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Technical Note

From EEG to BOLD: Brain mapping and estimating transfer functions in simultaneous EEG-fMRI acquisitions

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ABSTRACT

Simultaneous acquisition of electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) aims to disentangle the description of brain processes by exploiting the advantages of each technique. Most studies in this field focus on exploring the relationships between fMRI signals and the power spectrum at some specific frequency bands (alpha, beta, etc.). On the other hand, brain mapping of EEG signals (e.g., interictal spikes in epileptic patients) usually assumes an haemodynamic response function for a parametric analysis applying the GLM, as a rough approximation. The integration of the information provided by the high spatial resolution of MR images and the high temporal resolution of EEG may be improved by referencing them by transfer functions, which allows the identification of neural driven areas without strong assumptions about haemodynamic response shapes or brain haemodynamic's homogeneity. The difference on sampling rate is the first obstacle for a full integration of EEG and fMRI information. Moreover, a parametric specification of a function representing the commonalities of both signals is not established. In this study, we introduce a new data-driven method for estimating the transfer function from EEG signal to fMRI signal at EEG sampling rate. This approach avoids EEG subsampling to fMRI time resolution and naturally provides a test for EEG predictive power over BOLD signal fluctuations, in a well-established statistical framework. We illustrate this concept in resting state (eyes closed) and visual simultaneous fMRI-EEG experiments. The results point out that it is possible to predict the BOLD fluctuations in occipital cortex by using EEG measurements.

Introduction

In 1990, Ogawa et al. (1990) established the technical basis of functional magnetic resonance imaging (fMRI). Using the contrast provided by the paramagnetic nature of deoxy-hemoglobin, the authors concluded that changes on blood oxygen level dependent (BOLD) signal could be an indicative of local task-related neuronal activity. Probing the working brain under variable conditions as gas inhalation and insulin-induced hypoglycemia, Ogawa et al. (1990) concluded that changes observed in BOLD contrast are associated to changes in the oxygen levels induced by altered blood flow and metabolic demand as a consequence of neural activity.

Since this publication, many studies were dedicated to determine the coupling between the BOLD signal and neural activity. Logothetis et al. (2001) showed that BOLD contrast seems to reflect the afferent activity in a certain brain region and its consequent processing. In this way, the signal found in fMRI, which results from a variety of factors like changes in blood oxygen concentration, its volume and flow, is only an expression of the neuronal activity itself (Logothetis et al., 2001; Logothetis and Pfeuffer, 2004). The actual nature of the haemodynamic coupling is mainly bounded to neurophysiologic parameters like oxygen and glucose consumption, cerebral blood flow and neurotransmitter cycling (Shulman and Rothman, 1998). As these indexes of activity provide a multi-modal landscape of brain activity, the exploitation of transfer functions across different modalities of data acquisition is associated to two important points, tackled in this work: (i) the neural common information shared by different modalities can be studied by using one source of data to predict others; (ii) to avoid strong assumptions about haemodynamic response function (HRF) shape, delay and brain homogeneity.

On the other hand, reports of experiments with patients and healthy subjects using simultaneous acquisition of electroencephlography

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(EEG) and fMRI are frequent in the recent literature. This experiment setup allows non-invasive studies of the relationship between the BOLD signal and the electrical activity recorded on the scalp, taking advantage of the high spatial resolution of MRI and the high temporal resolution of EEG. In the context of epilepsy, EEG-fMRI has emerged as a tool for localizing the epileptogenic focus considering the association between fMRI signal changes and interictal events (Warach et al., 1996; Hamandi et al., 2004; Krakow et al., 1999; Salek-Haddadi et al., 2006). This issue is relevant for clinical applications, mainly in presurgical evaluation, whose area of resection is both necessary and sufficient for seizure ablation (Rosenow and Lüders, 2001; Zijlmans et al., 2007; Terra-Bustamante et al., 2007; Salgado et al., 2008). However, the EEG-fMRI technique can only record a fraction of epileptiform activity in EEG, and the fMRI signal analysis frequently assumes a fixed HRF. Currently, studies of epileptic spikes with EEG-fMRI have most widely used classical fMRI analysis methods: the general linear model (GLM) (Friston, 1995). In this approach, the signal at each voxel is regressed on a model constructed by convolving impulses corresponding to the timing of the spikes with one standard HRF, such as a gamma function (Lange and Zeger, 1997) or a difference of two gamma functions (Glover, 1999). Brookings et al. (2008) introduced an fMRI-constrained dipole source model. This approach take into account both BOLD variations and EEG measurements to spatially identify the focus of neural activity. However, the neural–vascular coupling described by the expected haemodynamic response function must be specified a priory. Grova et al. (2008) evaluated the concordance in identifying spikes spatial location between EEG and fMRI with simultaneous acquisition.

However, several reports showed variability in the shape of the HRF as a function dependent on regions, subjects, age, task, sex, sessions (Aguirre et al., 1998, Miezin et al., 2000, Handwerker et al., 2004), especially in epilepsy (Bénar et al., 2002, Lu et al., 2006, Gotman, 2008). These studies suggest that activation maps obtained using a specific model introduces bias in the results. Nevertheless, attempts have been posed about this model to capture responses that differs significantly from the standard HRF (Marrelec et al., 2003, Bagshaw et al., 2004; Kang et al., 2003). In this context, methods that do not rely on a specific shape and linearity of BOLD response may be atractive alternatives (Gotman, 2008; Bénar et al., 2002; Sturzbecher et al., 2009). Thus, it is necessary to investigate more sophisticated and flexible approaches to integrate the information in EEG and fMRI signals.

In addition, Gonçalves et al. (2006), de Munck et al. (2007) and Difrancesco et al. (2008) studied the correlation between BOLD fluctuations and the spectral power in specific frequency bands, such as alpha rhythm. These approaches are attractive, since they consistently allow the spatial localization of alpha sources, laying mostly at the occipital lobe and thalamus. Moreover, de Munck et al. (2007) introduced an exploratory analysis for both brain mapping and filter estimation linking BOLD variations and the power in alpha band in resting state acquisitions.

Despite the fact of being informative, there are only few studies exploring the direct dependence between BOLD and EEG signals, mainly due to some technical and methodological limitations. Recently, impressive works have been developed on model-based fusion of EEG-fMRI information (Daunizeau et al., 2007; Valdes-Sosa et al., 2009). Complementary to the previous studies, by providing an exploratory analysis of EEG-fMRI data, this work concentrates on the following questions: Is it possible to predict BOLD variations by using the information contained in EEG measurements? How to identify the regions in the brain where the BOLD is correlated to the EEG signals? How to describe the linkage between the signals acquired using both modalities using an input/output framework? Considering the specific characteristics of EEG-fMRI data, such as the large volume of temporal and spatial information, autocorrelation, sampling rate and computational issues, the proposed approach is based in on a data-driven analysis focusing the development of an exploratory tool. The novelty of this approach is the flexible direct mapping from electrical (EEG) to haemodynamic signals (BOLD) at EEG time resolution, avoiding strong assumptions about HRF or temporal aggregation of EEG data. The applicability and usefulness of the proposal is illustrated in three simultaneous EEG-fMRI datasets: two experiments with a visual stimulation paradigm and one resting-state acquisition.

Material and methods

EEG-BOLD transfer function

The main aim of this study is, from a specific EEG channel and a voxel in a volume, determine a function mapping the past values of the EEG signal to the present measures of BOLD signal (see Fig. 1, top). Thus, for a given voxel and a EEG channel, the main concern is to find a transfer function $f : \Re \rightarrow \Re$, such that:

$$y_t = f\left(x_t, x_{t-1/r}, x_{t-2/r}, \ldots, x_{t-p/r}\right) + \varepsilon_t,$$

where y_t is a measured BOLD signal at time t (in seconds), x_t is a measured EEG signal at time t, ε_t is a random error with zero mean, r is the EEG sampling rate (in seconds), and p is the maximum number of EEG past values considered. Therefore, if we find a transfer function f, by minimizing the error ε_t, it is possible to predict changes in BOLD signal only by using the present and past values of the EEG.

In this study, f is considered a linear transfer function, regarding the computation and estimation complexity. The previous equation can be written as:

$$y_t = \alpha + \sum_{l=0}^{p} \beta_l x_{t-l/r} + \varepsilon_t,$$

where α is the intercept and β_l is the transfer function coefficients. In summary, the estimation of the transfer function consists on estimating the parameters α and β_l ($l = 0,\ldots p$). An intuitive procedure to estimate these coefficients is to minimize the sum of squared errors between the prediction and observed values, i.e., the least square estimator.

Nevertheless, the first obstacle to obtain a direct mapping between EEG and BOLD signals is the difference between their sampling rates. One of the greatest advantages of EEG is its high temporal resolution, which is essential to characterize and measure the neural electrical activity. Actually, EEG signals are frequently sampled to the order of hundreds of Heartz, which allows a satisfactory evaluation of the power in delta, theta, alpha, beta and gamma frequency bands. In contrast, in order to achieve acceptable levels of signal-to-noise ratio in fMRI acquisitions, the sampling rate of BOLD is usually up to 1 Hz. Since the BOLD signal mirrors haemodynamic processes, it is expected to depend on neural activity in a lag up to 15 s (Buxton et al., 2004). Two common approaches to deal with this difference on sampling rate are: downsample the EEG signal (or power spectrum) to BOLD rate or compute an average of EEG (or power spectrum) within the BOLD sampling interval. In this paper, we introduce a new approach which deals with this problem but avoid downsampling or averaging, which may result in information loss. Suppose there is some features in the EEG signal that occur transiently and may reflect neural processes that contribute to the BOLD signal, after haemodynamic coupling. If the EEG signal were sub- or downsampled, this feature would be lost and thus relevant information is lost. Let the hypothetical example that described in Fig. 1 (bottom), a case when we have a short EEG variability after an EPI volume acquisition and a case where this variation occurs before the following volume acquisition. If the EEG signal was subsampled, the information about electrical activity would be lost in both cases. On the other hand, if the average EEG signal within the interval was considered as the electrical activity representative, the variability in EEG would be assumed to

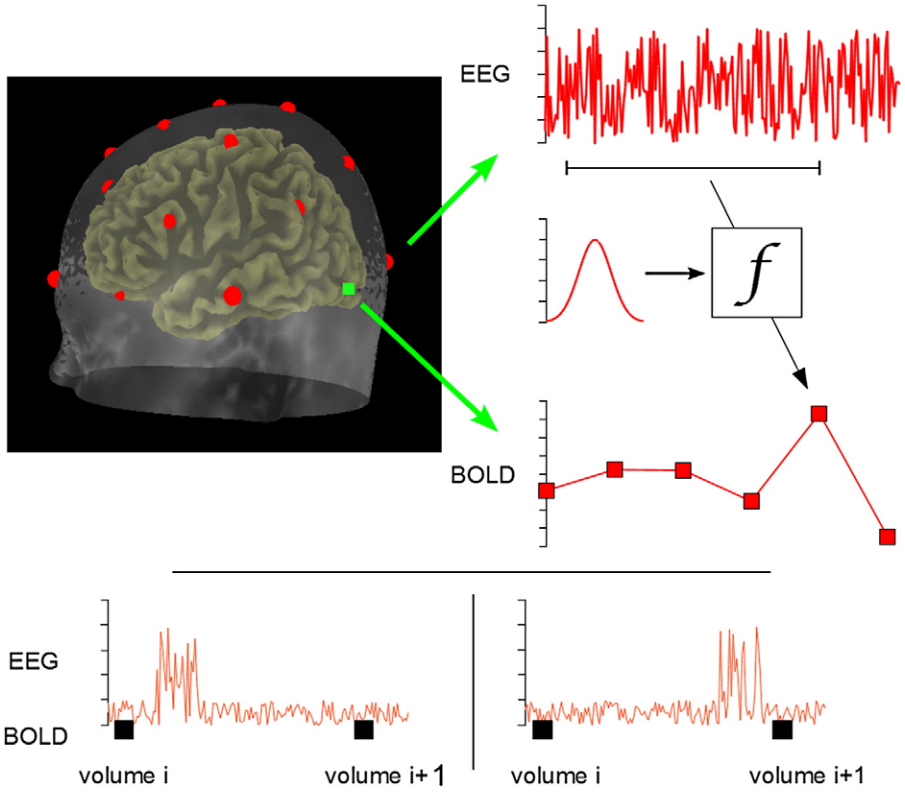

Fig. 1. Illustration describing the EEG-fMRI data. The EEG is registered at the scalp at high temporal sampling rates. The BOLD signal is measured at the cortex and provides high spatial resolution. The aim is to estimate the transfer function from EEG to BOLD, providing a brain mapping tool for multimodal data and also a input–output description of the linkage between electrical and haemodynamic signals.

contain the same information, ignoring the differences on delay and timing, which may be important to characterize the process (e.g., evoked potential studies). Thus, an approach, which avoids information loss due to subsampling, would be attractive in these cases.

The difference on sampling rate implies that the transfer function maps thousands of EEG measures to a single BOLD timepoint. This means that thousands of β_l ($l=0,\ldots p$) coefficients must be estimated. However, the numbers of fMRI volumes (BOLD signal length) are usually less than 1000, and thus, there are more parameters to be estimated than the number of observations. In statistics, this is named an "ill-posed" problem. There are some approaches developed to deal with this obstacle, such as ridge regression (Hoerl, 1962) or support vector regression (Gunn, 1997). Although these methods could be applied herein, this problem can be overcome more accurately if some prior information about the physiologic phenomena is considered.

Logothetis et al. (2001) have made substantial contributions regarding the interpretation of BOLD by demonstrating that this signal can be interpreted as low-pass filtered local field potentials. In addition, both Buxton et al. (2004) and Glover (1999) have concluded that the haemodynamic response curve can be described by a smooth function over time. These results are reasonable and in accordance with the physiological nature of BOLD signal (Ogawa et al., 1990), which depends on factors associated to the relative slow temporal variation, such as blood flow, volume and oxygenation.

These findings suggest that the β_l parameters present smooth variations through time (i.e., for $l=0,\ldots, p$). Thus, this information can be included in the estimation procedure as a constraint in the parametric space. A possible approach to take this information into account is to apply B-splines decomposition (Wahba, 1990). The main idea is to approximate a function g using the expansion:

$$g(t) = \sum_{i=1}^{m} \gamma i \psi i(t) + s(t),$$

where $\psi_i(t)$ is the B-splines function, γ_i is the expansion coefficient, m is the number of B-splines functions used in the expansion and $s(t)$ is the approximation error. The parameter m controls the smoothness degree of the expansion. By increasing m, the smoothness is decreased, but also is the approximation error (bias). In relation to the order parameter p, it should be large enough for covering the range of haemodynamic coupling. However, if it is unnecessarily large, it would lead to a lack of power in statistical tests, since the number of parameters to be estimated would be greater than necessary.

Thus, by integrating the transfer function concepts and B-splines smoothing and considering that the coefficients β_l can be described by a smooth function, the flow from EEG to BOLD can be described by:

$$y_t = \alpha + \sum_{l=0}^{p} \sum_{i=1}^{m} \gamma_i \psi_i(t - l/r) x_{t-l/r} + \varepsilon_t.$$

Note that in this case the transfer function is specified only by $(m+1)$ parameters, and thus, the overtfitting problems can be naturally overcome by considering the smoothness information. Furthermore, the implementation of this method consists mainly on the specification of the predictor matrix (the product between the B-splines function and the lagged values of x_t) in multiple linear regression models. Thus, the coefficients can be estimated using ordinary least squares and the hypothesis testing can be carried out using conventional statistical approaches. In addition, this is an attractive result since the significance of BOLD predictability, for a given voxel and a specific EEG channel, can be assessed using the F-statistics of regression analysis. Finally, in the cases when the random errors ε_t are serially autocorrelated, the Cochrane–Orcutt approach can be applied (Cochrane and Orcutt, 1949). The Cochrane–Orcutt approach consists on modeling the residuals as an autoregressive process and then using it to correct the variance of parameter estimates.

In resume, the transfer function from EEG signal to BOLD at a specific voxel can be estimated considering the smoothness of haemodynamic response. Furthermore, the predictive power can be statistically tested using the *F*-statistics, allowing the statistical parametric mapping of an EEG channel in a full fMRI volume analysis. Similarly to usual fMRI brain mapping based on GLM, which identifies the voxels where the BOLD signal can be explained by the expected haemodynamic response, the predictability mapping locates the brain region where the BOLD variations can be explained by the electrical activity measured on the scalp. Nevertheless, the latter approach does not require any assumption about function shape or delay, but only that the function to be estimated is smooth through time.

Simulations

Computational simulations were carried out for an initial evaluation of the proposed approach. The aim was to evaluate the quality of results provided by the method in cases where the true transfer function is known, i.e., in an artificial and controlled data. First, an input signal (EEG) is generated and filtered by using a known transfer function. The filtered signal is then subsampled resulting in the output signal (BOLD). We then compared the estimated transfer function and the true one, in order to check the consistency and reliability of the method.

Each set of simulations consisted on 200 series generated from the following model:

$$x_t = 0.6x_{t-1} + 0.2x_{t-2} + \eta_t,$$

$$HRF(t) = \Gamma\left(10 + \frac{t}{100}\right) - 0.2\Gamma\left(-5 + \frac{t}{100}\right)$$

$$y_t = \sum_{l=1}^{p} HRF(l)\tilde{x}_{t-l/r} + \frac{1}{\lambda}\varepsilon_t,$$

where Γ is the gamma density function (shape = 20, scale = 1), η_t is a Gaussian random variable with mean zero and variance one, $\tilde{x}_t$ is the x_t series normalized to mean of 0 and variance of 1, ε_t is a Gaussian AR (1) process with parameter of 0.2, mean of 0 and variance of 1, and λ is the signal-to-noise ratio parameter.

These sets of simulations focus on the evaluation of noise influences on the HRF estimation (transfer function parameters). Thus, we set λ parameter to 0.2, 0.4, 0.6 and 0.8. The total number of BOLD and EEG timepoints was set to 320 and 80,000, respectively. The estimated transfer function had a window length of 3750 timepoints and composed of 15 splines functions.

In addition, for the same model described previously and λ = 0.4, the evaluation of the number of functions to be included in the splines expansion was also carried out by setting *m* to 5, 10, 15 and 20.

Paradigms

This study is based in two different experiments: a visual stimulation and resting state (eyes closed). The visual stimulation experiment consisted in ABC block design with three conditions: fixation (baseline), right visual field stimulation and left visual field stimulation, using an MRI compatible goggles system. The fixation condition was the presentation of a static cross in the center of the visual field. The stimulus consisted on complimentary flickering half circular checkerboards (approximately 5 Hz, five blocks per condition, nine trials per block. The sequence of the experimental conditions was randomized, and block duration was approximately 18 s. The resting state experiment let subjects with eyes closed and without sleeping for about 14 min (460 volumes).

Data acquisition

Two healthy subjects (males, right-handed, ages 23 and 27 years old) participated in this study, which was approved by the local ethics committee. One subject was submitted to both resting state and visual stimulation experiments. The second one participated only in the latter.

The EEG data were acquired continuously at 5 kHz inside the MR scanner, using a compatible EEG amplifier (BrainProducts, Germany) and an elastic cap containing 32 Ag/AgCl electrodes, referenced to FCz, positioned in the 10–20 system.

The fMRI volumes were collected using a Siemens 3 Tesla MR system (Erlangen, Germany) using a T2*-weighted EPI sequences (TR = 1800 ms, TE = 30 ms, 64 × 64 matrix, FOV = 240 mm × 240 mm, slice thickness = 6 mm, gap = 0.6 mm, voxel size = 3.75 mm × 3.75 mm, with 18 slices covering the whole brain. One hundred and sixty volumes were collected during the visual stimulation experiment, and 450 volumes were acquired in the resting state run.

Data processing

The EEG signals were preprocessed for RF pulse and ballistocardio artifacts reduction (Allen et al., 1998, 2000), downsampled to 250 Hz and band-pass filtered (1 to 100 Hz). The fMRI volumes were preprocessed to correct for head movement, brain masked, and transformed to the Talairach and Tournoux (1988) coordinate system. Slice timing correction was not necessary, because there is no specification of haemodynamic response and the delay is implicit in EEG transfer function. Spatial smoothing was not applied in order to keep original spatial resolution. In the case of visual stimulation experiment, conventional brain activation maps based on the general linear model (GLM) were obtained using the software XBAM (www.brainmap.co.uk). The haemodynamic response was modeled by two Poisson functions with peaks at 4 and 8 s after the stimulus onset. The significance level was set at a cluster-wise *p*-value of <0.01.

Brain mapping and transfer function estimation

Considering that resting state conditions with eyes closed induce alpha power in occipital areas and the primary stimulation of visual areas, the BOLD predictability mapping in this study was carried out focusing solely on O1 channel. The preprocessed EEG signals were considered as predictors x_t in the smooth transfer function model described previously. This model was then fitted for all intracranial voxels, assuming the respective BOLD signal as the response variable y_t. For the brain mapping analysis, the number of functions for B-splines expansion was set to 10. For the ROI based analysis, the optimum number of functions was estimated by using leave-one-out cross-validation. The ROI analysis consisted in averaging the BOLD time series across the mapped voxels at occipital cortex and then use this BOLD signal to estimate the transfer function between O1 and BOLD. The leave-one-out cross-validation method consisted of, for each observation, remove it from the sample and predict its value using the other observations. The optimum number of functions is the one minimizing the sum of the squares of prediction error. In addition, similarly to other haemodynamic response described in the literature (Glover, 1999; Buxton et al., 2004), the transfer function length was set to a window of 15 s, resulting in 3750 EEG values. The predictability significance was tested using the fitted model *F*-statistics, including Cochrane–Orcutt AR(1) correction for auto-correlated errors.

Results

Simulation results are described in Fig. 2. The average and standard deviation intervals of the estimated transfer function suggest that the

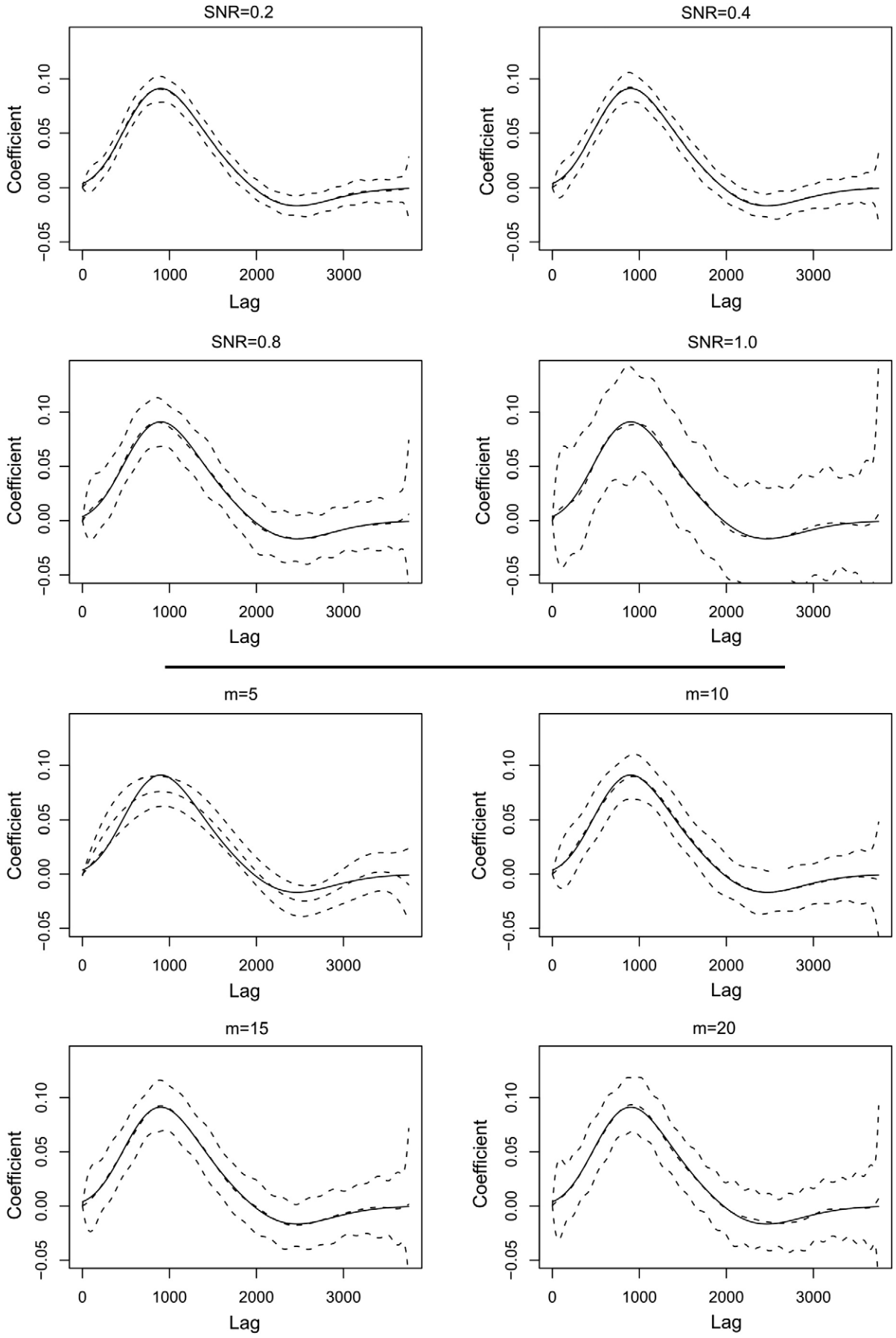

Fig. 2. Simulations results at four different levels of signal-to-noise ratio and components of splines expansion. The solid line describes the true transfer function. The dashed lines describe the average and one standard deviation intervals for the estimated function.

Table 1
Brain regions for which the BOLD signal can be predicted by the EEG measurements at O1 (uncorrected p-value <0.001, cluster size equal or greater than 10 voxels).

Resting state	Talairach coordinates							
	X	*Y*	*Z*	Size	*z*-value	Side	BA	Area
	−8	−90	29	11	4.14	L	19	occipito-parietal cortex
	0	−71	46	15	4.22	–	7	parietal cortex
	22	−68	63	10	3.83	R	7	parietal cortex
Visual–subject 1	11	−64	−6	11	4.94	R	18	occipital cortex
Visual–subject 2	−15	−82	0	24	4.14	L	18	occipital Cortex

proposed method is consistent and suitable to the problem. It is important to highlight that, if only five functions are included in the expansion, the curve estimates are extremely biased.

For the resting state experiment, the maps of voxels for which the BOLD signal can be predicted by the signal measured at the channel O1 are described in Table 1 and represented in Fig. 3a (uncorrected p-value <0.001, cluster size equal or greater than 10 voxels). Note that, as expected, the identified regions lay mostly at occipital and parietal cortex. The illustration in Fig. 3b depicts the signal at channel O1 and the average BOLD signal between the voxels of the mapped cluster.

Table 1 (uncorrected p-value<0.001, cluster size equal or greater than 10 voxels, the voxels dimension were $3.75 \times 3.75 \times 5.72$ mm) and Figs. 4 and 5 describe the corresponding areas for the visual stimulation experiment. Similarly to the resting state results, the areas are mostly located at parietal and occipital lobes.

The estimated transfer functions between the EEG to BOLD for the three datasets are shown in Fig. 6. Note that for the visual experiment, there is an inversion of the sign of transfer function estimates between the two subjects (see Discussion). The power spectrum of EEG filtered by the estimated transfer function is shown in Fig. 7. Notice that, since

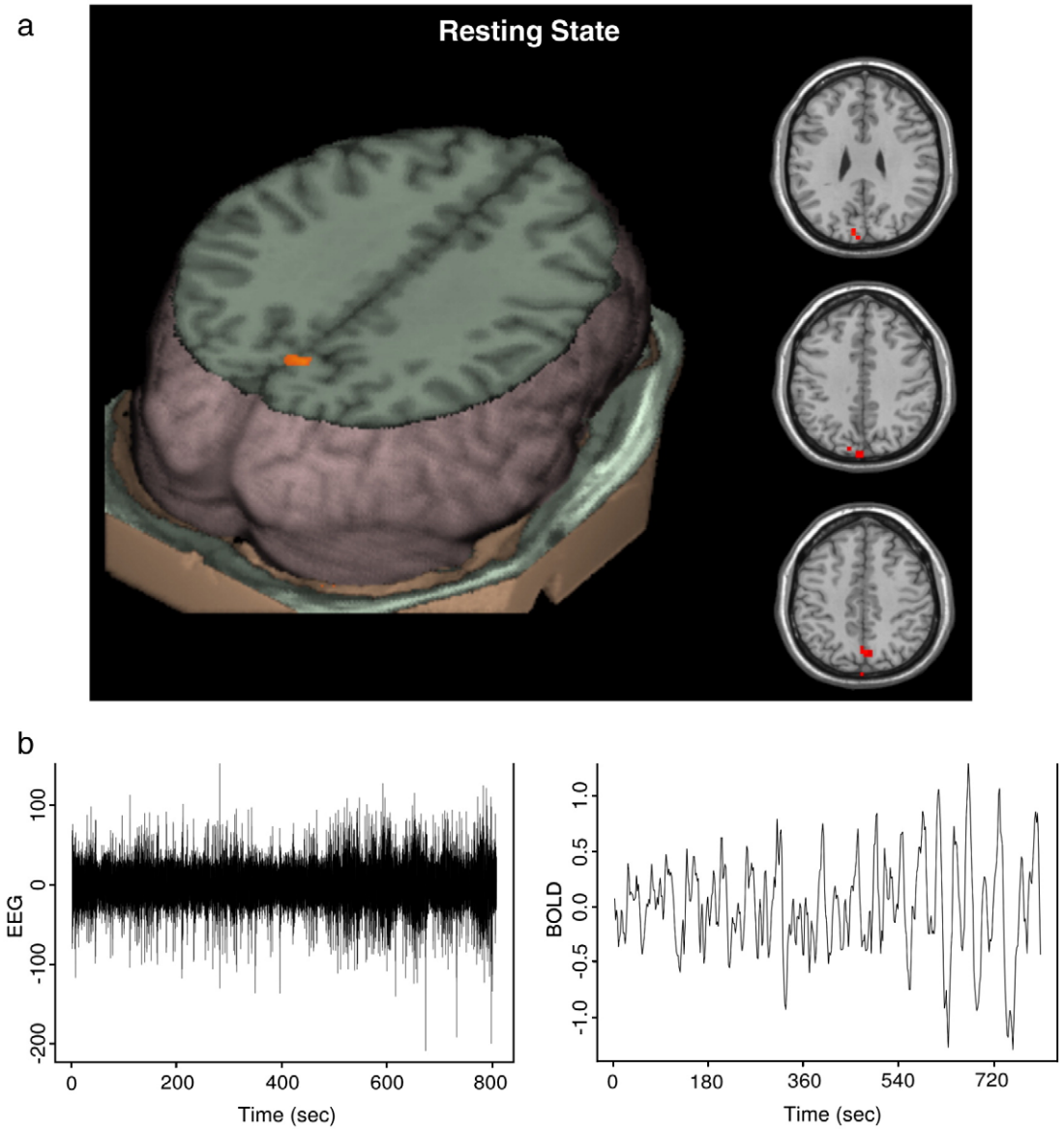

Fig. 3. Resting state (eyes closed): (a) brain mapping of the regions for which the BOLD signal can be predicted by the EEG signal at O1. (b) EEG signal registered at channel O1 and the cluster average BOLD signal which can be predicted by the former.

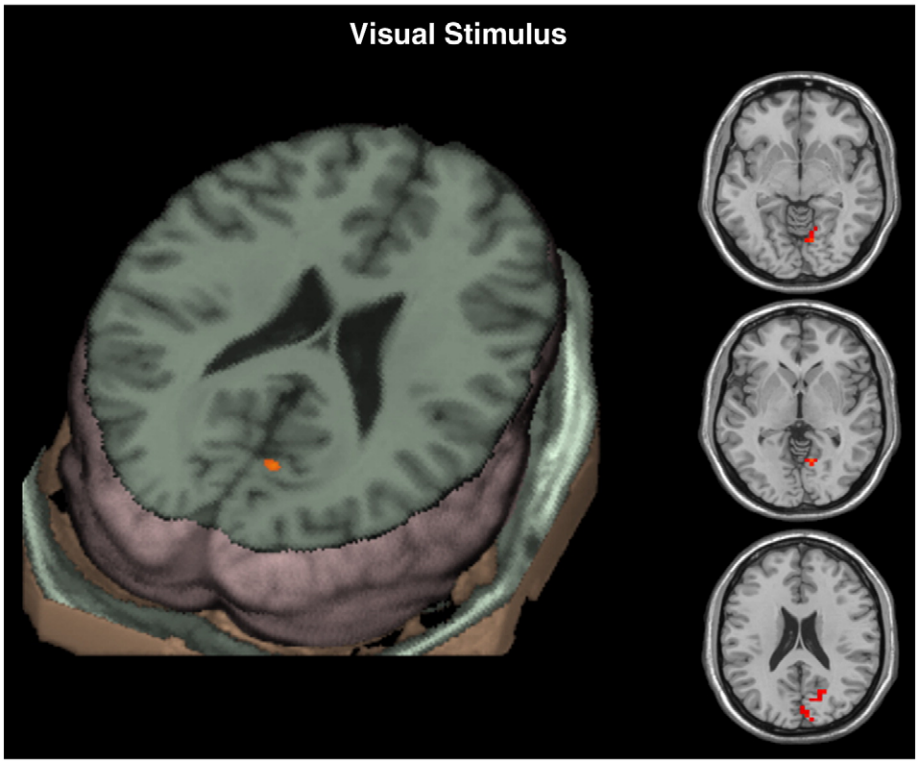

Fig. 4. Visual experiment – subject 1: brain mapping of the regions for which the BOLD signal can be predicted by the EEG measurements at O1.

the transfer function was assumed to be smooth, it actually plays the role of a low-pass filter. In Fig. 8a the time-varying power in alpha band during the resting state experiment is depicted. Figs. 8b and c show the observed BOLD (at occipital ROI) and the fitted signal by using the O1 measurement as predictor and the estimated transfer function. Finally, Fig. 9 describes conventional GLM activation maps for the two subjects under visual stimulation paradigm.

Discussion

The aim of the present study was to introduce a new method to explore the relationship between electrical and haemodynamic measurements in simultaneous EEG-fMRI acquisitions. Although neuronal activity is associated with both BOLD and EEG, the direct correlation between these signals is not trivial. The BOLD signal measured in the scanner is a result of a long chain of neural and haemodynamic processes, while EEG measures the relative variations of electric potentials induced by currents radial and tangential to the scalp. The data acquisition of both modalities is subject to a number of artifacts and implicit filtering which makes difficult the description of neural and haemodynamic coupling. The proposed approach is based on the estimation of transfer functions which connect EEG to BOLD, in a whole brain voxel-by-voxel analysis. Furthermore, the proposed approach may also be generalized to consider power bands correlations by replacing the EEG signal by an estimate of the time-variant power spectrum at specific bands. The simulations and application to resting state and visual stimulation datasets suggest that the proposal can be useful for both brain mapping and in extracting additional information about the underlying neuro-haemodynamic processes.

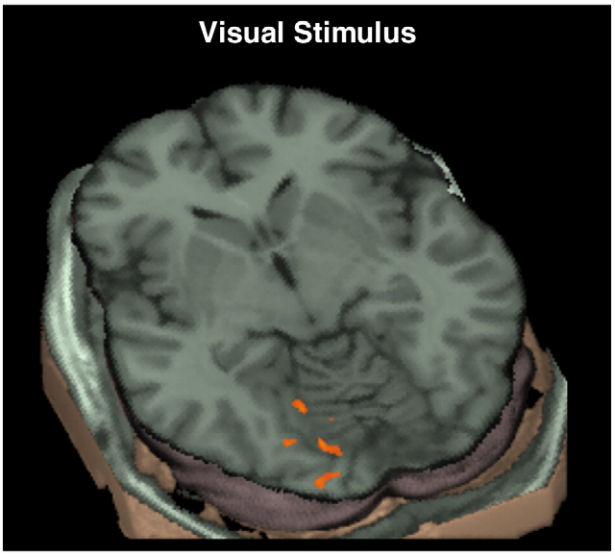

Fig. 5. Visual experiment – subject 2: brain mapping of the regions for which the BOLD signal can be predicted by the EEG measurements at O1.

The computational simulations point out that the transfer function estimation in the present context is feasible. Nevertheless, the quality of results depends on the noise level. As expected, the standard deviation of estimates is negatively associated with the signal-to-noise ratio. In addition, note that if only five functions are included in splines expansion, the transfer function estimates become extremely biased. For m greater and equal to 10, the bias seems to be negligible. On the other hand, the inclusion of a large number of functions leads to a lack of power in statistical tests, since more parameters would be estimated.

The analysis of resting state (eyes closed) acquisition suggests that the BOLD signal at medial face of occipito-parietal cortex can be predicted by the electrical variations measured at O1 channel (Fig. 3). This result confirms the expectation that even in resting state conditions, the observed BOLD signal at these regions mirrors fluctuations of local neural activity (Logothetis et al., 2001). In fact, spontaneous alpha rhythms (see Fig. 8a) have been shown to play a role in haemodynamic fluctuations under resting state condition (Difrancesco et al., 2008; Laufs et al., 2003). In a remarkable study, Mantini et al. (2007) have shown that there is a variety of rhythms

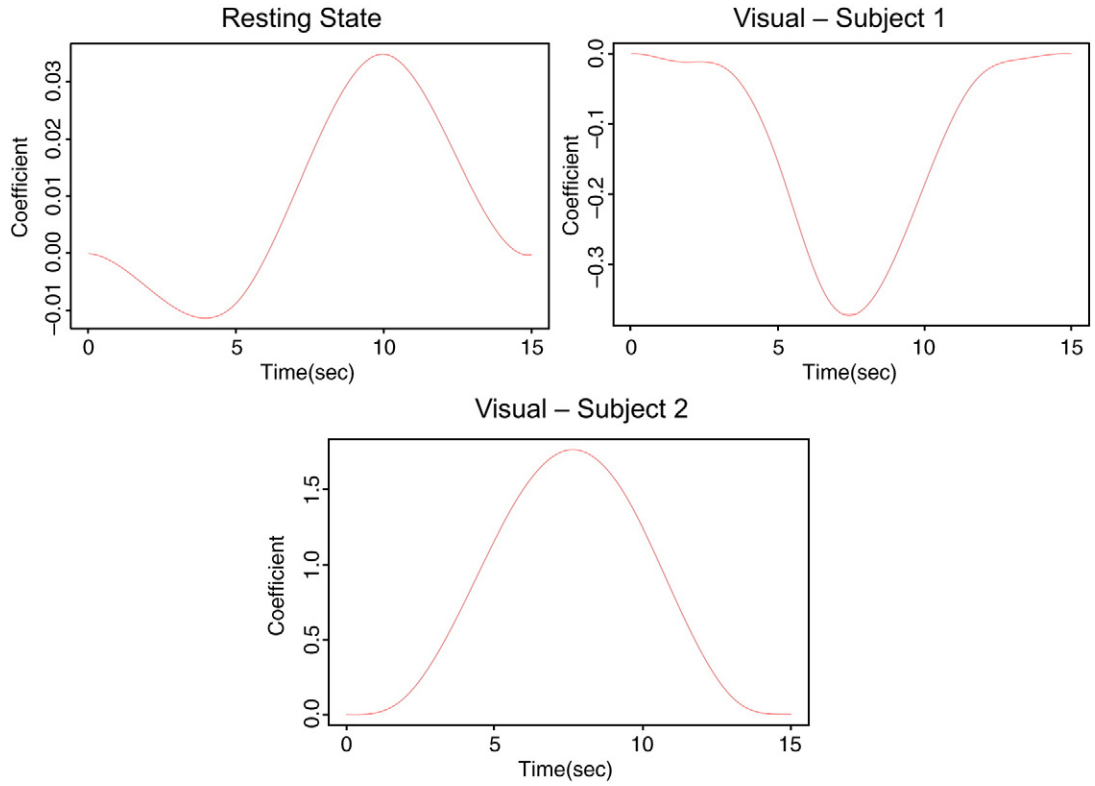

Fig. 6. Estimated tranfer functions from EEG to BOLD for each experiment. The signal registered at O1 channel was assumed to be the input and the average BOLD signal within the mapped clusters the output.

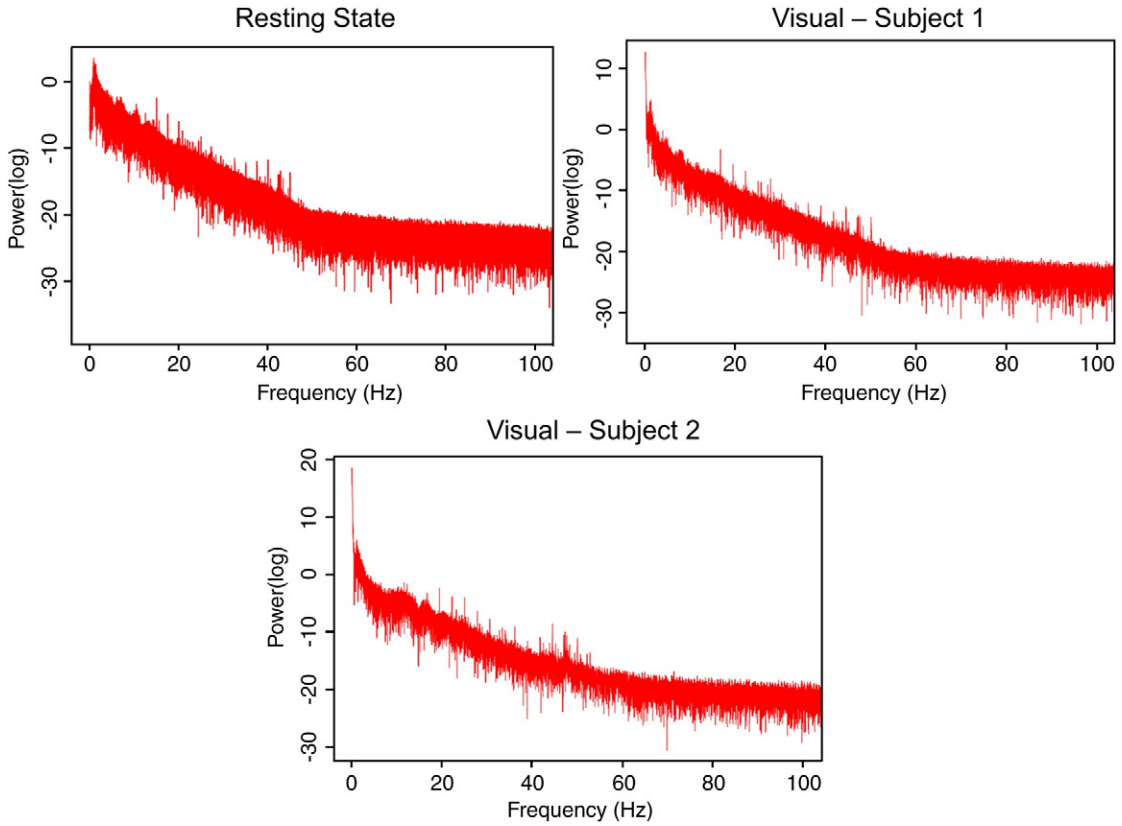

Fig. 7. Spectrum of EEG signal filtered by the estimated tranfer function (from EEG to BOLD) for each experiment. Note that as expected, the energy is mostly concentrated in low frequencies.

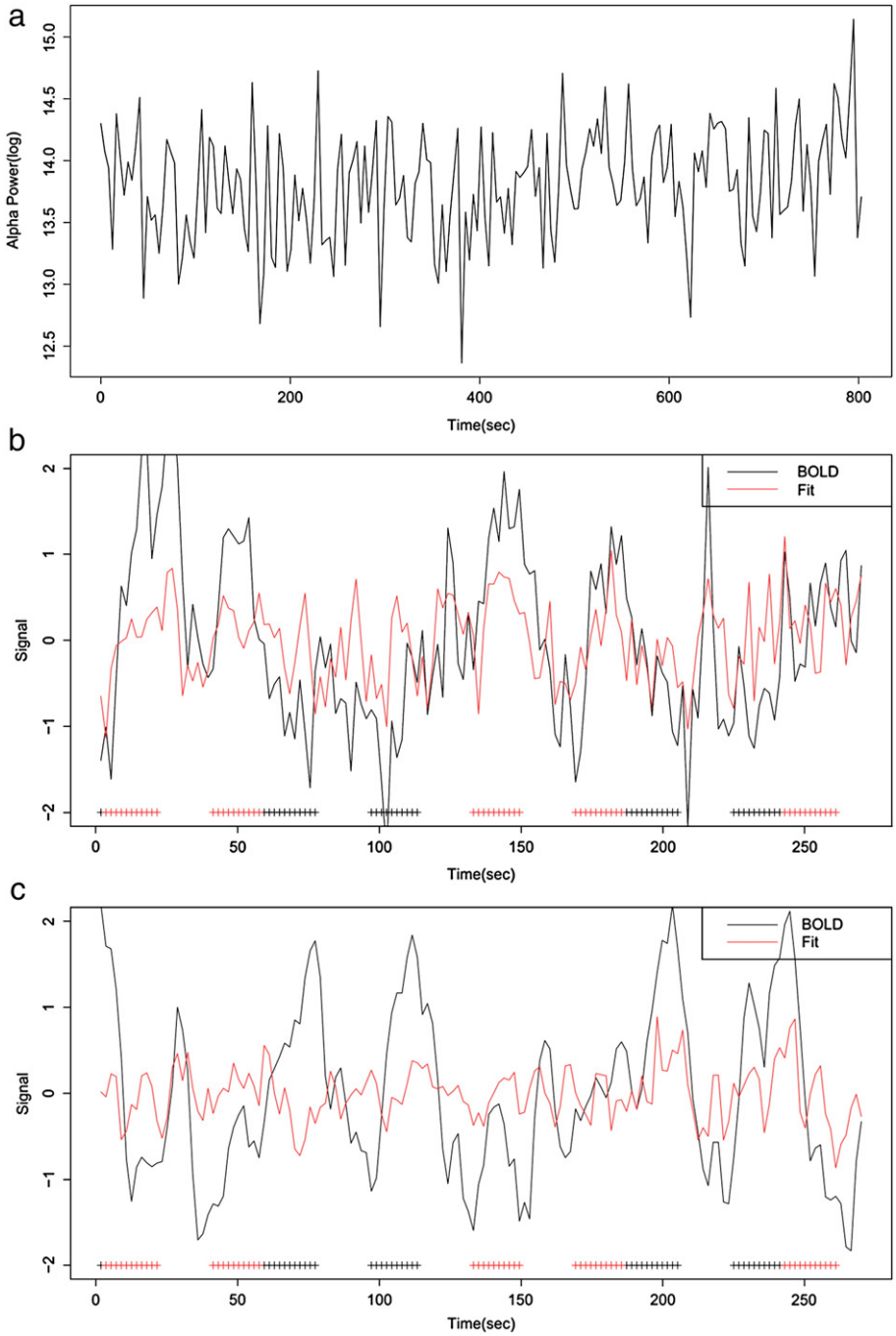

Fig. 8. (A) Time-varying power at alpha band in the resting state experiment. (B and C) Observed and fitted BOLD signal at the occipital cortex ROI for the two subjects under visual stimulation paradigm. The bottom marks indicate the blocks for right (black) and left (red) visual field stimulation.

within other frequency bands (mainly delta, theta and beta) participating in electrical spontaneous fluctuation, and provided spectral signatures of resting state networks.

In this study, the main focus was not on the correlation between the power at specific bands and BOLD changes, but on the estimation of a transfer function linking electrical activity to haemodynamic responses. Actually, the brain mapping is a result of the measurement of transfer function effectiveness at each voxel, in a statistical hypothesis testing framework. Note that the proposed analysis is carried out in a data-driven fashion, in which is not necessary to specify the haemodynamic response function nor its shape or delay. This flexibility provides an exploratory approach for highlighting voxels with predictable BOLD and not only the regions following a pre-specified response pattern, as in usual GLM-based analysis of EEG-fMRI data (e.g., for mapping the epileptogenic focus). Furthermore, the estimated transfer function at resting state (Fig. 6) is composed by a slight undershoot between 4 and 5 s and a peak between 9 and 10 s. This characteristic may mirror a metabolic landscape linking, related to the requirements of stimuli processing, and a basal state that feeds forward the controlling cascade.

In addition, the mapping results for the visual stimulation experiment suggested that the signal measured at O1 channel contains information to predict the BOLD observed at primary visual areas for both subjects. Figs. 8b and c evidence that the fitted values by using O1 information were fairly close to the observed BOLD signal, mainly for subject 1. In addition, the BOLD signal for subject 1 (ROI

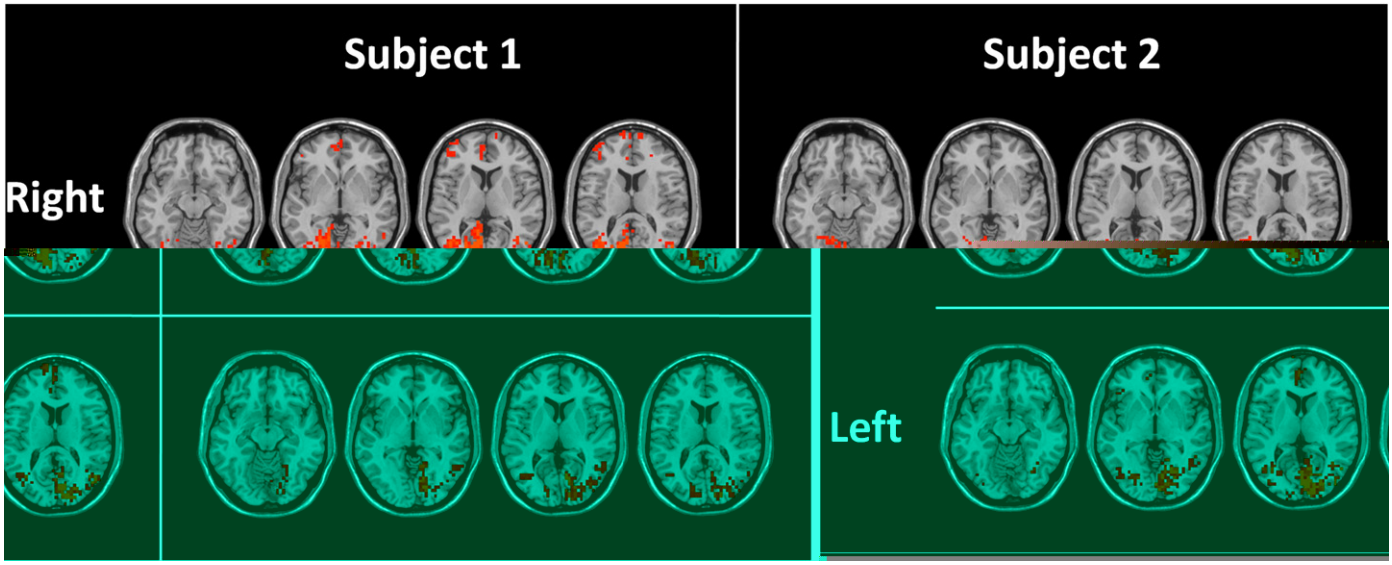

Fig. 9. Brain activation maps for right and left visual stimulation obtained using the general linear model (cluster-wise p-value <0.01).

located mostly at right hemisphere) seems to respond mainly for left visual field stimulation, while for subject 2 (ROI located at left hemisphere), the response seems to be selective for right visual field stimulation. The fitted BOLD using O1 signals have shown analogous results. This result is in accordance with the findings in Singh et al. (2003), which studied the correlation between evoked potential EEG and BOLD in a non-simultaneous acquisition but under the same visual stimulation protocol. Singh et al. (2003) have shown consistent (eight subjects) correlated changes between the strength of EEG channels and BOLD responses at the occipital lobe. In addition, we observe clearly that the transfer functions for both subjects are very similar for the visual experiment. However, the sign of the transfer function is the opposite between the two subjects. On the other hand, for subject 1, O1 contained information to predict only the BOLD signal at the ROI at right hemisphere. These results were unexpected but seem to be robust in the data, since the mapped area was in the visual cortex and the fitted values are relatively close to observed ones (Fig. 8b). These results may be related to electrode positioning, signal polarity or several other confounders, but this discussion or possible interpretations in this specific case are out of the scope of the present study. The conventional GLM-based activation maps shown in Fig. 9 point out that BOLD response are spatially more diffuse than the ones using the transfer function approach. However, this result is expected, since the latter does not use any information about experimental condition. In other words, the experimental condition induces changes in EEG signal, which is then used to localize the voxels with BOLD response predicted by them.

In resting state experiments, de Munck et al. (2007) have shown that the BOLD signal in Thalamus was correlated with alpha power, but this structure was not highlighted in our illustrative example. A possible explanation is that we did not applied a Fourier transform to the EEG signal and it may contain other components (e.g., noise or other bands) which are not related with alpha, leading to a lack of power in brain mapping for this band. Furthermore, the electrode was spatially closed to occipital cortex but far away from Thalamus, which may allow the amplification of other components in the signal related to cortical but not subcortical activity.

One question that may arise is that positive and negative potentials in EEG may analogously contribute to the metabolism and this property is not taken into account in the transfer function estimation procedure. In fact, this is an important point that may constrain the applicability of the proposed approach. However, in the examples illustrated in this work, most of EEG at O1 channel had the same sign. In resting state data 82% of the signal were negative (the reference is an electrode between Pz and Cz). For the two visual stimulation dataset, the percentages were 89% and 99%. Thus, we believe the sensitivity of the method was not so influenced by the sign constraint in this case. However, the conclusion is that the sign of raw EEG data should be first checked before submitted to the analysis, in order to produce interpretable results.

It is important to mention and emphasize that the proposed method is not suitable for EEG dipole source localization. In fact, the approach is an exploratory analysis and all extracted information and conclusions should be interpreted from a predictive power perspective. The results obtained using this approach may suggest that it can be used as a data-driven method for integrating haemodynamic and electric potentials information to identify the source of EEG measurements at specific channels. However, correlation and predictability are not enough to infer causality or effective influences. The BOLD signal of regions which are not the source of dipoles captured by EEG may be predicted by some channels, due to functional connectivity networks. In these cases, the information contained in an EEG channel may be used to predict the BOLD of several areas which are functionally connected to the “source” one. EEG measured at scalp may be a problem, since the signal is a mixture of effects of different sources mixed by the lead field, which may result in a lack of spatial specificity of the HRF. Furthermore, indirect influences of other brain areas may operate as confounders and it is difficult to take them into account in a data-driven analysis. However, the proposed approach aims to find possible neuro-electrical substrates of haemodynamic fluctuations of BOLD signal and not describe a integration process or brain mapping of current sources. Actually, the spatial localization of electrical sources involves several other variables and anatomical constraints such as cortical surface orientation, electrode coordinates, etc, and more complex models such as LORETA (Pascual-Marqui et al., 2002) and sLORETA (Pascual-Marqui, 2002) should be applied. Advanced model-driven analysis dealing with this issue can be found in Grova et al. (2008) and Valdes-Sosa et al. (2009).

In addition, a further limitation of this approach is that the estimates' quality and statistical power for brain mapping are highly dependent on both EEG and fMRI signal-to-noise ratio. This limitation implies that it is desirable to acquire fMRI data at magnetic fields up to 3 Tesla or using long runs to obtain a large number of volumes. Furthermore, MRI environment is extremely hostile for EEG registration, due to the ballistocardiogram and radio-frequency pulse artifacts. In this sense, the successful application of the method relies

on the use of an adequate MRI-compatible EEG system and on an efficient artifacts removal algorithm.

In this study, the mapping results of some experiments point out that the laterality differ across subjects or even identified voxels at the opposite hemisphere of O1 channel location. In fact, we believe that the occipital cortex of both hemispheres should be mapped to occipital channels. However, this expectation may not be confirmed due to electrode positioning (mainly in electrode caps setup) and/or low signal-to-noise ratio, resulting in lack of power to identify relevant voxels. However, from all intracranial voxels, only the occipital and parieto-occipital ones were identified as correlated with O1 for the two experiments, which may indicate the method is consistent.

Future works include extending the concepts of this exploratory analysis to a model-based approach, with main concern on its integration with biophysical models (Sotero et al., 2008) and dipole source models (Hämäläinen and Ilmoniemi, 1994; Pascual-Marqui et al., 2002). At the present data-driven form, the approach regards only the correlations between EEG and BOLD signals, when actually, there is a local neural latent trigger driving both signals. In addition, a possible unification of these methods is including constraints in model based analysis, in order to comprise the relationships between EEG and BOLD described by the exploratory analysis.

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