°, voxel-size 2.5×2.5×2.5, slices 40, FoV 230×230mm). After this acquisition, the EEG cap was removed and a T1-weighted (voxel-size 0.9×0.9×0.9mm, TR=1820ms, TE=3.11ms, FoV 350×263×350mm) and a T2-weighted (voxel-size 1×1×1mm, TR=5000ms, TE=355ms, FoV 260×228×176mm) was performed for registration purposes.

2.2 Subjects

EEG-fMRI acquisition was performed routinely in drug resistant epilepsy patients, candidates for brain surgery. All patients were native Greek speakers. A summary for the cohort is presented in Table 1.

| Patient_1 | Patient_2 | Patient_3 | Patient_4 | Patient_5 | Patient_6 |
|-----------|-----------|-----------|-----------|-----------|-----------|
| Age       | 20        | 11        | 10        | 22        | 16        | 32        |
| Epileptic Focus | Right Temporal Lobe | Right Precentral Gyrus | Right Rostral Middle Frontal Gyrus | Undetermined | Right Insula/hematoma | Left Precentral/Postcentral |

2.3 Preprocessing
2.3.1 FMRI. FMRI preprocessing steps were performed with FMRIB’s Software Library (v. 5.0.7) [11]. In summary, images were skull-stripped, motion corrected, spatially smoothed with a Gaussian kernel of 6mm at full width at half maximum and pre-whitened to ensure that voxels’ timeseries is independent to one another. Registration was performed to align each subject’s fMRI data to each anatomical T1-weighted image using the BBR algorithm implemented in FMRIB’s Software Library. ICA components were extracted and the components associated with various types of noise, including movement, was manually identified and linearly regressed out from the signal.

2.3.2 EEG. EEG preprocessing was performed with EEGLAB toolbox and FMRIB plugin for EEGLAB [12] [9]. Gradient artifact were removed before resampling the timeseries to 500Hz. Then, qrs complexes were detected and the three principal components most correlated to qrs’s waveforms were removed from the signal. After that, a bandpass filter was applied with cutoff frequencies at 0.5Hz and 60Hz. Electrodes’ timeseries were average referenced before an expert neurologist marked up the IED in different groups according to the topography of each one. At this point, the IED type of interest for each subject was picked.

2.4 Statistical Analyses.
Statistical analyses of fMRI timeseries were implemented in FMRIB’s Software Library. More specifically, the general linear model (GLM) was performed. Cardiac rhythms derived from ECG electrode were used as a slice specific regressor of no interest. On top of that, volumes associated with steep movement (>1mm) were regressed out of the model using a single column for each one with zeros in every line except the line corresponding to the volume of the movement.

2.4.1 Original Events. First, the IED events as they were marked by the neurologist were convolved with a Gamma function and was used as regressors in the GLM. Because we couldn’t assume that the patient brain will have a normal hemodynamic response, we ran the statistical analyses for various peaks of the Gamma function (3sec, 4.5sec, 6sec, 7.5sec) as well as various statistical thresholds to determine which model fits better the data for each subject. All subjects’ data were best fitted with a Gamma function peaking at 4.5s, except Patient_2 that was best fitted with a Gamma function peaking at 6s. After determining the correct parameters of Gamma function and statistical thresholding for each subject, they were used in all the others statistical analyses with the inaccurate events.

2.4.2 Inaccurate Events. For each subject ten statistical analyses were performed, except the original one. In the first six analyses the duration of each event was changed (500ms at the beginning, 500ms at the end, 1s at the beginning, 1s at the end, 500ms at the beginning and 500ms at the end, 1s at the beginning and 1s at the end). In the next two analyses some events were deleted from the original events (25% and 50%), while in the last two some random timing events were added on top of the original (10% and 25%).

![Figure 1: IEDs of interest for each subject and the corresponding statistical parametric map of fMRI originating from the original events.](image-url)
3. Results

Results show that fMRI statistics with GLM regressors is sensitive to all of these effects, namely, the correct timing of the IEDs, events that was falsely not marked as IEDs or the marking of events that was not IEDs. In Figure 1, the original statistical parametric maps alongside with the IED of interest that produced those maps are shown. In general, when time was added at the beginning of the events the cluster of interest (Table 1) was remained in the map of fMRI, in some cases with lower statistical significance. On the other hand, when time was added at the end of the events the fMRI map seems to be affected in unpredicted ways, clusters were appearing while others were disappearing, the cluster of interest were shrinking or even not shown. When the 25% of the events where missing the cluster of interest was not changed in five out of the six patients, but when 50% of the events where missing the cluster of interest appeared only in one patient. In both cases where random events were introduced, 10% and 25%, in three out of six patients the cluster of interest appeared.

Interestingly, in Patient_3 the cluster of interest appeared in all the maps of fMRI while in Patient_5 it only disappeared when 50% of IEDs where missing. In Patient_2, the statistical maps where almost the same with the original when the duration of the events was change, but there were no significant cluster when events were missing or random events were introduced.

4. Conclusion

In this study, we examined the effect that inaccuracy in the identification of IEDs in the time series of EEG, will have in the statistical parametric map of fMRI in the concurrent continues EEG-fMRI. By changing the duration and the amount of IEDs from the original events that was marked from an experienced neurologist, we were able to unravel that introducing events that are not real IEDs is producing unpredicted results when compared to IED events that were missing. Furthermore, as far as the duration of the events is concerned, the IED waveform should be taken as a whole and no more than that. When this is not possible, extra care should be given in finding the end of the event rather than the beginning as it produces results that are closer to the original.

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