26th NATIONAL RADIO SCIENCE CONFERENCE (NRSC2009)

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March 17-19, 2009, Faculty of Engineering, Future Univ., Egypt

Modeling the Interaction of Brain Regions Based on Functional Magnetic Resonance Imaging Time series

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Abstract

We propose a model that describes the interaction of several Brain Regions based on Functional Magnetic Resonance Imaging (FMRI) time series to make inferences about functional integration and segregation within the human brain. The method is demonstrated using dynamic causal modeling (DCM) using real data to show how such models are able to characterize interregional dependence. We extend estimating and reviewing designed model to characterize the interactions between regions. A further benefit is to estimate the effective connectivity between these regions. All designs, estimates, reviews are implemented using Statistical Parametric Mapping (SPM), one of the free best software packages used for design models and analysis for inferring about FMRI functional magnetic resonance imaging time series.

1. Introduction

Human brain is a complex system, contains roughly 100 billion neurons, linked with up to 10,000 synaptic connections [1]. These neurons communicate with one another by means of long protoplasmic fibers called axons, which carry trains of signal pulses called action potentials distant parts of the brain or body and target them to specific recipient cells. From a philosophical point of view, it might be said that the most important function of the brain is to serve as the physical structure underlying the mind. From a biological point of view, though, the most important function is to generate behaviors that promote the welfare of an animal. Brains control behavior either by activating muscles, or by causing secretion of chemicals such as hormones.

The operations of individual neurons and synapses are now understood in considerable detail, but the way they cooperate in ensembles of thousands or millions has been very difficult to decipher. Methods of observation such as Electroencephalography (EEG) recording and FMRI tell us that brain operations are highly organized, FMRI based on blood oxygenation level-dependent (BOLD) signal has become one of the most prominent and powerful tools in cognitive neuroscience [3]. Most FMRI studies found in the literature focus on the detection of neuronal activation and brain mapping via statistical analysis. However, understanding cortical dynamics is a crucial step toward inferring cortical functioning.

Several evidences [4–6] suggest that modeling the interactions between different brain structures is paramount to understand the mechanisms guiding specific cognitive behavior. However, the determination of parameters involved in cortical dynamics is still an open question. A number of techniques are being used to detect patterns of interaction between cortical areas, most connectivity studies have investigated temporal correlation as a measure of connectivity [5].

Brain connectivity characterization used for understanding of how sensory processing is carried out; however, conventional imaging methods such as FMRI measure BOLD responses but do not have the temporal resolution to resolve the sequence of responses that occur within a circuit. Although the timescale of BOLD signals is not at the same level as neuronal spiking, interactions can be investigated by means of either functional or effective connectivity analysis. Whereas functional connectivity refers to coherence of activity across the brain, effective connectivity identifies how the activity in one brain region influences another.

Functional connectivity is simply a statement about the observed correlations; it does not comment on how these correlations are mediated. For example, at the level of multiunit micro-electrode recordings, correlations can result from

stimulus locked transients, evoked by a common afferent input, or reflect stimulus-induced oscillations; phasic coupling of neural assemblies, mediated by synaptic connections. Effective connectivity is closer to the notion of a connection and can be defined as the influence one neural system exerts over another, either at a synaptic (c.f. synaptic efficacy) or cortical level. Although functional and effective connectivity can be invoked at a conceptual level in both neuroimaging and electrophysiology they differ fundamentally at a practical level.

Two types of connectivity between brain regions, first is functional connectivity measures a correlation between activity in spatially separate neural regions and cannot directly establish causality and then it does not require anatomical model, to measure the interaction between brain regions we need the second which is the effective connectivity that measures influence of one neural system on another, allows testing of causal hypotheses and requires an anatomical model.

The Functional connectivity is the temporal correlation between spatially remote neurophysiological events. One of the methods used for analyzing the functional connectivity is Seed-voxel correlation analyses that depends on the selection of the seed voxel derived from the activation maps. Hence, as the activation detection is based on the similarity between the observed BOLD signal in a voxel and an expected haemodynamic curve. The correlation connectivity analysis is close to an activation mapping but this method is limited because the choice of seed-voxel is random which can be affected by some noise effects. For that there are other methods to analyze effectively such as Principal Components Analysis (PCA), Singular Value Decomposition (SVD), Partial Least Squares (PLS) or Independent Component Analysis (ICA).

All of methodologies used to analyze the functional connectivity can not be used to model the interactions between events of brain regions. Other statistical methods, such as the structural equation modeling (SEM), are more attractive to overcome this shortcoming. Buchel and Friston [4] modeled the occipitoparieto frontal network involved in attention tasks using SEM. Zhuang et al. [7] applied SEM to a bimanual motor coordination experiment. Rowe et al. [8] modeled the prefrontal cortex in a color selection task. SEM is limited that it is valid for static model as also Psychophysiological Interactions, PPI.

One of the best model used to infer not only the interaction but also the causality is dynamic causal model (DCM), proposed by Friston et al. [9]. However, these models approaches require a complete pre specification of the connectivity structure. Additionally, as DCM is estimated via Bayesian algorithms, it also requires the prior densities of the parameters of interest.

Modeling interactions among neuronal populations at a cortical level uses neuroimaging hemodynamic or electromagnetic time series. It presents the motivation and procedures for DCM of evoked brain responses. The aim of this modeling is to estimate, and make inferences about, the coupling among brain areas and how that coupling is influenced by changes in experimental context. . Friston, Harrison and W. Penny [10] applied DCM which represents a fundamental departure from existing approaches to effective connectivity because it employs a more plausible generative model of measured brain responses that embraces their nonlinear and dynamic nature. The basic idea is to construct a reasonably realistic neuronal model of interacting cortical regions. This model is then supplemented with a forward model of how neuronal or synaptic activity is transformed into a measured response. This enables the parameters of the neuronal model to be estimated from observed data

2. Methods

The Interaction between Brain regions effectively modeled by DCM, is accomplished by using a dynamic input–state– output model with multiple inputs and outputs. The inputs correspond to conventional stimulus functions that encode experimental manipulations. The state variables cover both the neuronal activities and other neurophysiological or biophysical variables needed to form the outputs.

2.1. Model Theory

DCM is used to test the specific hypothesis that motivated the experimental design. It is not an exploratory technique; as with all analyses of effective connectivity the results are specific to the tasks and stimuli employed during the experiment. In DCM designed inputs can produce responses in one of two ways. Inputs can elicit changes in the state variables (i.e., neuronal activity) directly. For example, sensory input could be modeled as causing direct responses in primary visual or auditory areas, Fig. 1 illustrates this schematically [10]. The important implication here for experimental design in DCM is that it should be multifactorial, with at least one factor controlling sensory perturbation and another factor manipulating the context in which the sensory- evoked responses are promulgated throughout the system (cf., psychophysiological interaction studies; Friston et al., 1997) [7]. In particular it highlights the two distinct ways in which inputs or perturbations can elicit responses in the regions or nodes that compose the model. In this example there are five nodes, including visual areas V1 and V4 in the fusiform gyrus and the superior temporal gyrus STG. Stimulus-bound perturbations designated u_1 act as extrinsic inputs to the primary visual area V1. Stimulus-free or contextual inputs u_2 mediate their effects by modulating the coupling between V4 and BA39 and between BA37 and V4. For example, the responses in the angular gyrus (BA39) are caused by inputs to V1 that are transformed by V4, where the influences exerted by V4 are sensitive to the second input. The dark square boxes represent the components of the DCM that transform the state variables z_i in each region (neuronal activity) into a measured (hemodynamic) response y_i. Experimental factors as inputs that belong to the class that produces evoked responses or to the class of contextual factors that induces changes in coupling.

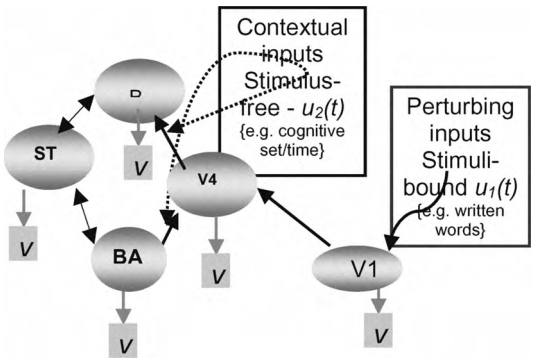


Fig.1. A schematic illustrating the concepts underlying dynamic causal modeling (DCM)

The first class comprises trial- or stimulus-bound perturbations whereas the second establishes a context in which effects of the first sort evoke responses. This second class is typically trial-free and established by task instructions or other contextual changes. Measured responses in high-order cortical areas are mediated by interactions among brain areas elicited by trial bound perturbations. These interactions can be modulated by other set-related or contextual factors that modulate the latent or intrinsic coupling among areas. The dynamic causal model here is a multiple-input multiple- output system that comprises m inputs and l outputs with one output per region. The m inputs correspond to designed causes (e.g., boxcar or stick stimulus functions). The inputs are exactly the same as those used to form design matrices in conventional analyses of fMRI and can be expanded in the usual way when necessary (e.g., using polynomials or temporal basis functions).[10] In principle, each input could have direct access to every region. However, in practice the extrinsic effects of inputs are usually restricted to a single input region.

2.2. Hemodynamic Priors

Before specifying model based on DCM it is necessary to model the entire hemodynamic response of each of l region which produces a measured output that corresponds to the observed BOLD signal stated as in figure 2. Equations has been described by Buxton et al. [14], five hemodynamic parameters important for model fitting, but of no interest for statistical inference. These parameters are required to compute the observed BOLD response and are not influenced by the states of other regions. Central to the estimation of effective connectivity or coupling parameters are the first state variables of each region. Each region has five state variables.

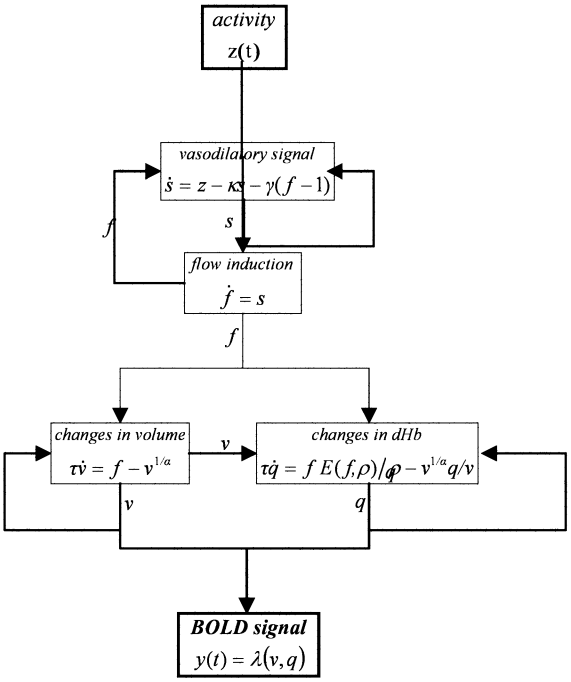


Fig 2. Schematic shows the architecture of the hemodynamic model

Schematic of figure 2 shows the architecture of the hemodynamic model for a single region, neuronal activity induces a vasodilatory and activity-dependent signal s that increases the flow f. Flow causes changes in volume and deoxyhemoglobin (v and q) [10]. These two hemodynamic states enter the output nonlinearity Eq. (4) to give the observed BOLD response y. This transformation from neuronal states z_i to hemodynamic response v_i is encoded graphically [13] briefly for 1 region neural activity z_i causes an increase in vasodilatory s_i that is subject to regulatory feedback.

$$\dot{s} = z - \kappa s - \gamma(f-1)$$

$$\dot{f} = s\,,\ \tau\dot{v} = f - v^{1/\alpha}$$

$$\tau\dot{q} = f\,E(f,\rho)/\rho - v^{1/\alpha}q/v \qquad (1)$$

Inflow f_i responds in proportion to vasodilatory signal with changes in blood volume v_I and deoxyhemoglobin content q_i, Outflow is related to volume $f_{out} = v^{1/\alpha}$ through Grubb's exponent α [15]. The oxygen extraction is a function of flow,

$$E(f,\rho) = 1-(1-\rho)^{1/f} \qquad (2)$$

Where ρ is resting oxygen extraction fraction The BOLD signal is taken to be a static nonlinear function of volume and deoxyhemoglobin that comprises a volume-weighted sum of extra- and intravascular signals

$$y_i = \lambda(v_i, q_i)$$

$$y_i = V_o(\rho_i(9 - 7q_i - 2v_i) - 2\frac{q_i}{v_i} + 0.2v_i + 1.8) \qquad (3)$$

Where Vo = 0.02 is resting blood volume fraction, for above equations is related to BOLD FMRI [10]. The second step in the following section is to implement based on DCM and SPM (Statistical Parametric Mapping, software package for

analyzing, inferring, model designing and reviewing FMRI time series) and states first the statistical priors to be added with hemodynamic priors to construct over all model and estimating it with Expectation Maximization, EM, Algorithm.

2.3. Implementation

DCM is used effectively due to the limitations of other methodologies such as, PPI and SEM to interpret the causality. DCM treats the brain as a deterministic nonlinear dynamic system that is subject to inputs and produces outputs. Effective connectivity is parameterized in terms of coupling among unobserved brain states (e.g. neuronal activity in different regions). The objective is to estimate these parameters by perturbing the system and measuring the response.

2.3.1. Characterizing Neural Model

Brain regions [16] which we used to specify the interaction and connectivity between them are primary visual cortex, V1 is anatomically equivalent to Brodmann area. Visual area V5, also known as visual area MT (middle temporal), is a region of extrastriate visual cortex that is thought to play a major role in the perception of motion, the integration of local motion signals into global percepts and the guidance of some eye movements. 4-Phenyl-4-(1-piperidinyl)-cyclohexanol, PPC, is an organic chemical which is often found as a metabolite of phencyclidine, the dorsolateral prefrontal cortex, DL-PFC or DLPFC, consists of the lateral portions of Brodmann areas and is connected to the orbitofrontal cortex. Its function is responsible for motor planning, organization, and regulation.

In this paper we design or specify, estimate and review model for interactions between V1, V5, PPC and PFC under external events based on DCM implemented by SPM. There are the direct or extrinsic influence of inputs on brain states in any particular area and the intrinsic or latent connections that couple responses in one area to the state of others, also changes in this intrinsic coupling induced by inputs. Although, in some instances, the relative strengths of intrinsic connections may be of interest, most analyses of DCMs focus on the changes in connectivity embodied in the bilinear parameters. The first set of parameters is generally of little interest in the context of DCM but is the primary focus in classical analyses of regionally specific effects.

Consider a linear DCM where we observe the states directly and there is only one state variable per region[10]. State the equation of DCM,

$$\begin{aligned} \dot{z} &= F(z,u,\theta) \\ \dot{z} &= (A+\sum u_j B^j)z + Cu \\ A &= \frac{\partial F}{\partial z} = \frac{\partial \dot{z}}{\partial z}, B^j = \frac{\partial^2 F}{\partial z \partial u_j} = \frac{\partial}{\partial u_j}\frac{\partial \dot{z}}{\partial z} \\ C &= \frac{\partial F}{\partial u} = \frac{\partial \dot{z}}{\partial u} \end{aligned} \tag{4}$$

where A is connectivity matrix, Jacobian, represents the first order connectivity or interaction without inputs among the regions. Effective connectivity is the influence that one neuronal system exerts over another in terms of inducing a response A where it is intrinsic coupling. Latent connectivity, in the absence of experimental perturbations. B^j is reperesenting the change in coupling or interaction between regions according to the j inputs, B^j. Induced connectivity, represent the entire coupling changed over A in the present of inputs j. finally C is the representation of extrinsic coupling or over the regions due to inputs j. Model parameters is A, B^j, C, in the form $\theta^c = \{A, B^j, C\}$ called the connectivity matrices. Now there are two types of parameters, hemodynamic θ^h and neural θ^c

2.3.2. Estimation neural and Hemodynamic models

The over all parameters $\theta = \{\theta^h + \theta^c\}$, two models integrated and made quite expedient by capitalizing on the sparsity of stimulus functions commonly employed in fMRI designs[17]. The modeled neuronal dynamics (z) is transformed into area-specific BOLD signals (y) by a hemodynamic forward model

$$\begin{aligned} y &= \lambda(x) \\ \dot{x} &= f(x,u,\theta) \\ x &= \{z,s,f,v,q\} \end{aligned} \tag{5}$$

The forward model can be made into an observation model by adding error and confounding or nuisance effects
The following approach is described by Friston [17]

$$y = h(u,\theta) + X\beta + \varepsilon \tag{6}$$

An approximation for the first term in the equation $h(u,\theta)$ to $J\Delta\theta, \Delta\theta = \theta - \eta_{\theta|y}$ and $J = \partial h(u,\eta_{\theta\{y}) / \partial\theta$. For the hemodynamic prior parameters θ^h, $\{\kappa,\gamma,\tau,\alpha,\rho\}$, estimates by prior mean η_θ and variance C_θ in [10] to be 0.65 per second, 0.015 for κ, 0.41per second, 0.002 for γ, 0.98 s, 0.0568 for τ, 0.32, 0.0015 for α and 0.34, 0.0024 for ρ

To complete parameters estimations for the neural model we used iterative EM scheme [17] and [10] to estimate conditional expectation $\eta_{\theta|y}$ and covariance $C_{\theta|y}$ of the parameters, assuming confound X (t) [10] to be low order discrete cosine set to model the low frequency drift and a constant term., by Bayes' theorem applied with EM get posterior probability, prediction, of θ parameters based on y. Bayesian parameter estimation under Gaussian assumptions is done by means of EM and gradient ascent. in two steps, E-step is compute, the conditional mean $\eta_{\theta|y}$, expansion point of gradient ascent and the conditional covariance $C_{\theta|y}$ the object function derived from above equations [10-17] F, it is iterative function for each parameter, iteration of F function until convergence.

$$\begin{aligned} F = \frac{1}{2}(-(y-h(\theta))^T C_e^{-1}(y-h(\theta)) - (\theta_{\theta|y} - \theta_p)^T \times \\ C_p^{-1}(\theta_{\theta|y} - \theta_p) - \log|C_e| - \log|C_p| + \log|C_{\theta|y}|) \end{aligned} \tag{7}$$

While M-step is for Estimation of hyperparameters λ_i for error of covariance components Q_i and the covariance component $C_i = \sum \lambda_i Q_i$.

3. Results and Discussion

As mentioned that interaction between brain region applied in four brain regions V1, driven by any kind of visual stimulation (direct input "photic"), V5 explained through an increase in the influence of V1 $\rightarrow$ V5 whenever the stimuli are moving (modulation by "motion") and PFC $\rightarrow$ PPC and PPC $\rightarrow$ V5 is enhanced by attention.

The designs and Datasets made under three inputs visual, photic, motion and attention is implemented using Statistical Parametric Mapping Software package SPM5 (www.fil.ion.ucl.ac.uk/spm/software/spm5/). Modulating three inputs as shown in figure 3, each input has specific effect to change the entire interactions between regions. Models are constructed after considering both neural and hemodynamic responses. Each of these models has its specific parameters. The observational model is the combination and integration model of these two models after adding confound with its assumptions. Parameters of hemodynamic model is estimated as a priors by mean and variance and other parameters of neural model estimated by EM algorithm which is one of the best algorithm of biological incomplete data. Figure 4 states that outputs or prediction of each region, V1, V5, PPC and PFC. Prediction or outputs varies according to the inputs and what presets of the model.

Each region in the visual system affects and interacts with the others and may be the connection between them be effective according to the stimulus or the interaction. V1 is affected by Visual stimulus or photic, also motion affects the interaction between V1 and and V5 while attention affect the interactions between PFC $\rightarrow$ PPC and PPC $\rightarrow$ V5 as shown in figure 5, also show the A matrix, intrinsic connectivity, the diagonal is means no interaction PPC $\rightarrow$ V5 connection value 0.1007, PFC $\rightarrow$ V1 connection value 0.5563 and both V1 and V5 is affected by each other one is strong value 0.9213 and other 0.1269. The effective connectivity B^j between regions due to the external inputs is shown in figure 6, (a) due attention input and (b) show the effect of photic only external to V1 value of the connection is 0.2316.

The response due to the first order kernel as shown in figure 7 for all four regions V1, V5, PPC and PFC, photic, visual input affects more on V1 for both neural and hemodynamic for this region whereas PFC the lowest one affected by photic.

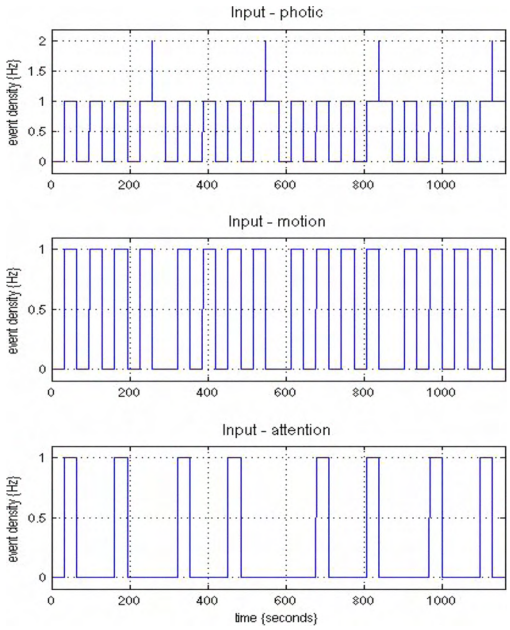


Fig. 3. Three inputs U_i, visual (photic), motion and attention represented by event

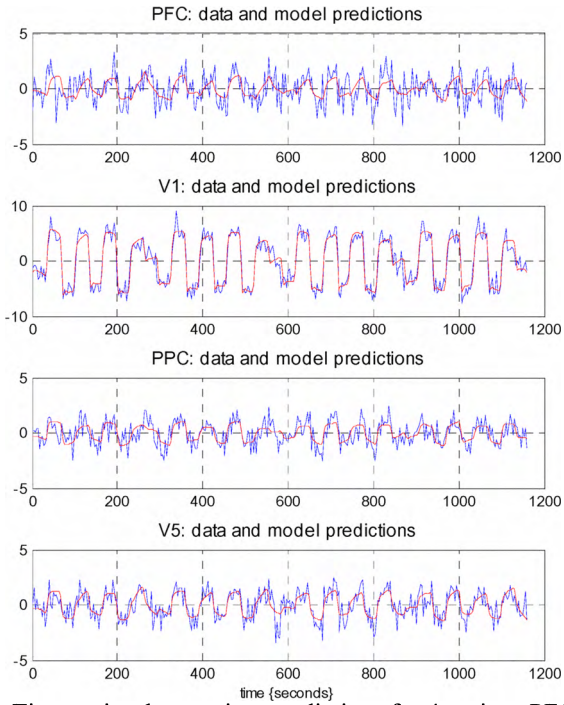


Fig.4. Time series data against predictions for 4 regions PFC, V1, PPC and V5.

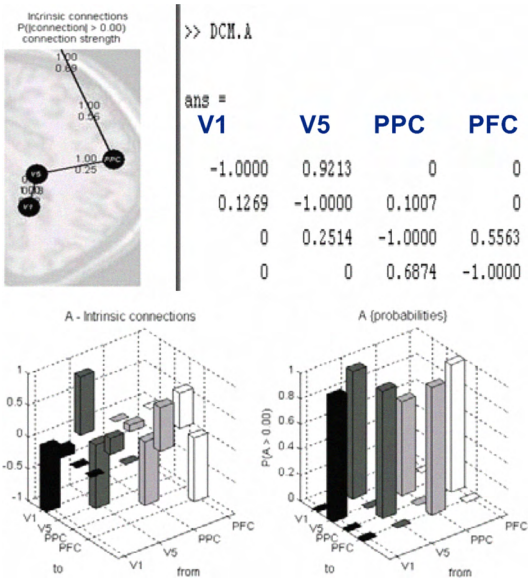
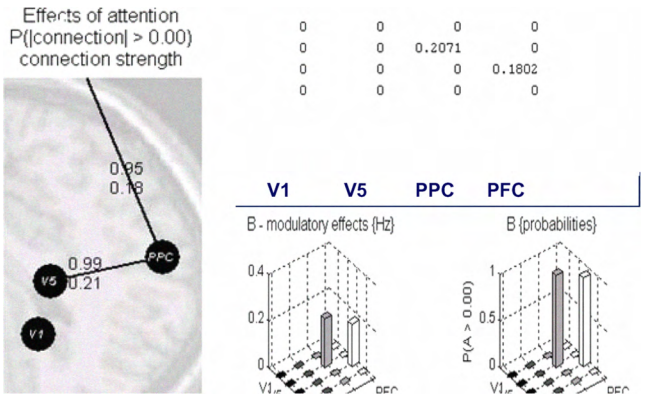
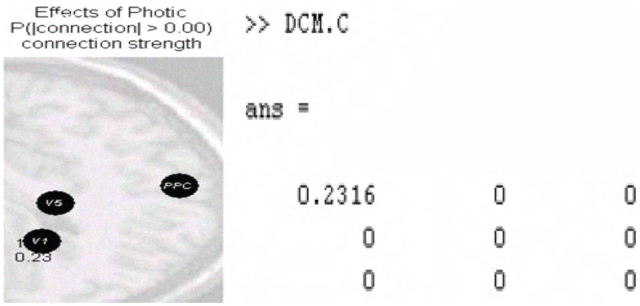


Fig. 5. Intrinsic connection or interaction between region V1, V5, PPC and PFC



(a)



(b)

Fig. 6. The effect of inputs on the response of the brain regions, (a) is the effect of attention over all four region B^j (b) is the effect of photic showing that it is only affect V1

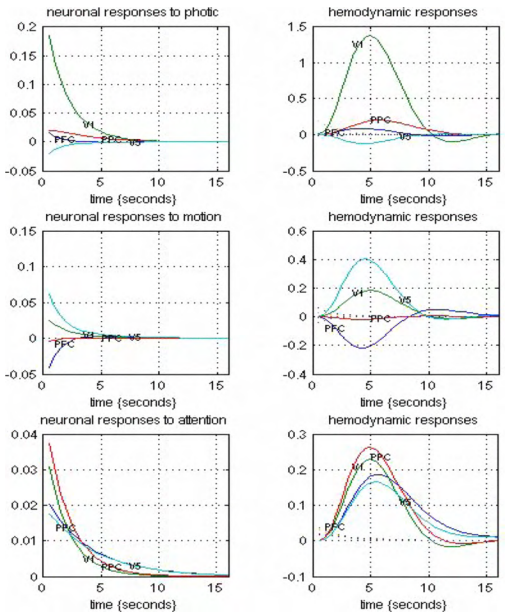


Fig 7. Response of each region (neural and hemodynamic) by all three external inputs.

4. Conclusions

We develop for this model design, estimate and review for the analysis of effective connectivity and see the interaction between Brain region and selecting the four regions related to the visual system V, V5, PPC and PFC using experimentally designed inputs and brain responses. In this context, parameters correspond to effective connectivity and, in particular, parameters reflect the changes in connectivity induced by inputs. However, unlike all previous approaches to connectivity in neuroimaging, the DCM describes responses to designed deterministic inputs, as opposed to treating inputs as unknown and stochastic.

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