The impact of different HRFs in simultaneous EEG/fMRI studies in epilepsy

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Introduction: Simultaneous acquisition of electroencephalography (EEG) and functional MRI (fMRI) has been widely used in focal epilepsy studies to correlate hemodynamic response to interictal EEG spikes. For statistical analysis of fMRI data, it is common practice to use a standard model of the HRF to analyze every kind of studies. However, HRFs vary across sessions, subjects, individuals and brain regions, and the use of one standard HRF would contribute to false positives and negatives and to a loss of relevant information, which would lead to a decrease of total correlation of the processed fMRI data. Knowledge about how HRF's affect the statistical analysis of focal epilepsy cases is essential for the comprehension of these studies.

Goals and Methods: We compare the activated areas and t-statistic scores obtained with different HRFs (varying their shape and timing) and to see which BOLD HRF should be used in focal epilepsy studies. To evaluate the accuracy of each tested HRF, a quantitative and qualitative analysis of each resulting BOLD activation map with the high resolution EEG map and the malformative lesion detected for each patient (on T1-weighted MR images) was also performed. The fMRI data analysis was performed using the FSL software package. Applying a general linear model to the time series of fMRI data, the correlation between the response and the detected epileptic discharges is obtained by statistically analyzing the associated fMRI time series for each voxel, through t-statistical maps and scores. Thus, different HRFs and its particular parameters can be selected to convolve with the activation design, and produce different activation maps. We tested a Gamma variate function (a normalization of the probability density function of the Gamma function), a Gaussian kernel, a Double-Gamma function (a preset function of one positive Gamma function at normal lag, and a small, delayed, inverted Gamma, to simulate the late undershoot), and in order to get more flexible models, a set of gamma and another of sine basis functions were also used.

A functional MRI was performed while simultaneously recording the EEG (19 electrodes at standard 10–20 positions). The EEG/fMRI images were acquired in 4 to 6 blocks per patient, providing 20 to 30 min of simultaneous monitoring. All MRI images were obtained on a 1.5T Signa CV/i-NV/i (GE) using a BOLD EPI sequence with: 100-150 brain volumes; TE = 50 μs, TR = 3-2.275 s; 16-24 EPI images per volume; FOV = 24x24 cm; 64x64 matrix, Sl Th = 7.0 mm and a Flip Angle of 90˚. The simultaneous EEG was recorded with a Neuroscan cap (MagLink, Neuroscan, El Paso, TX, U.S.A.). Our fMRI data was analysed with FSL, correcting for movement and slice acquisition time and smoothed with a Gaussian kernel of FWHM 5 mm, and using a local autocorrelation correction with z statistic images generated. The correction for the multiple comparison problem was done using a cluster threshold with p = 0.05. We studied seven patients with focal epilepsy and detectable malformative lesions.

Discussion: The BOLD activation maps obtained for all the tested HRFs for each patient showed a significant variability in the number, localization and intensity of the detected BOLD clusters. The set of Gamma basis functions showed more linearity across patients, since in most of the cases we could find an activation with a high level of significance compatible with the anatomical MRI localizations and EEG of lesional and epileptogenic regions. However, there was also a relevant number of false positives across different parts of the brain, resultant from this HRF misestimates. In some cases we obtained better results using other HRFs where Gamma variate should be emphasized, since there was the same larger and high significance level activation cluster, noticing a clear decrease in the number of secondary activations. The variation of lag and shape of the HRFs proved to have a very important weight in the increase of signal to noise ratio. We were able to find a quite restricted range of values for the lag and half-width of the Gamma and Gaussian waveform that seems to produce a better match with this kind of signal.

Conclusion: Based on the HRFs we have analyzed, we realized that it is not possible to determine a gold standard procedure about which HRF should be used to produce the most accurate BOLD statistical maps. This decision should be taken individually, since it may vary across patients and affected regions.

Figure 1 - Influence of different HRFs in the final BOLD activation images for patient one of the studied patients.