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EEG-informed fMRI analysis during a hand grip task*

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Abstract— **In the last decade, an increasing interest has arisen in investigating the relationship between the electrophysiological and hemodynamic measurements of brain activity, such as EEG and (BOLD) fMRI. In particular, changes in BOLD have been shown to be associated with changes in the spectral profile of neuronal activity, rather than with absolute neural power. On the other hand, though, recent findings showed that different EEG rhythms are independently related to changes in the BOLD signal: therefore, it would be important to distinguish between the contributions of the different EEG rhythms to BOLD fluctuations when modeling the relationship between EEG and BOLD. Here we proposed a novel method to perform EEG-informed fMRI analysis, so that the EEG regressors take into account both the changes in the spectral profile and the rhythms distinction. We applied it to EEG-fMRI data during a bimanual motor task in healthy subjects, and compared the results with those obtained by regressing fMRI data onto a single regressor covering the entire range of frequencies, ignoring the distinction between different EEG rhythms. Our results showed that the proposed method better captures the correlations between BOLD signal and EEG rhythms modulations, identifying task-related well localized activated volumes.**

I. Introduction

Since its discovery in the early 1990s, the blood oxygen level-dependent functional magnetic resonance imaging (BOLD-fMRI) has rapidly gained a dominant position in neuroscience research. One of the most popular approach to combine EEG and fMRI measurements consists in using temporal- or frequency-specific information derived from EEG to obtain regressors of interest usable in the common General Linear Model (GLM) framework (EEG-informed fMRI). In 2010, [1] introduced a model on the basis of the theory developed by [2], who proposed that BOLD activations are accompanied by an increase of the "average" frequency of the EEG neural activity. In this "Heuristic" model, though, only one regressor covering the entire frequency range was used, without any distinction between the different EEG rhythms. To bridge this gap, we intend to study how the alpha and beta EEG rhythms selectively contribute to the BOLD fluctuations during a motor task, by constructing a design matrix including a different "Heuristic" regressor for each of the EEG rhythms. The performances of this new model will then be compared with those of the original "Heuristic" model, considering as reference the results obtained with the classical stimulus onset-based analysis.

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II. Material and Methods

A. Subjects and task

Five right handed healthy adult volunteers (3 male, 2 female, aged 39,2 ± 16,3 years) participated in the study which was performed at the "IRCCS Istituto Neurologico Carlo Besta", Milan, Italy. The motor task consisted of an initial rest period (20 s), followed by blocks (20 s each) of right and left handgrip alternately, and ended with another rest period (20 s), with an overall durations of 420 s.

B. EEG-fMRI acquisition and preprocessing

EEG was simultaneously acquired with fMRI using an MR-compatible EEG amplifier (SD MRI 32, Micromed, Treviso, Italy) and a cap providing 30 Ag/AgCl electrodes positioned according to the 10-20 system. Extra electrodes were used to obtain electrocardiogram (ECG) and electromyogram (EMG). Impedances were kept below 5 kΩ. fMRI images were acquired on a 1.5 T MR scanner (Magnetom Avanto, Siemens AG, Erlangen, Germany). An axial gradient-echo echo-planar sequence was used to generate the functional images (TR = 2000 ms, TE = 50 ms, 21 slices, 2x2 mm2 in-plane voxel size, 4 mm slice thickness, no gap), resulting in a total of 210 functional scans for each subject. EEG and fMRI data were preprocessed using the FMRIB plug-in of the toolbox EEGLAB (http://www.fmrib.ox.ac.uk/eeglab/fmribplugin) and SPM5 software package (http://www.fil.ion.ucl.ac.uk), respectively.

C. Modeling EEG-fMRI relationship

We chose as representative time series the first principal component of C3 and C4 channels [1], which are known to be the most involved electrodes in a motor protocol [3]. The resulting signal $\tilde{s}(t)$ was analyzed in the time-frequency domain by convolution with complex Morlet wavelets, *w(f,t)*, having a frequency range from 1 to 40 Hz in 0.5 Hz steps. From the time-varying power of the signal, the power timecourses for five EEG rhythms (δ (1-4 Hz), θ (5-8 Hz), α (8-12 Hz), β (12-30 Hz) and γ (30-40 Hz)) were extracted. A first set of regressors were obtained following the approach of [1]. The "Heuristic" model (HEU, as we refer from now on) regressor is given by

$$r_{HEU}(t) = \sqrt{\sum_{f=1}^{n_f} f^2 \tilde{P}(f,t)}, \qquad (1)$$

where $\tilde{P}$ indicates the normalized power spectrum and n_f is the number of frequencies considered in the time-frequency decomposition. We then introduced a novel model, that we called "Heuristic Bands" (HEU-B) model: it assumes both that the BOLD signal is a linear combination of activity in the different frequency bands, as in [4], and that increasing in BOLD signal is associated with a shift in the EEG spectral profile to higher frequencies, as in [2], [1]. The five regressors of the HEU-B model are, therefore, given by:

$$r_{HB}(t)_a = \sqrt{\sum_{f=f_{min}}^{f_{max}} f^2 \tilde{P}(f,t)}, \quad (2)$$

where $a = [f_{min}, f_{max}]$ is the considered EEG rhythm bandwidth.

E. Stimulus onset-based fMRI analysis

To investigate the effect of the experimental task, a stimulus onset-based fMRI analysis was first performed using regressors constructed on the basis of the motor events detectable from the EMG recording. The two resulting boxcar functions (i.e. for right and left handgrips) were then convolved with the SPM canonical Hemodynamic Response Function (HRF), including its time and dispersion derivatives. Movement parameter estimates produced by realignment procedure were also included as confounding regressors, in order to remove residual movement artifacts. The group level analysis was then implemented following an FFX approach [5] and inference on the estimated regressors were performed using a *t*-test (p<0.05, FWE). We then performed anatomical and functional labeling of the active areas using the probability maps of the Anatomical Automatic Labeling (AAL) SPM toolbox [6] and SPM Anatomy Toolbox [7].

F. EEG-informed fMRI analysis

In order to be used as regressors in the GLM, $r_{HEU}(t)$ and $r_{HB}(t)_a$ time series were downsampled to match fMRI acquisition and then convolved with the canonical HRF and its time and dispersion derivatives. The results for each of the two models were summarized using an FFX approach [5] and inference was performed using F-test (p<0.05, FDR corrected for multiple comparisons). The contrast analysis on HEU-B model was performed on alpha and beta regressors only, since our aim is to investigate the BOLD correlates of alpha and beta rhythms, which are known to be the most directly involved in motor performance [8], [9].

In order to compare the two models and to understand which one best captures the correlations between EEG frequency oscillations and the BOLD response, we included in the same FFX design matrix the regressors obtained from both HEU and HEU-B models. The use of a single GLM design matrix comprising different models allowed to highlight BOLD variability that could be explained by a specific model and not by others [10].

III. Results

A. Stimulus onset-based fMRI analysis

The results of the first fMRI analysis, which we refer to as Stimulus Onset (SO) model from now on, showed activations related to the performed motor task. In Fig. 1 the main effect of right and left handgrip is shown. The clusters were located in left and right postcentral gyri and in left and right precentral gyri, and all of them corresponded to functional areas involved in motor execution.

The right handgrip-related cluster shows a size of 1510 voxels, with a maximum *t*-score of 14.58 at [-44 -22 60] mm, Talairach coordinates; it is located in left postcentral gyrus (50% of the cluster) and left precentral gyrus (48% of the cluster) and the corresponding Brodmann Areas (BAs) are the following: Left BA6 (606.3 voxels), Left BA1 (275 voxels), Left BA4a (167.8 voxels), Left BA3b (142.1 voxels), Left BA4p (111.8 voxels), Left BA2 (43.5 voxels), Left BA3a (7 voxels). The left handgrip-related cluster has a size of 595 voxels, with a maximum *t*-score of 8.26 at [40 -16 58] mm; it is located in right precentral gyrus (84% of the cluster) and right postcentral gyrus (16% of the cluster) and it involves the following BAs: Right BA6 (344.8 voxels), Right BA4a (123.4 voxels), Right BA1 (58.1 voxels), Right BA3b (38 voxels), Right BA4p (12.9 voxels).

B. EEG-informed fMRI analysis

Fig. 2 and 3 show correlations between BOLD and EEG regressors used in separate design matrices.

The contrast vector analysis on HEU model regressor revealed four main clusters. The first one, having a size of 2494 voxels, shows a maximum *F*-score of 11.17 at [0 -54 60] mm and it is located in right superior parietal lobule (19% of the cluster), right postcentral gyrus (17%), right precuneus (15%), left precuneus (13%); the involved BAs are Right BA7 (502.1 voxels), Right BA5 (354.9), Left BA7 (235), Right BA2 (219.3), Right BA17 (175.4), Left BA5 (175.4), Right BA4a (102.8), Right BA1 (70.1), Right BA18 (66.5), Left BA18 (39.7), Right BA4p (19), Right BA6 (16.3), Left BA4a (8.4), Left BA3b (5.4), Left BA3a (3.3). The second cluster has an extent of 620 voxels, with a maximum *F*-score of 11.81 at [66 -36 30] mm; it is located in right superior temporal lobule (35% of the cluster), right supramarginal gyrus (33%), right middle temporal gyrus (31%) and it corresponds to Right BA40 (407.8 voxels). The third cluster has a size of 474 voxels, with a maximum *F*-score of 9.45 at [32 10 66] mm, and it is located in right superior frontal lobule (53% of the cluster), right middle frontal gyrus (21%), right precentral gyrus (17%); it involves Right BA6 (104.5 voxels) and Right (BA4p (0.3). Finally, the fourth cluster shows an extent of 343 voxels, with a maximum *F*-score of 9.59 at [2 8 54] mm and located in right superior frontal lobule (53% of the cluster), right middle frontal gyrus (21%), right precentral gyrus (17%); it involves Right BA6 (168 voxels) and Left BA6 (53.3).

The contrast vector analysis on alpha and beta regressors in HEU-B model shows four main clusters as well. The first one, having a size of 1213 voxels, shows a maximum *F*-score of 17.06 at [32 -34 69] mm and is located in right postcentral gyrus (55% of the cluster) and right precentral gyrus (37%); the involved BAs are Right BA6 (389.4 voxels), Right BA1 (257.4), Right BA4p (184), Right BA4a (143.6), Right BA3b (133.8), Right BA3a (13.8), Right BA2 (3.5). The second cluster has an extent of 1009 voxels, with a maximum *F*-score of 22.53 at [-36 -22 70] mm; it is located in left postcentral gyrus (54% of the cluster) and left precentral gyrus (43%) and it involves Left BA6 (339.9 voxels), Left BA1 (216.8), Left BA4a (129.8), Left BA4p (110.1), Left BA3b (97.8), Left BA2 (12.5), Left BA3a (12.5). The third cluster has a size of 107 voxels, with a maximum *F*-score of 10.87 at [28 4 62] mm, it is located in right superior frontal

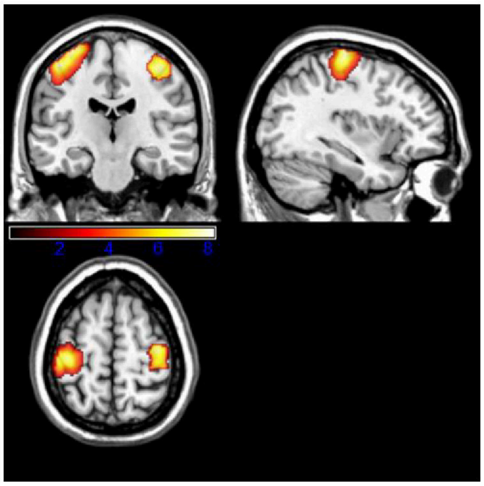


Figure 1. Effect of right and left handgrip sumperimposed on the same T1 template (group analysis over 5 subjects, p<0.05, FWE). Neurological convention (right at the right side).

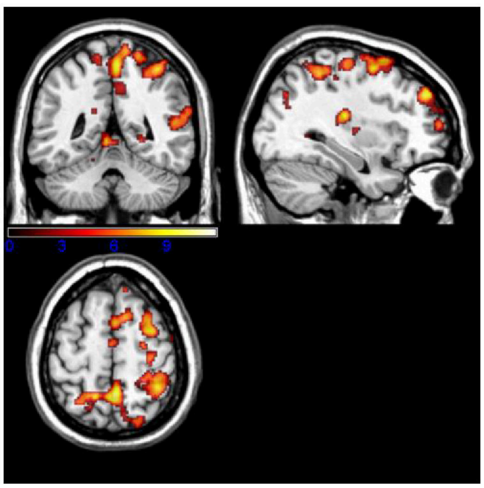


Figure 2. Contrast vector analysis results for the HEU model (group analysis over 5 subjects, p<0.05, FDR). Neurological convention (right at the right side).

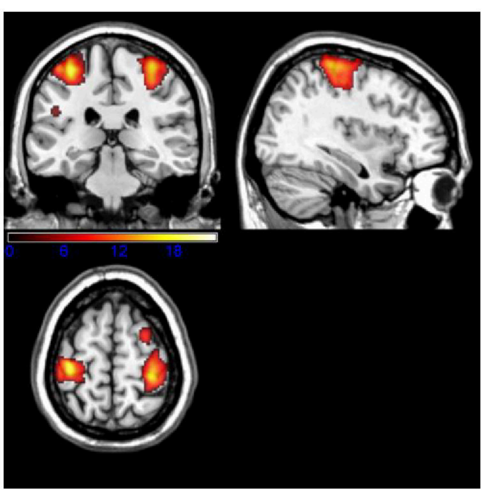
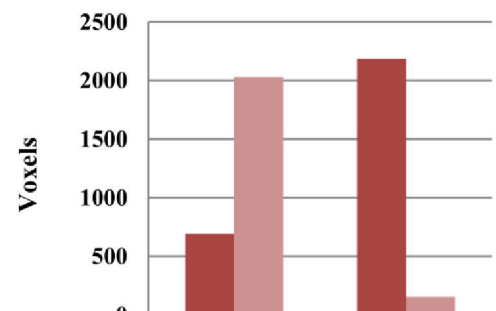


Figure 3. Constrast vector analysis results for the HEU-B model, contrast on alpha and beta regressors (group analysis over 5 subjects, p<0.05, FDR). Neurological convention (right at the right side).

gyrus (95% of the cluster) and right middle frontal gyrus (5%) and it corresponds to Right BA10 (101.65 voxels). Finally, the fourth cluster shows an extent of 46 voxels, with a maximum F-score of 7.78 at [-48 -26 26] mm and located in left supramarginal gyrus (76% of the cluster); it involves Left BA40 (21.8 voxels) and Left BA39 (15.7).

Although all regressors correlated with BOLD signal, HEU-B model produced higher maximal F-scores. In Fig. 4, the significant voxels resulting from the contrast vector analysis on each model are classified according to their relative functional brain areas. In order to evaluate the ability of the two proposed models to identify the task-related activations, we built two main classes: "motor" areas, corresponding to functional brain areas that were activated in the SO model, and "non-motor" areas, including all other areas. The HEU-B model produced the highest number of voxels belonging to the "motor" areas (2027.6 voxels), while the HEU model produced the greatest amount of significant "non-motor" voxels (2186.2), with a relatively few amount of "motor" ones (691.2).

We then performed a pairwise comparison between HEU and HEU-B models. We used the regressors of the two models in the same design matrix, in order to explore the correlations between EEG and BOLD that are uniquely attributable to each model within the pair. Once again, the Heuristic Bands model was the only one that correlated with motor areas activation (Fig. 5).



	HEU	HEU-B
Motor	691.2	2186.2
Non-motor	2027.6	156.45

Figure 4. Significant voxels classification according to functional areas: voxels belonging to the same areas activated in SO model are considered as "motor" (values are tabulated below bars).

IV. Discussion

In this work, we investigated the relationship between neural activity and BOLD signal in simultaneously acquired EEG and fMRI data during a motor task in healthy human subjects. We compared two different models (Heuristic and Heuristic Bands) used to build regressors from the EEG signal, in order to explore the correlations between each of them and the fMRI data. Since our purpose was to evaluate the performances of the different models, we chose to use data acquired during a motor task, where functional activations related to the task execution are well known. We showed that the correlations between BOLD and EEG signals is better captured by a model which takes into account both the EEG spectral shifting and the different EEG rhythms.

Moreover, we validated the choice of taking the projection on the first PC of a subset of channels of interest as representative EEG signal, a method that can be easily extended to other task-related activations/deactivations.

A. Localization of task-related alpha- and beta-rhythms correlates

Our attention was then turned to analyze in detail the brain regions identified as BOLD correlates by the Heuristic Bands model, which showed both task-related activations as well as different functional areas not primarily involved in the task execution. As can be noticed in Fig. 4, most of the voxels that showed correlations with the HEU-B regressors belong to the same functional areas resulting from the SO model, revealing a co-localization of alpha and beta rhythms with task-related BOLD activity. Contrast vector analysis on alpha and beta regressors showed activations in the primary somatosensory cortex Brodmann areas (BA) 1, 2 and 3, in the primary motor cortex (BA 4) and supplementary motor area (BA 6). In addition to task-related correlates, the contrast vector analysis also identified other functional areas: in particular, correlations are found in BAs 10, 39 and 40. These extrarolandic regions could represent an attentional network related to the task management. BA 10 (anterior prefrontal cortex) has been shown to be activated during prospective memory paradigms (i.e. those involving carrying out an intended action after a delay) [11], BA 39 (angular gyrus) has been proven to be involved in mental number representation [12] and BA 40 (supramarginal gyrus) has been shown to be important for attention to limb movements [13].

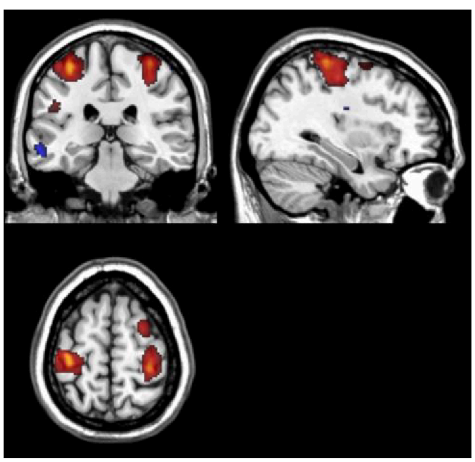


Figure 5. Two-way model comparison between HEU and HEU-B models (HEU = blue, HEU-B = red; p<0.001, uncorrected for HEU regressor; p<0.05, FDR for HEU-B regressor). Neurological convention (right at the right side).

V. CONCLUSION

Understanding the nature of the link between neuronal activity and BOLD signal plays a crucial role in improving the interpretability of BOLD imaging and relating electrical and hemodynamic measures of human brain function. Finding the optimal way to model the relationship between these two techniques is nowadays an open issue. In the longer term, however, a replacement of such "asymmetric" [2] regression approaches by "symmetric" fusion tools would be desirable in order to address complex issues [14]. Furthermore, we expect the EEG-fMRI approach to be useful for studying other types of EEG rhythms, such as gamma rhythms of high frequency oscillations [15], and other types of task-related activations/deactivations.

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