33rd Annual International Conference of the IEEE EMBS
Boston, Massachusetts USA, August 30 - September 3, 2011

INVESTIGATON OF THE NEURONAL EFFICACY AND EEG SOURCE POWER UNDER STEADY-STATE VISUAL STIMULATION

A. Deniz Duru, S. Burcu Erdogan, I. Kasikci, A. Bayram, A. Ademoglu and T. Demiralp

Abstract— **Understanding the nature of the link between neuronal activity and BOLD signal plays a crucial role i) for improving the interpretability of BOLD images and ii) on the design of more realistic models for the integration of EEG and fMRI. The aim of this study is to investigate the neural mechanism underlying hemodynamic behavior in a series of visual stimulation frequencies and explore possible implications for the neurovascular coupling. We studied the relationship between electrophysiological and hemodynamic measures by performing simultaneous steady state electroencephalography (EEG) and fMRI recordings in a healthy human subject during a series of visual stimulation frequencies (6 Hz, 8 Hz, 10 Hz, 12 Hz). BOLD amplitudes were computed for voxels within an anatomical mask which was obtained by mapping the significantly active voxels using general linear modelling (GLM) on fMRI data. On the same anatomical map, EEG power time series belonging to the fundamental frequency and its harmonics due to the stimulation are estimated using a distributed source imaging technique. The neuronal efficacies which represent the vascular inputs driving the BOLD response are estimated by use of an extended version of Balloon model. A nonlinear relationship is demonstrated between the mean EEG source powers and the neuronal efficacies driving the BOLD response. The result suggests that BOLD signal which is an indicator of the metabolic demand of both synchronized and non-synchronized neuronal activities; changes independent of EEG activity which is a measure sensitive to the synchronicity of neuronal activity.**

I. INTRODUCTION

Functional magnetic resonance imaging (fMRI) based on blood oxygenation level dependent (BOLD) signal has been extensively used to investigate sensory and cognitive responses in human subjects [**?**]. Accurate interpretation of these signals requires knowledge of the relationship between the hemodynamic response and the neuronal activity that underlies them. The observed fMRI response to a stimulus is the complex result of several cascaded processes including stimulus induced neural activity, neurovascular coupling and hemodynamic response [**?**]. Many of the previous studies focusing on the BOLD response demonstrated that while longer duration stimuli behave in an approximately linear manner, shorter duration stimuli produce responses larger than those predicted from a simple linear model. The hemodynamic response non-linearity could arise from one of these processes or a mixture of them. Regarding the hemodynamic response effect, the Balloon model has been suggested to account for the nonlinear convolution of rCBF and BOLD signal [**?**]. Its predictions are consistent with the experimental results measured by simultaneous BOLD and perfusion imaging technique [**?**]. Because blood flow could not be measured by BOLD fMRI, Friston et al. (2000) extended the Balloon model by using the stimulus input as an index of neural activity, instead of the cerebral blood flow [**?**]. Although some of the previous studies [**?**], [**?**] considered both hemodynamic and neuronal nonlinearities; the absence of actual measurements of neuronal activities in these studies makes it difficult to clearly seperate the two effects. Simultaneous recordings of electroencephalography (EEG) and fMRI make it possible to investigate the spatiotemporal correlation between the electrophysiological activities and the hemodynamic responses in human subjects. Although there are many investigations being carried out which take advantage of this combinational technique, the spatiotemporal correlation between the two modalities has not been well-known [**?**], [**?**]. The aim of this study is to investigate the relationship between the hemodynamic response to brain activation and the underlying neural mechanism by performing simultaneous EEG-fMRI measurements. Steady state EEG-fMRI data are recorded simultaneously from a healthy volunteer where flickers are presented at 6, 8, 10 and 12 Hz. The steady state electrical responses of the brain are processed by solving the EEG inverse problem with an imaging approach which allows for a design of spatiotemporally optimized filter function that maps the EEG data at the sensor space to the current distribution in the source space. The BOLD signal is nonlinearly deconvoluted to obtain the neuronal efficacy (as originally described in [**?**], [**?**]) which represents the vascular inputs driving the BOLD response and the interplay between the two indices are studied.

II. METHODS

A. EEG-fMRI Data Recording

Steady-State EEG-fMRI are recorded simultaneously from a healthy volunteer where flickers are presented at $6, 8, 10$ and 12 Hz. Repetion time of the scanner is 2.98s. Each session starts with 29.8s baseline recording followed by three blocks each consisting of 44.7s of stimulation and 44.7s baseline recording yielding a total period of 298 s (100 volume images). A Philips 1.5 T MR system is used to acquire $T2^*$ weighted images using a gradient echo EPI sequence with repetition time $TR = 2981$ms, echo time $TE = 50$ms, flip angle $FE = 90^o$, matrix size =

This work was supported by a grant from TUBITAK with the project code $108S101$ and Bogazici University Research Fund under the Project code 5192.

A. Deniz Duru, S. Burcu Erdogan, Ali Bayram and Ahmet Ademoglu are with the Institute of Biomedical Engineering, Bogazici University, Kandilli, 34684, Istanbul, TR, berdogan83@gmail.com

Itir Kasikci and Tamer Demiralp are with the Department of Physiology at Istanbul Medical School, Istanbul University, 34093, TR

64×64, 32 axial slices and voxel size $= 3.59$mm $\times 3.59$mm $\times 4$mm. A high resolution (1mm$\times$ 1mm $\times$1mm) T_2 weighted individual anatomical MR scan is also taken from the same subject to perform segmentation, registration and template normalization using SPM to align the fMRI space with the template used for EEG forward modeling.

EEG is recorded simultaneously by using an MR compatible EEG amplifier (BrainAmp MR+, Brain Products, Germany) with 30 channels for EEG and a channel for ECG. The EEG signal is sampled with a rate of 5000 Hz and filtered between 0.01 and 250 Hz. Gradient and ballistocardiographic artifacts in the EEG are removed by using Brain Analyzer software.

B. Hemodynamic Model

Friston et al. [**?**] have extended the Balloon model [**?**] to include the relationships between phsiological (i.e. neuronal synaptic activity and a flow inducing signal) and hemodynamic processes. This extended model is simply named as the hemodynamic system in our paper. A set of four nonlinear ordinary differential equations governs the dynamics of the intrinsic variables which form the underlying states of the BOLD signal. These state variables are the flow inducing signal (s), the cerebral blood flow (f_{in}), the cerebral blood volume (v) and the total deoxyhemoglobin content (q).They are all normalized to their resting state values. We start with

$$\dot{f_{in}} = s \tag{1}$$

The flow inducing signal is generated by neuronal responses to the input stimulus function ($u(t)$) by

$$\dot{s} = \epsilon u(t) - \kappa_s/s - \kappa_f(f_{in} - 1) \tag{2}$$

ϵ, κ_s and κ_f are parameters that represent the efficacy with which input causes an increase in flow signal, the rate constant for signal decay and the rate constant for autoregulatory feedback from blood flow. Inflow determines the rate of change of volume through

$$\begin{aligned} \tau\dot{v} &= f_{in} - f_{out}(v) \\ f_{out}(v) &= v^{1/\alpha} \end{aligned} \tag{3}$$

Eqn. **??** says that normalized venous volume changes reflect the changes between inflow f_{in} and outflow f_{out} from the venous compartment with a time constant (transit time) τ. Outflow is a function of volume and can be modeled with a single parameter α [**?**]. The change in normalized total deoxyhemoglobin voxel content $\dot{q}$ reflects the delivery of deoxyhemoglobin into the venous compartment minus that expelled

$$\tau\dot{q} = f_{in}\frac{E(f_{in}, E_0)}{E_0} - f_{out}(v)q/v \tag{4}$$

$E(f_{in}, E_0)$ is the fraction of oxygen extracted from inflowing blood and E_0 is the resting net oxygen fraction by the capillary bed. The BOLD signal y(t)

$$y(t) = V_0(k_1(1-q) + k_2(1-q/v) + k_3(1-v) \tag{5}$$

$$\begin{aligned} k_1 &= 7E_0 \\ k_2 &= 2 \\ k_3 &= 2E_0 - 0.2 \end{aligned}$$

is taken to be a static nonlinear function of volume (v) and deoxyhemoglobin content (q) where V_0 is the resting blood volume fraction.

C. System Identification

Bayesian estimation requires informative priors on the parameters which are specified in terms of sample mean and covariance, over voxels, of the parameters reported in Friston et al (2000) [**?**].The priors for efficacy parameter are taken to be relatively flat with an expectation of zero and a variance of 16 per second. Only the biophysical parameters (κ_s, κ_f, τ, α, E_0) have informative priors. The efficacies are assumed to be independent of the biophysical parameters with zero covariance. Bayesian inference procedure for nonlinear observation models of the form

$$y = h(\theta, u) + \boldsymbol{e} \tag{6}$$

is applied under Gaussian assumptions about the parameters θ and errors $\boldsymbol{e} \approx N(0, C_\epsilon)$. Assuming the posterior density of the parameters is approximately Gaussian, the problem reduces to finding its first two moments, the conditional mean $\eta_{\theta|y}$ and covariance $C_{\theta|y}$.

D. Deriving the Efficacy Parameter on EEG-fMRI Activation Mask

Prior to the EEG-fMRI correlation analysis, the fMRI preprocessing (realignment, slice timing correction, spatial normalization and spatial smoothing with an 8 mm isotropic full width at half maximum (FWHM) Gaussian kernel) and statistical analysis were performed using SPM8 software (Wellcome Department of Imaging Neuroscience, UCL). Activated regions were identified for each frequency and modality independently. The indices of the BOLD responses derived from hemodynamic modeling are the vascular inputs, parameterized by neuronal efficacies (ϵ). Neuronal efficacies are calculated for each voxel on the common active region of the EEG and fMRI activation maps by using the Bayesian Inference of the hemodynamic system [**?**]. The stimulation function $u(t)$ modeling the input of hemodynamic system comprises of a train of spikes indexing the presentation of visual stimulation and was fixed for all cases of changing stimulation frequencies. Each session is modeled as a boxcar function convolved with a canonical hemodynamic response function. The statistical model includes global, low frequency and motion-related confounds. Only voxels surviving a T threshold of $p < 0.05$ are considered. The analysis of all conditions shows that the activated regions are primarily located in primary visual cortex (Fig. 1, Bonferroni correction, $p < 0.05$).

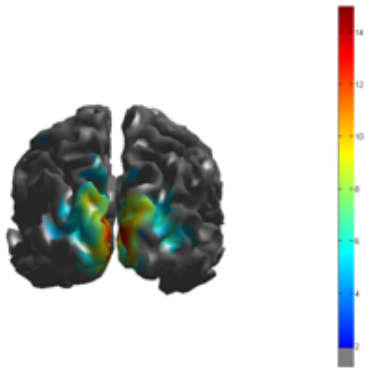

Fig. 1. The activated regions of all conditons are located primarily at the visual cortex (The color indexes the T value).

E. EEG Source Reconstruction

EEG source reconstruction procedures project the scalp EEG data to the grey matter source space by solving the inverse problem. Inverse problem requires constructing a head model and solving the solution of the forward problem.The forward problem of EEG, which enables computation of the electrical potentials on the scalp surface given the source positions and strengths, is solved using the Boundary Element Method (BEM) with the Center of Gravity (COG) approach on a realistic head model as shown in Fig 2. The human head is modeled as three homogeneous isotropic conductor layers; the outermost surface being the boundary for the scalp, the intermediate for the skull and the innermost surface being for the brain. The triangulated head model that we use in this study is obtained from the templates of the SPM library. $n_e = 29$ electrode locations are registered to the scalp surface by spline interpolation using the 10-20 electrode placement, inion-nasion and pre-auricular coordinates. Forward problem is solved to compute the lead field matrix H, using the $n_s = 5124$ vertex points of the segmented cortical mesh on which the electrical sources are oriented normal to the gray matter.

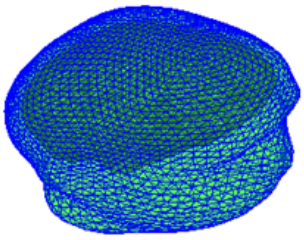

Fig. 2. The realistic head model obtained from SPM canonical templates consists of triangulated surfaces covering the scalp, skull and brain.

The forward model of EEG is given by a two-level hierarchical model

$$Y = Hj + \epsilon^{(1)} \tag{7}$$

$$j = \epsilon^{(2)} \tag{8}$$

where Y represents a $n_e \times n_t$ data matrix of channels $\times$ time, j is $n_s \times n_t$ matrix of source activity, $\epsilon^{(1)}$ denotes the observation error and $\epsilon^{(2)}$ represents the unknown source activity.

$$Cov(vec(\epsilon^{(1)})) = V^{(1)} \otimes C^{(1)} \tag{9}$$

$$Cov(vec(\epsilon^{(2)})) = V^{(2)} \otimes C^{(2)} \tag{10}$$

$V^{(1)}$ is the temporal correlation matrix of the observation noise $\epsilon^{(1)}$ and it is assumed to be an identity matrix in this study. The symbol $\otimes$ stands for the Kronecker product. The temporal correlation structure of the sources $V^{(2)}$, is constrained by the first 200 principal eigenvectors of a Gaussian auto-correlation matrix with standard deviation ($\sigma = 2$), windowed with a rectangular function of $n_t = 1000$ denoted as F [**?**]. F transforms the temporal covariance structure of the sources to a subspace that embeds the temporal covariance structure of the sensors. The spatial covariance structure of the sensor space is assumed as an identity matrix and given as

$$C^{(1)} = \lambda_1^{(1)} Q_1^{(1)} \tag{11}$$

The spatial covariance structure of the source space is

$$C^{(2)} = \lambda_2^{(2)} Q_1^{(2)} + \lambda_3^{(2)} Q_2^{(2)} \tag{12}$$

where $HQ_1^{(2)}H^T$ is the spatial smoothing (spatial coherence) constraint projected to the sensor space formed by applying a Gaussian kernel ($\sigma = 10$mm) to the geodesic distances between the vertices of the triangles forming the source manifold. $HQ_2^{(2)}H^T$ is similarly projected as the probability constraint for voxels for their belonging to the gray matter tissue. The hyperparameters of the covariance constraints λ_1^1, λ_1^2 and λ_2^2 are estimated using restricted maximum likelihood (ReML) algorithm defined by Phillips et al. [**?**].

F. EEG Data analysis

For each stimulation frequency, EEG data is downsampled to 1000 Hz and split into 100 blocks. EEG inverse problem is solved and the energy of each source is computed for each temporal block. For each source location, a 100 point EEG energy power time series is reconstructed temporally corresponding with the fMRI BOLD response.

III. RESULTS

Measures of the hemodynamic and electrophysiological responses to changing stimulation frequencies in the alpha band are evaluated on an EEG-fMRI active region which corresponds to a voxel cluster in the primary visual cortex. The mean EEG power sources are calculated by averaging the EEG power during the activation period. Figure 3 illustrates the changes in EEG power with neuronal efficacies at each active voxel at all frequencies. The same relation is also illustrated between the average efficacy and EEG source power of all voxels at each frequency with a line plot. A linear correlation analysis was carried out between the EEG mean power changes and the neuronal efficacies and the regressive results show that the relationship is nonlinear (Fig.3, $R^2 = 0.43$).

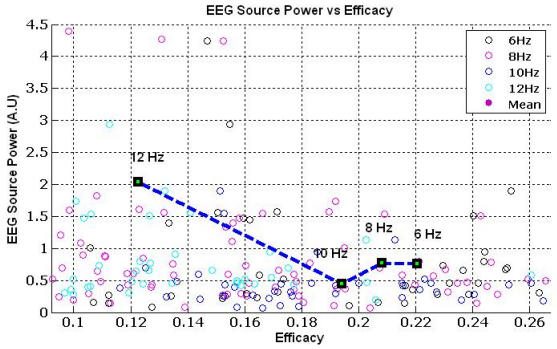

Fig. 3. The correlation between mean powers of EEG current sources and the neuronal efficacies derived from the BOLD signal over the active voxels within the anatomical mask. Each circle represents the efficacy power relationship for a particular active voxel at the stimulation frequency studied.

IV. DISCUSSION

This study shows that in a flashing visual stimulation experiment, there is no significant correlation between EEG power and BOLD signals as a function of changes in the stimulation frequency in the alpha band. In some of the previous studies [**?**], [**?**], at high spatial resolutions, the BOLD signals have been shown to be linearly linked with electrophysiological activity, measured by local field potential (LFP) and/or multiple unit activity (MUA). However; recent findings illustrate that the relationship between the hemodynamic responses and the local electrophysiological activities is nonlinear [**?**], [**?**], [**?**] which may be due to the fact that the hemodynamic signal at a specific position integrates electrophysiological activity over a broader spatial region, likely larger than the location with the LFP and MUA [**?**] and probably at supramilimeter scales [**?**]. Consistent with these studies, our results illustrate that the conversion of neural activity into a vascular input is not a linear process. The nonlinear relationship between the mean EEG powers and the neuronal efficacies driving the BOLD response suggests that BOLD signal which is an indicator of the metabolic demand of both synchronized and non-synchronized neuronal activities; changes independent of EEG activity which is a measure sensitive to the synchronicity of neuronal activity.

V. CONCLUSIONS AND FUTURE WORKS

A. Conclusions

We use simultaneous EEG-fMRI recordings to study the correlation of hemodynamic responses and electrophysiological activity in human primary visual cortex. The study may give insight to further studies that aim at finding a transfer function to the dynamic mechanism of neurovascular coupling

B. Future Works

The method employed on a single subject data will be implemented for multiple subjects and a group study will be performed to see whether such a nonlinear trend is valid on a larger population. The frequency range will also be extended to beta and gamma bands.

VI. ACKNOWLEDGMENTS

The authors gratefully acknowledge the support of Neuropsychiatry Istanbul Hospital for fMRI experiments.

REFERENCES

[1] S. Ogawa, T. M. Lee, R. Stepnoski, W. Chen, X. Zhu and K. Ugurbil, 2000, "An approach to probe some neural systems interaction by functional MRI at neural time scale down to milliseconds", *Proc. Natl. Acad. Sci. U.S.A*, 97, pp. 11026–11031.

[2] O. J. Arthurs, S. Boniface, 2002, "How well do we understand the neural origins of the fMRI BOLD signal?", *Trends Neurosci.* 25 (1), pp. 27–31.

[3] R. B. Buxton, E.C. Wong, L.R. Frank, 1998, "Dynamics of blood flow and oxygenation changes during brain activation: the Balloon model", *Magn. Reson. Med.* 39, pp. 855–864.

[4] R. D Hoge, J.Atkinson, B. Gill, G. R Crelier, S. Marrett, G. B Pike, 1999. "Linear coupling between cerebral blood flow and oxygen consumption in activated human cortex", *Proc. Natl. Acad. Sci. U.S.A.* 96, pp. 9403–9408.

[5] K. J, Friston, A. Mechelli, R. Turner, C. J. Price, 2000, "Nonlinear responses in fMRI: the Balloon model, Volterra kernels, and other hemodynamics", *NeuroImage* 12, pp. 466–477.

[6] K. L. Miller, W. M. Luh, T. T Liu, A. Martinez, T. Obata, E. C Wong, L.R. Frank, R. B. Buxton, 2001, "Nonlinear temporal dynamics of the cerebral blood flow response", *Hum. Brain Mapp.*, 13 (1), pp. 1–12.

[7] A. M Dale, E. Halgren, 2001, "Spatiotemporal mapping of brain activity by integration of multiple imaging modalities", *Curr. Opin. Neurobiol.*, 11 (2), pp. 202–208.

[8] J. Riera, E. Aubert, K. Iwata, R. Kawashima, X. Wan, T. Ozaki, 2005, "Fusing EEG and fMRI based on a bottom-up model: Inferring activation and effective connectivity in neural masses", *Philos. Trans. R. Soc.*, London, Ser. B, 360, pp. 1025–1041.

[9] K. J. Friston, 2002, "Bayesian estimation of dynamical systems: an application to fMRI", *NeuroImage*, 16, pp. 513–530.

[10] R. L. Grubb, M. E. Rachael, J. O. Euchring, and M. M. Ter-Pogossian, 1974, "The effects of changes in PCO_2 on cerebral blood volume, blood flow and vascular mean transit time", *Stroke*, 5: pp. 630–639.

[11] G. Rees, K. J. Friston, C. Koch, 2000, "A direct quantitative relationship between the functional properties of human and macaque V5", *Nat. Neusci.* 3, pp. 716–723.

[12] N. K. Logothetis, J. Pauls, M. Augath, T. Trinath, A. Oeltermann, 2001, "Neurophysiological investigation of the basis of the fMRI signal", *Nature* 412, pp. 150–157.

[13] A. Devor, A. K. Dunn, M. L. Andermann, I. Ulbert, D. A. Boas, A. M. Dale, A.M., 2003, "Coupling of total hemoglobin concentration, oxygenation, and neuronal activity in rat somatosensory cortex", *Neuron* 39, pp. 353–359.

[14] M. Jones, N. Hewson-Stoate, J. Martindale, P. Redgrave, J. Mayhew, 2004, "Nonlinear coupling of neuronal activity and CBF in rodent barrel cortex", *NeuroImage*, 22, pp 956–965.

[15] S. A. Sheth, M. Nemoto, M. Guiou, M. Walker, N. Pouratian, A. W. Toga, 2004, "Linear and nonlinear relationships between neuronal activity, oxygen metabolism, and hemodynamic responses", *Neuron*, 42, pp. 347–355.

[16] A. Devor, I. Ulbert, A. K. Dunn, S. N. Narayanan, S. R. Jones, M. L. Andermann, 2005, "Coupling of the cortical hemodynamic response to cortical and thalamic neuronal activity", *Proc. Natl. Acda. Sci. U. S. A.*, 102, 3pp. 822–827.

[17] D. S. Kim, I. Ronen, C. Olman, S. G. Kim, K. Ugurbil, L. J. Toth, 2004, "Spatial relationship between neuronal activity and BOLD functional MRI", *NeuroImage*, 21, pp. 876–885.

[18] K. Friston, R. Henson, C. Phillips, and J. Mattout, "Bayesian estimation of evoked and induced responses", *Human Brain Mapping*, vol. 27, pp. 722-735, 2006.