Fusing EEG and fMRI based on a bottom-up model: inferring activation and effective connectivity in neural masses

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The elucidation of the complex machinery used by the human brain to segregate and integrate information while performing high cognitive functions is a subject of imminent future consequences. The most significant contributions to date in this field, known as cognitive neuroscience, have been achieved by using innovative neuroimaging techniques, such as electroencephalogram (EEG) and functional magnetic resonance imaging (fMRI), which measure variations in both the time and the space of some interpretable physical magnitudes. Extraordinary maps of cerebral activation involving function-restricted brain areas, as well as graphs of the functional connectivity between them, have been obtained from EEG and fMRI data by solving some spatio-temporal inverse problems, which constitutes a top-down approach. However, in many cases, a natural bridge between these maps/graphs and the causal physiological processes is lacking, leading to some misunderstandings in their interpretation. Recent advances in the comprehension of the underlying physiological mechanisms associated with different cerebral scales have provided researchers with an excellent scenario to develop sophisticated biophysical models that permit an integration of these neuroimage modalities, which must share a common aetiology. This paper proposes a bottom-up approach, involving physiological parameters in a specific mesoscopic dynamic equations system. Further observation equations encapsulating the relationship between the mesostates and the EEG/fMRI data are obtained on the basis of the physical foundations of these techniques. A methodology for the estimation of parameters from fused EEG/fMRI data is also presented. In this context, the concepts of activation and effective connectivity are carefully revised. This new approach permits us to examine and discuss some future prospects for the integration of multimodal neuroimages.

Keywords: bottom-up models; EEG and fMRI data fusion; motor coordination; autoregressive models; dynamic systems

1. INTRODUCTION

Understanding how the brain operates while performing cognitive functions is a matter of remarkable importance that has been the focus of attention of many neuroscience researchers for a number of years. In spite of substantial advances, researchers have yet to establish whether some of the functional specializations during higher-level processing (i.e. motor coordination, language, perception, attention, etc.) are confined to well-delimited regions, or if they simply originate from neuronal masses interacting with diffuse spatial bounds (see Fuster 2000 for a very controversial discussion of modularity). What is more, it is still unclear whether the cognitive events emerge within neuronal masses as: (i) sequential episodes that include feed forward/back aspects of interactions or (ii) concomitant global modes of activations. Hence, it is

of utmost importance in the cognitive neurosciences (Gazzaniga 2000) to determine both the *segregation* (the functional isolated modules) and the *integration* (their interrelationships) of brain functions in a general context of causal dynamic systems (see Horwitz 2003; Lee *et al.* 2003 for revisions of the state of the art). The recognized role that oscillations and synchronicity at the level of neuronal spiking play in cooperating and competing neuronal populations has brought into reflection the relationship that these theoretical concepts hold with basic cellular physiology.

The use of satisfactory psychophysiological paradigms has allowed the separation of a particular function into multiple single components that can be strictly localized in time and space. In the last few years, researchers working on theoretical issues of neuroscience have centred their attention on studying not only ‘where’ these components are generated inside the brain (i.e. ‘activation’ maps) but also ‘what’ natural influences they exert on each other while the original function is carried out (i.e. ‘effective connectivity’ maps). In humans, investigations about this issue have been possible by using non-invasive functional

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neuroimaging techniques, such as electroencephalogram (EEG) and functional magnetic resonance imaging (fMRI). The introduction of these techniques has allowed neuroscientists to assess the spatio-temporal variations of certain physical magnitudes inside the brain by simply exploring their external echo/macrosopic reflections, which are inevitably polluted by instrumental errors (Baillet *et al.* 2001; Casey *et al.* 2002). By using EEG and fMRI data together we are able to overcome the limitations that these techniques present in terms of their ability to localize single functional components in time and space, and at the same time, maximize the potential of both (Makeig *et al.* 2002). This is the main motivation for developing concurrent EEG and fMRI data recording systems (Goldman *et al.* 2000; Salek-Haddadi *et al.* 2003).

However, even at present, these techniques are being used independently to explore some aspects of both activations and effective connectivity maps during particular experimental paradigms (see Carew *et al.* 2003; Friston *et al.* 2003; Marrelec *et al.* 2003; Galka *et al.* 2004; Miwakeichi *et al.* 2004; Penny *et al.* 2004; Trujillo-Barreto *et al.* 2004; Yamashita *et al.* 2004). There have been few attempts to develop methods that make use of the complementary potentialities of EEG and fMRI data that have recently emerged (Dale *et al.* 2000; Kruggel *et al.* 2001; Goldman *et al.* 2002; Martinez-Montes *et al.* 2004). In these very impressive contemporary works, sophisticated statistical methods have been introduced to extract as much information as possible from a data-driven strategy (i.e. the authors tend to use what they refer to as a top-down approach). In many cases, the latter interpretation of the results is incomplete and the association with physiological parameters is overlooked completely. Fortunately, modern comprehension of many of the basic physiological mechanisms associated with brain functions (Magistretti & Pellerin 1999; Kim 2003; Leopold *et al.* 2003; Logothetis 2003a; Thompson *et al.* 2003), ranging from the emerging electrical episodes in the neural circuitry to the imminent vascular changes induced mostly by metabolic and oxygen demands, has brought into light a tremendous opportunity to develop sophisticated biophysical models (see also Attwell & Iadecola 2002 for an excellent discussion of the physiological basis of neuroimages). The main motivation of this paper is to create a first-order *bottom-up approach*, establishing a solid bridge between the physiological profiles and the EEG/fMRI data that make posterior interpretations of the results possible. A bottom-up approach satisfies the foremost posture of the participants in a recent series of workshops on 'functional brain connectivity' (i.e. organized in Düsseldorf 2002; Cambridge 2003 and Havana 2004), who strongly recommended that any macroscopic notion of activation and effective connectivity should be based on the underlying neuronal substrate. The physical foundations of EEG and fMRI are exposed below, in order to introduce to the readers the main motivations sustaining our novel model-driven strategy, permitting a natural

establishment of some mesoscopic variables with physiological connotations.

The causal course of events during the execution of brain functions originates at the level of synapses, which constitute the basic ingredient for the crosstalk between neuronal assemblies. The local field potential in the vicinity of certain elemental volumes can be thought of as a magnitude that summarizes a large amount of rapidly varying (in the order of millisecond) processes occurring during synaptic transmissions (i.e. neurotransmitters migrating from the synaptic cleft, the membrane transport phenomena at the neuron-astrocytes juncture, and the electrotonic propagation of postsynaptic potentials, etc.). Although the synapses are very small, the specific geometry and hierarchical organization of neurons in some cerebral structures facilitates the summation of synchronized local field potentials (henceforth this mesoscopic effect will be referred to as 'synaptic activity') additionally contaminated with physiological noise, which creates a significant primary current source that can be observed in remote places owing to the volume conductor properties of the head (Nunez 1981; Niedermeyer & Lopes Da Silva 1999). The EEG represents the voltage differences that these primary current sources produce between lead electrodes situated on the scalp. Unfortunately, the primary current sources yielded in differentiated locations inside the brain are blurred and mixed during the observation process, although the temporal structure of their dynamics is preserved due to the quasi-instantaneous propagation of the ohmic currents (Plonsey & Heppner 1967). In order to obtain a three-dimensional reconstruction of the density of primary current sources extending along the whole cerebral volume from the EEG signals (only recorded by a few sensors), an inverse problem must be solved. This problem has presented imaging engineers with a mammoth task that has occupied much of the last 30 years. The electrophysiological inverse problem, as it is referred to, does not have a unique solution (i.e. it is ill-posed, see Riera *et al.* 1998 for a theoretical viewpoint); hence, additional information must be used to constrain the possible meaningless solutions. Even now, there are intense debates about the competence of most of the methods proposed in the literature to solve the problem, a fact that has recently resulted in a lack of motivation among researchers using EEG data to localize functional components in the space. Even so, its high temporal resolution, low production cost and simplicity of use in experimental manipulations explain why the EEG has continued to be one of the most attractive techniques.

On the contrary, in the last few years, the use of suitable experimental manipulations with the fMRI technique has re-established a high level of enthusiasm among imagers, and a large amount of studies reporting on the accurate spatial localization of functional components have been published. The fMRI technique permits the direct observation of the blood oxygenation level dependent (BOLD) signal inside the brain with a very high spatial resolution, but is deficient in its definition of time ($\sim$ s). The BOLD signal tracks the temporal evolution of a nonlinear competitive balance between the cerebral blood volume (CBV)

and the content of deoxy haemoglobin (dHb) (Buxton *et al.* 1998), both defined in an element of physical volume that mainly comprises post-capillary venous compartments. In the haemodynamic approach (Friston *et al.* 2000), dynamic changes in these two intrinsic physiological magnitudes are governed by an increase or decrease in the cerebral blood flow. A mesoscopic variable, henceforth referred to as *haemodynamics*, will be used to summarize these physical phenomena at the vascular level, which also contain physiological noise. Although the mechanisms for brain vascular control are yet to be completely understood, it is at present accepted that the local regulator role being played by nitric oxide release is closely coupled with synaptic activity during cerebral blood flow variations. In the last few years, motivated by the discovery that cholinergic axons from the basal forebrain may be connected to certain perivascular structures (i.e. smooth muscle bands or plastic strips at the arterioles and the pericytes-sphincter-like depressions at the pre-capillary branching points), it has been conjectured that a more global vascular controlling system of electrical origin may coexist (Attwell & Iadecola 2002; Harrison *et al.* 2002). The interrelationship between the synaptic activity and the cerebral blood flow has been modelled locally and linearly in the haemodynamic approach by introducing a flow-inducing signal (maybe related to the nitric oxide release). In an EEG/fMRI fusion model, the linear assumption at the electro-vascular interface oversimplifies the local antagonist effect between excitatory and inhibitory postsynaptic potentials.

In this paper, a two-dimensional autoregressive model with exogenous variables (ARx) is introduced to describe both the self-dynamics of the ‘mesoscopic’ variables (i.e. synaptic activity and haemodynamics) and their interrelationships. A static nonlinear function is proposed to describe the electro-vascular coupling through a flow-inducing signal. The mesostates in the elemental volumes, containing a bunch of synapses and vascular networks, relate to EEG and fMRI data by means of ‘macroscopic’ observation equations, also formulated. There are recent findings (Harrison *et al.* 2002; Logothetis 2003b) that give us confidence to hypothesize that the number of synapses highly correlate with the density of capillary beds in the cortex. This quasi-linear states model, put forward to account for the evolution of the electrophysiological and haemodynamic states, takes advantage of the EEG data to search for the temporal location and causal order of single functional components, while the fMRI data is utilized in a common strategy to achieve accurate spatial localizations. In the case of fMRI data, causal relationships between events are occluded inside BOLD because haemodynamic changes occur in a very slow temporal scale as a consequence of the pronounced low-pass filter of the vasomotor system. In the EEG data, spatial configurations of events are not distinguishable owing to the spreading effect produced by the volume conductor. However, both observation types share a common aetiology at the physiological level, which is a central premise in this paper. In addition, the simultaneous use of EEG and fMRI recordings allows us to obtain data in the same

experimental conditions, and more importantly, enables us to develop a common model for the physiological noise. The least-square estimators of the mesostates and observational model parameters are presented in Appendix A.

The mesostates can be defined at different levels of the brain architecture; hence, the dimensionality of the ensuing identification problem depends on which physical scale is chosen to separate the individual components in time and space. The physical dimensions of the system can be extremely dissimilar, ranging from being a colossal problem when trying to identify voxel-wise dynamics, to a simpler problem when assuming a structure-wise organization (i.e. using *a priori* a model for the activation and effective connectivity maps on a set of macroscopic structures defined by standard brain atlases). Fortunately, the introduction in neuroscience of imaging techniques such as the anatomical MRI and the very new diffusion tensor imaging (a revision and discussions about the possible future implications can be found in this issue; Behrens & Johansen-Berg 2005) has enriched the pool of accessible information about the structural design and organization of cerebral tissues. The use of these techniques has made the segmentation of different brain structures possible, as well as the characterization of the natural fibre tracks that physically bond them, without emphasizing the directionality of neuronal activity propagation (in this issue Parker & Alexander 2005 used the ‘persistent angular structure’ method to determine, in practicable terms, the probabilistic density function of the fibres orientation). Recently, three-dimensional ‘brain atlases’ are being widely used as common standards in neuroscience research, in which precise statistical information about the variability of anatomical structures (Mazziotta *et al.* 2001) is incorporated, along with grey matter connection graphs (Wakana *et al.* 2004). In this paper, regions of interest (ROI) with a structure-wise demarcation are introduced in the context of the structural probabilistic atlas developed at the McConnell Brain Imaging Centre, Montreal Neurological Institute, Montreal. Analysing only those structures involved during a task performance considerably reduces the dimensionality of the time-space identification problem in this case. Additionally, information about relevant nerve fibre tracks is used *a priori* to sidestep the estimation of the effective connectivity between brain structures physically disconnected (obtained from ‘The Fiber Tract-Based Atlas’, Research Center at Kennedy Krieger Institute, Johns Hopkins University Medical School, Baltimore).

Nevertheless, while trying to fuse EEG and fMRI data, a project of extreme computational complexity, several practical difficulties will inevitably present themselves. The most significant are: (i) in order to use multimodal data in a unified scenery, the co-registration concern remains a challenge in spite of the current technical advances; and (ii) large electrical field distortions inside a conductor will be produced by either a strong static magnetic field or a low radio-frequency perturbation. In this paper, the positions of electrodes and a few external landmarks were determined by using a three-dimensional positions-indicator system (Isotrack II, Polhemus Product).

Figure 1. The experimental paradigm consists of 12 subsequent task-blocks. In a task-block, the stimuli lasted for 40 s, preceded by 30 s of resting condition. The subject was asked to perform either right- (checkerboard) or left-hand (tones) finger tapping synchronized with flickering cues (at a frequency of 2 Hz). The order of the stimuli mode was randomly distributed to avoid subject expectation during decision-making about which hand was to be used.

The co-registration between the electrodes and the individual anatomical MRI, normalized to the Talairach coordinate system, was performed using affine transformations. An isotropic and piecewise homogeneous volume conductor model of the head was assumed, which included three compartments (i.e. the brain, the skull and the scalp). The surfaces limiting the compartments were tessellated using a simplified version of the method MacDonald (1997) employed, in which a triangulated sphere is deformed towards the target object. The electric lead field (ELF) was numerically calculated using a vector boundary elements method (BEM), which permitted a realistic description of the properties of the volume conductor (Riera & Fuentes 1998). Furthermore, the pulse artefacts (owing to the ballistocardiogram) were detected using a method available in the literature (Ellingson *et al.* 2004). In this paper, however, a novel method based on a wavelet-based strategy and an equivalent dipole model is proposed to account for both local blood-pulse transients and global effects on the EEG data induced by the ballistocardiogram, respectively. The scanner artefacts were removed using the methods provided by the BRAIN VISION ANALYSER software. The whole methodology was applied to EEG and fMRI data obtained simultaneously in a block-design experimental paradigm while a subject carried out a motor coordination task triggered by visual and auditory cues.

2. METHODS

(a) Experiment

A right-handed, normal volunteer (a 38 year old male) was used in the experiment. The subject was asked to perform a block design motor task consisting of synchronized finger tapping when indicated by cues flashing at a frequency of

2 Hz (lasting for 200 ms). A visual cue (a checkerboard) indicated that the subject should execute the task with the right-hand, while an auditory cue (tones) indicated left-hand tapping. In each task-block, the task lasted for 40 s, preceded by 30 s of resting condition indicated by a cross shown at the centre of the screen. The stimulus modality (either the checkerboard or tones) for each task-block appeared in a random sequence. The whole experiment consisted of 12 task-blocks (see figure 1).

A 1.5 T scanner (Vision, Siemens, Erlangen, Germany) was used in this study. Comfortable foam padding around the posterior area of the head and ear fixation blocks were used to minimize head movement. The following parameters were used during fMRI data acquisition. The inter-scan interval was 1 s. Each volume consisted of eight slices from the top to bottom of the head, with a voxel size of 3×3 mm in plane, of 10 mm slice thickness and with a 5 mm gap covering the whole brain. T2-weighted, gradient-echo, echo-planar imaging sequences (TE=60 ms, flip angle (FA)=90 degrees) were used. The anatomical reference was obtained with a spoiled gradient-echo sequence (recovery time=9.7 ms, echo time TE=4 ms, FA=12 degrees) consisting of 96 slices, each with a voxel size of $1.25 \times 0.9 \times 1.92$ mm.

The BrainAmp MR system was used to record EEG data (sampling interval 200 μ s) concurrently with BOLD signals inside the MRI scanner environment. The parameters of the BrainAmp MR system were as follows: lower cut-off frequency (0.016 Hz), upper cut-off frequency (250 Hz), signal range/resolution (± 16 mV/500 nV), in-phase suppression (>90 dB), input noise (2 μ V pp) and input impedance (10 M Ω). A BUA-64 adapter box was used in addition to an external rechargeable battery. The 10/20 array of electrodes (see figure 2(a), 24 channels of EEG with a common left ear reference) was fixed to the head by means of the BrainCap-MR 64 channel-Melquest with 5 k Ω resistors (see figure 2(b)). An abrasive electrolyte gel (Abralayt 2000) was applied to guarantee electrode impedance below 5 k Ω . The positions of the electrodes were accurately determined after running

Figure 2. (a) The 10/20 system is shown (black circles) as a subset of electrodes in the general 10/10 system. Electrode No. 27 was used to record the EKG signal. A total of six polygraphic channels were used to correct the influence of eye movement on the EEG and to monitor electromyogram signals. The reference electrode was placed on the left ear and the signal from the right ear was also recorded by using the A2 channel. (b) The BrainCap-MR 64 channel-Melquest with 5 k Ω resistors.

Figure 3. The correction of the scan artefacts. (a) A channel of EEG contaminated by artefacts during three scanning intervals. (b) Each interval contains a sequence of an invariant waveform time-locked with the slice acquisition moment. (c) The EEG after artefact correction.

the experiment by using a three-dimensional positions-indicator system (Isotrack II, Polhemus Product).

(b) Data pre-processing

The individual fMRI images were realigned to remove movement-related artefacts, and the slice timing was adjusted to that of the middle slice. The anatomical reference and fMRI images were co-registered and spatially normalized to the Talairach coordinate system using affine transforms with both linear and nonlinear parameters (translations, rotations, zooms and shears). The scanner artefacts in the EEG

recordings, those occurring because of strong changes in the magnetic fields inside the magnetic resonance tomograph, were automatically detected and corrected (Allen *et al.* 2000) using BRAIN VISION ANALYSER V1.04 software (see figure 3(a,c)). The start of the scanning, detected by applying the gradient method, was used as a reference point or mark for setting a proper timing for the average of the global scan signal (figure 3(b)). Additionally, baseline correction, down-sampling to 200 Hz, signal recalibration and filters (low-pass and band-rejection) were applied to guarantee correct artefact elimination.

Figure 4. The bottom-up biophysical model for the fusion of EEG and fMRI. The system includes two blocks (green shaded boxes): (a) a fast dynamics linear subsystem (the continuous-line box) emulating the neuron–astrocyte interrelationship at the synaptic interface, with a linearly filtered input ‘the evoked transients e_t^v ’ (i.e. the filter emulates an integrator at the electrophysiological level inside the neurons); and (b) a slow dynamics linear subsystem (the dashed-line box) that mimics haemodynamics at the level of the micro-vascular building block. The connection between the fast and slow subsystems is only in one direction (i.e. synaptic activity creates a metabolic/oxygen demand, and will, therefore, induce an increase of blood flow via vascular regulation mechanisms). The factors χ_k will define the linear filter relating $f_v(\alpha_t^v)$ with the flow-inducing signal. The magnitudes ρ_v and ω_v will determine the strength and sensitivity of the nonlinear effect at the electro-vascular coupling (function $f_v(\cdot)$ on the top). The magnitude α_t^v reflects changes in the synaptic activation, and summarizes many phenomena at the synaptic level. The magnitude β_t^v captures fluctuations in the blood volume v at the post-capillary venous compartment owing to unbalanced inner f_{in} and outer $f_{out}(v)$ blood flows, which could also include a dependency with the concentration of deoxy haemoglobin.

(c) EEG and fMRI fusion model

In this subsection, quasi-linear coupled state equations that describe the evolution of the mesoscopic variables are formulated on the basis of a biophysical model. The unknown mesostates relate to EEG and fMRI data by means of macroscopic observation equations.

(i) The coupled state equations

The bottom-up approach includes two different levels of dynamics: the fast synaptic activity at the neuron–astrocytes interface and the slow haemodynamics at the micro-vascular building block (figure 4).

The mesostates α_t^v , associated with the synaptic activity at the v th area (i.e. electrophysiological signalling), satisfy a fast dynamic subsystem (equation (2.1)).

$$\alpha_t^v = \sum_k A_k^v \alpha_{t-k}^v + e_t^v + \zeta_t^v, \quad (2.1)$$

where

$$e_t^v = \sum_{v' \neq v} \sum_k \Phi_k^{vv'} \alpha_{t-k}^{v'} + \sum_k \phi_k^v s_{t-k}. \quad (2.2)$$

The magnitudes A_k^v determine the causal relationship for the self-dynamics of the v th area. The random process $\zeta_t^v \sim N(0, \kappa_\alpha^v)$ defines the physiological white noise introduced at the level of synaptic cleft, with variance κ_α^v . The external force e_t^v , representing the evoked transient, is considered to be an exogenous variable to the subsystem (equation (2.2)). The evoked transient is made up of both types of influences, the one coming from supplementary brain areas (i.e. determined through the effective connectivity coefficients $\Phi_k^{vv'}$, for all k -lag $\forall k=1, \dots$) and the excitation originated from afferent pathways, related to the stimulus. Notice that coefficients $\Phi_k^{vv'}$ do not account for nearest-neighbours synaptic activity, but the other extreme, they do describe long-range connections.

The mesostates β_t^v , associated with the haemodynamics at the level of vasculature, satisfy the slow dynamic subsystem (equation (2.3)) with two exogenous variables: (i) the flow-inducing signal η_t^v and (ii) the stimulus sequence s_t (with a physical delay d) being weighted by the factors θ_k^v ; a term introduced to account for any vascular control mechanism which is not synaptically mediated (i.e. cholinergic fibres from the basal forebrain innervating some type of smooth muscles or pericytes; Attwell & Iadecola 2002).

$$\beta_t^v = \sum_k B_k^v \beta_{t-k}^v + \eta_t^v + \sum_k \theta_k^v s_{t-k-d} + \zeta_t^v, \quad (2.3)$$

where

$$\eta_t^v = \sum_k \chi_k f_v(\alpha_{t-k}^v). \quad (2.4)$$

The random process $\zeta_t^v \sim N(0, \kappa_\beta^v)$ defines the physiological white noise at the vascular level, with variance κ_β^v . The parameters B_k^v will determine the haemodynamics response function and the auto-correlation function for the vascular subsystem (Riera *et al.* 2004). The synaptic activity α_t^v is thought to be a trigger that induces variations in the flow-inducing signal η_t^v , where the vasculature acts as a low-pass filter χ_k (equation (2.4)). The static–nonlinear function $f_v(\cdot)$, relating the synaptic activity and the flow-inducing signal, is still enigmatic and the challenge to define it could motivate joint works between physiologists and theoreticians. It is the belief of the authors that both excitatory and inhibitory postsynaptic activities must induce a comparable increase of metabolic/oxygen consumption; hence, in our paper, this function is assumed to be both symmetric and positive $f_v(\alpha) = \rho_v(1 - \exp(-\alpha^2/\omega_v))$. The magnitude ρ_v is directly related to an area-dependent scaling factor for the global synaptic activity while generating the haemodynamic response; consequently, it permits us to deal with the

Figure 5. The area (red sphere) in the postcentral gyrus in the left hemisphere. The centre of the area (which corresponds to the position of the equivalent dipole) coincides with the voxel with maximum value of the t -test. The extension of the area is also determined from the t -test. The green arrow indicates the normalized orientation of the dipole (estimated from data). Real values were used for this illustration.

dissimilarities in the physical dimension between the EEG and fMRI data. The magnitude ω_v could be mainly associated with the susceptibility of the flow-inducing signal to fluctuations of α_t^v . The sensibility of the v th area to the stimulus sequence s_t is summarized by the parameters ϕ_k^v and θ_k^v , whose spatial distributions are comparable to the θ -MAP previously presented by Riera *et al.* (2004) to describe the activation of the primary brain areas in fMRI studies.

(ii) Observation equations

By intuition, the magnitudes α_t^v and β_t^v are directly proportional to the amplitudes of the postsynaptic potentials (thus, to the primary current source) and of the vascular changes (thus, to the rate of CBV/dHb), respectively; a mesoscopic effect originating within certain ROI (henceforth referred as the v th area). These areas are assumed to be artificial spheres. It is assumed that each constituent structure in the probabilistic atlas of the McConnell Brain Imaging Centre (Montreal Neurological Institute, Montreal) encloses a single active area (although the model can be generalized to include multiple areas within a simple structure). The primary current source in each area is represented by a single dipole located at the centre of the sphere. In this paper, these centres, and also the radii of the spheres, were estimated by searching for the maximum and the extension (by the thresholding technique) of the on-off contrasts SPM99 t -test images within the particular structure (figure 5). This construct facilitates the formalization of the mathematical equations that relate the EEG and fMRI observations with the mesostates.

- The EEG observation equation is given by the solution of the forward problem for the particular volume conductor model (i.e. lead field vector $\mathbf{K}_e(\mathbf{r}_v)$), with $\mathbf{m}_v$ being the normalized orientation of the dipole of the v th area and $\mathbf{r}_v$ the location of its centre (equation (2.5)). Both dipole location and its normalized orientation do not depend on

time. The EEG instrumental error is represented by the white noise $\varepsilon_t^e \sim N(0, \sigma_e^2)$. The time-series of voltage differences between the electrode e and a common reference is represented by V_t^e , with $e=1, \dots, N_e$. The number of electrodes and areas are labelled by N_e and N_v respectively

$$V_t^e = \mu_t^e + \sum_{v=1}^{N_v} \mathbf{K}_e(\mathbf{r}_v) \cdot \mathbf{m}_v \alpha_t^v + \varepsilon_t^e \quad (2.5)$$

The magnitude μ_t^e summarizes any nuisance effect on the EEG data (i.e. a global effect of the ballistocardiogram and a temporal DC c^e). A single dipole, with fixed position $\mathbf{r}_0$ and normalized orientation $\mathbf{m}_0$ but time varying strength b_t is used to model the global effect in the ballistocardiogram (equation (2.6)).

$$\mu_t^e = \mathbf{K}_e(\mathbf{r}_0) \cdot \mathbf{m}_0 b_t + c^e \quad (2.6)$$

A time-varying wavelet-based method is used *a posteriori* to remove the remaining nonlinear/non-stationary local blood-pulse transient in the EEG data (Wan *et al.* 2005). The wavelet coefficients are calculated for each pulsation cycle with zero-padding. After some boundary conditions are assumed between subsequent cycles, a virtual time-series of wavelet coefficients can be constructed. An m -dimensional embedding window moved along this time-series allows us to obtain a phase-diagram representation of the cardio-pulsation; hence, fluctuations around stable trajectories can be interpreted as coefficients associated with residual EEG signal. Finally, the EEG data is recovered after applying a filter in the inverse wavelet transformation, reducing the effect of the unforeseen wavelet coefficients.

- The temporal dynamics of the BOLD signal $y_t^{v_i}$ in the voxel v_i , belonging to the v th area, is related to the mesostates β_t^v in that area by equation (2.7), where the MRI instrumental error is defined by $\varepsilon_t^{v_i} \sim N(0, \sigma_v^2)$.

$$y_t^{v_i} = \mu_t^{v_i} + \beta_t^v + \varepsilon_t^{v_i}. \quad (2.7)$$

The nuisance effects on the BOLD signals are included in the model using a voxel-dependent potential drift $\mu_t^{v_i} = \sum_{k=0}^{\hat{\delta}} \gamma_k^{v_i} t^k$, which is represented by a nonlinear polynomial series.

(d) Volume conductor model

The head was considered, in the first approximation, as a series of N mutually nonintersecting compartments ($R_1, R_2, \dots, R_N$), where each successive compartment is enclosed in the other, and the exterior compartment is R_{N+1} (air; see figure 6(a)). The conductivity σ_j for any compartment R_j was assumed constant (note that $\sigma_{N+1}=0$). This type of volume conductor is designated as a piecewise homogenous volume conductor. There is evidence of anisotropic properties in head tissues (Hoeltzell & Dykes 1979); however, in this paper we shall consider only the isotropic case. The static approach for living tissues, which neglect displacement and eddy currents inside the head, was also assumed (Plonsey & Heppner 1967). The surface $S_{j,j+1}$ is the boundary separating the inner and outer compartments R_j and R_{j+1} . The vector $\mathbf{n}_j(\mathbf{r})$ denotes the normal for this surface at the position $\mathbf{r}$. By convention, it was oriented from the inner to the outer compartment. The lead electrodes were co-registered with the anatomical reference by using a linear transformation that matches the positions of a set of four external landmarks (i.e. a red capsule containing nifedipine; Adalat from Bayer) in the anatomical reference system with

Figure 6. (a) A schematic of the isotropic and piecewise homogeneous volume conductor model. In the figure, different parameters of the model are presented ($\mathbf{n}_j(\mathbf{r})$ normal of the surface $S_{j,j+1}$, the conductivity σ_j for compartment R_j). (b) A three-dimensional visualization of the lead electrodes (see yellow spots), after being co-registered with the anatomical reference. The red capsules were used as external landmarks to obtain the linear transformation from the anatomical reference to the Isotrack II system. (c) The triangulated surfaces are overlapped in different three-dimensional views (obtained with a trial version of the MAGIC COMMUNICATOR software 'V2.3.0.7 for Intel X86').

their relative positions in the Isotrack II reference system (see figure 6(b)).

The anatomical reference was used to obtain a three-dimensional parametric representation of those surfaces delimiting the compartments (i.e. inner/outer skull and scalp, see figure 6(c)). The tessellation of each surface was obtained by multiple deformation of a triangulated sphere towards the target object (MacDonald 1997). The number of triangles used for each surface was 1200, obtained from 602 nodes. The positions of the lead electrodes, external landmarks and the descriptors of the surfaces (i.e. triangles vertexes and normal vectors) were transformed to the Talairach coordinate system using the above-mentioned affine transformation obtained from SPM99.

An analytical expression for $\mathbf{K}_e(\mathbf{r})$ is difficult to find directly. However, a procedure exists for obtaining the ELF by using the reciprocity theorem, which is formulated as follows:

- (i) under passive conditions (no primary current source in any compartment R_j) a DC current I_{er} applied to a lead electrode will induce for each compartment R_j an ohmic current density $\mathbf{J}_j(\mathbf{r})$, which can be calculated by solving a second kind of Fredholm integral equation system

(equation (2.8)).

$$4\pi\alpha_j\mathbf{J}_j(\mathbf{r}) = 4\pi\mathbf{J}_\infty(\mathbf{r}) - \sum_{k=1}^N \frac{(\sigma_k - \sigma_{k+1})}{\sigma_k} \oint_{S_{k,k+1}} \nabla' \left(\frac{1}{|\mathbf{r} - \mathbf{r}'|} \right) \times (\mathbf{J}_k(\mathbf{r}') \times \mathbf{n}_k(\mathbf{r}')) d\mathbf{r}'^2, \quad (2.8)$$

with $\alpha_j = 1$ for $\mathbf{J}_j(\mathbf{r}) \in R_j$ and $\alpha_j = (\sigma_j + \sigma_{j+1})/2\sigma_j$ for $\mathbf{J}_j(\mathbf{r}) \in S_{j,j+1}$. The term $\mathbf{J}_\infty(\mathbf{r})$ represents the induced ohmic current density if considering the volume conductor as an infinite and homogeneous medium

$$\mathbf{J}_\infty(\mathbf{r}) = \frac{I_{er}}{4\pi} \left(\frac{(\mathbf{r} - \mathbf{r}_e)}{|\mathbf{r} - \mathbf{r}_e|^3} - \frac{(\mathbf{r} - \mathbf{r}_r)}{|\mathbf{r} - \mathbf{r}_r|^3} \right).$$

The function $\mathbf{J}_\infty(\mathbf{r})$ must be evaluated on the surface $S_{N,N+1}$ avoiding the singularities in the lead electrode

$$\mathbf{J}_\infty(\mathbf{r}) = \mp \frac{I_{er}}{4\pi} \frac{(\mathbf{r} - \mathbf{r}_{r,e})}{|\mathbf{r} - \mathbf{r}_{r,e}|^3} \quad \text{if } \mathbf{r} = \mathbf{r}_{e,r}.$$

- (ii) The reciprocity theorem establishes

$$\mathbf{K}_e(\mathbf{r}) = -\frac{\mathbf{J}_1(\mathbf{r})}{I_{er}\sigma_j}.$$

The ELF can be evaluated numerically by using a BEM (see Riera & Fuentes 1998 for details).

Figure 7. The output of the SPM99 Toolbox (i.e. t -test and design matrix for the experimental paradigm). The panels show the results from contrasting the checkerboard (a) and tones (b) stimulations with the resting condition.

3. RESULTS

(a) Determining active areas (ROI)

A standard SPM99 statistics analysis was performed, contrasting the 'on' condition (for both modalities of stimuli) with the 'off' condition (representing the resting stage). The t -test SPM99 using 'glass images' (maximum intensity projections) is presented in figure 7 for both stimuli. The significant structures are also listed below.

In order to determine the areas involved during the performance of the motor task, the maximum value of the t -test and the extension of the surrounding neighbourhood was found for each structure (i.e. 71 segmented zones) of the probabilistic atlas. A list with the t -test value and the positions of the hotspots for the significant structures is presented in table 1 for both visual (a) and auditory (b) modalities.

(b) Removing ballistocardiogram and DC components from the EEG

The ballistocardiogram was modelled as described in §2. Figure 8(a) shows (i) an EEG channel contaminated with the ballistocardiogram. (ii) The electrocardiogram (EKG) signal was used to automatically identify the latency of the QRS complex¹. The minimum value of the R wave was used to determine the marks. The mark-locked averaged signal for the EEG and the EKG channels is shown on the right. There are significant differences between the waveform of averaged signal in the EKG channel and its corresponding magno-effect in any of the EEG

channels. This illustrates that the physical basis underlying the contamination of EEG data by the ballistocardiogram is more complicated than a simple addition of passive signals synchronized with the heart's pulse. In figure 8(b), two channels (F4 and Cz) with different levels of the ballistocardiogram signal are presented. The original data (red) overlaps with the residual (black) obtained after removing the global effect, simulated in this case by a single dipole (i.e. the model identification procedure included fitting a single dipole and estimating the temporal DC). The least-square estimators of the dipole's parameters ($\mathbf{r}_0, \mathbf{m}_0$) and its time-varying amplitude b_s , as well as the temporal DC c^e are presented in Appendix A (equations (A 5)–(A 7)).

The position and normalized orientation of the equivalent dipole for this experiment were $\mathbf{r}_0 = (-28, -30, -50)$ and $\mathbf{m}_0 = (0.93, -0.05, 0.37)$, respectively. The dipole is localized very close to the main segment of the left internal carotid artery, which could be used to provide future physiological interpretations of the global effect on the EEG data produced by the ballistocardiogram. The DC shifts for these two channels are also shown in figure 8 ($c^{F4} = 44.39$ and $c^{Cz} = -6.03$). However, the ballistocardiogram cannot be modelled only by an equivalent dipole and a temporal DC. There are local blood-pulse transients that seem to be related to nonlinear and/or non-stationary components, which can be eliminated by using the wavelet-based methodology described above. Figure 9a shows a segment of an EEG (channels F4

Table 1. A summary of the results for each structure in both hemispheres of the probabilistic atlas (The columns represent the names of the areas, the maximum values of the *t*-test inside the structures and the Talairach coordinates of the maximum.)

regions	right		left	
	<i>t</i> -test	position	<i>t</i> -test	position
<i>(a) visual</i>				
postcentral gyrus	—	—	18.443 4	−42, −22, 56
lingual gyrus	15.639 8	6, −84, 0	14.813 1	−4, −80, −8
cuneus	15.257 1	4, −92, 14	14.088 9	−4, −98, 10
cerebellum	11.494 1	6, −72, −14	14.143 7	−28, −78, −24
med. occip. temp. gyrus	13.150 6	16, −74, −10	12.482 6	−28, −74, −16
occipital pole	12.234 6	22, −96, 35	11.720 7	−10, −100, 6
superior occip. gyrus	11.753 8	26, −92, 22	10.845 4	−6, −96, 20
lateral occip. temp. gyrus	10.859 9	28, −78, −20	11.260 5	−32, −68, −18
precentral gyrus	—	—	9.097 8	−32, −18, 66
<i>(b) auditory</i>				
postcentral gyrus	17.554	40, −26, 60	—	—
precentral gyrus	10.371 8	36, −18, 48	—	—
cerebellum	5.262 1	32, −70, −38	9.471 5	−12, −50, −22
med. occip. temp. gyrus	4.041 8	14, −68, 10	8.302 8	−20, −52, −12
superior temp. gyrus	8.081 9	54, −14, 4	4.850 1	−48, −28, 12

Figure 8. *(a)* The time-series corresponding with *(i)* an EEG and *(ii)* the EKG channels, with the marks used to average the QRS complex (left side). *(b)* The EEG results after removing the global effect of the ballistocardiogram (i.e. described by a single dipole) and correcting the temporal DC. The DC values can be read on the right. The blue arrow shows the timing of some nonlinear/non-stationary transient that cannot be removed with the global equivalent dipole. One particular transient is distinguished with a blue circle.

Figure 9. (a) Illustration of the EEG data contaminated with nonlinear and/or non-stationary local transients (black curve) and after applying the wavelet-based method (red curve). (b) As an example, a final EEG panel is presented.

and Cz) before and after correcting these transients (for details see the blue circle). The physical origin of these transients is thus not straightforward to understand. The EEG data after removing the global effects and local transients induced by the ballistocardiogram remain typical patterns (figure 9b).

(c) Removing potential drift in the fMRI

The potential drifts of BOLD signals were estimated for all those voxels belonging to areas of the significant structures (see the least-square estimator in Appendix A; equation (A 8)). As an example, the BOLD signals corresponding to the hotspots of the postcentral gyrus in both hemispheres ((a) left hemisphere, (b) right hemisphere) are shown in figure 10. The estimated potential drifts (smooth curves) are overlapped in these panels. The potential drift in fMRI

signal could have a physiological interpretation (see Riera *et al.* 2004). As it should be, there is a very clear correspondence between the time courses of the BOLD signal amplitudes in each hemisphere and the on-off stages of the particular stimulus modality.

(d) Identification of the mesostates and model parameters

The model identification was carried out after selecting the most significant structures involved in the execution of the particular brain function (motor coordination) from table 1. The lingual and superior temporal gyri (in red) were included in the analysis because visual and auditory stimuli were used to indicate to the subject which hand is to be used. The important role played by the cerebellum (in green) in memory-timed finger movements has been

Figure 10. The time-series corresponding to the hotspots of the active areas for the postcentral gyrus. (a) Postcentral gyrus left; (b) postcentral gyrus right. The potential drift (smooth curve) after model fitting is overlapped with the BOLD signal for these particular voxels. The experimental paradigm is presented below the graphs.

demonstrated using fMRI data (Kawashima *et al.* 2000). The postcentral gyrus (in blue) represents the most relevant structure owing to the fact that tapping with fingers requires the recruitment of a large number of neurons in the motor cortex. The subject was not allowed to look at the hands; hence, some sort of sensorial (precentral gyrus, in grey) feedback should be implied during settling on the fingers timing. The three-dimensional illustration of the structures used in the analysis is offered in figure 11(c).

The 24-channel EEG and fMRI data, after being corrected by their specific nuisance effects ($\mu_t^e \rightarrow$ EEG and $\mu_t^v \rightarrow$ fMRI), were used to estimate (equations (A 1)–(A 4)) the mesostates α_t^v and β_t^v (see the results of a single block in figure 11(a); a summary of the symbols is provided in Appendix B). For the particular case of BOLD signals, all voxels within each area were included. The standard deviations of the instrumental errors $\{\sigma_{e_s}, \sigma_{v_s}\}$ were determined from the non-explained EEG/fMRI data. Once the mesostates were calculated, α_t^v was evaluated in the static-nonlinear function $f_v(\cdot)$ (the results are shown in figure 11(b)). The entire time-series corresponding to mesostates α_t^v shows stationary behaviour; hence, its variance was considered as an outstanding gauge of the parameter ω_{vs} mainly associated with the susceptibility of η_t^v to slight variations of α_t^v . In order to compare the amplitude of the synaptic activity in each area, the scaling factors were fixed $\rho_v=1$ for all structures. The flow-inducing signal was evaluated using the Kaiser class filter χ_k with windows

parameter $\alpha < 1$, convolves with a boxcar of around 3 s in length (figure 11(c)). The variations in the flow-inducing signal for each structure do not obey the on-off patterns (the horizontal grey bars) in either the visual and auditory modality. In view of this magnitude being directly related to the local postsynaptic potentials, the convincing results reported previously, using simultaneous observations of fMRI and intracortical recordings of neural signals at a microscopic level in visual cortex of monkeys (Logothetis *et al.* 2001), are quite the opposite to our findings when employing echo/macroscale observations in humans. However, single trials of either visual or auditory stimuli were repeated at a frequency of 2 Hz within a block, which permitted us to take out those events related responses from the synaptic activity (500 ms duration). It is proper to point out that significant signals, time-locked to the stimulus onset, coexist despite prominent physiological noise. Figure 11(b) shows the signals originating from averaging the single trials within a block for both stimulus modalities. These facts could motivate neuroscientists to reconsider the following questions: (i) is the electrophysiological sign (i.e. synaptic activity) an absolute and unique mechanism for triggering vascular changes? and (ii) are EEG and BOLD recordings strongly contaminated versions of more informative signalling inside the brain?

The estimated dipoles normalized orientations for both stimulus modalities, with indeterminate signs, are presented in table 2.

Figure 11. (a) The time-series corresponding to the estimated mesostates dynamics (top panels), the evaluation of the static-nonlinear function $f_v(\cdot)$ on the synaptic activities α_t^v (middle panels), and the flow-inducing signals η_t^v (bottom panels). The horizontal grey bars are used to highlight the task period inside the block. (b) The events-related synaptic activities are emphasized in isolated boxes. The stimulus for a single trial persists for 200 ms (horizontal black bar). The colours used for curves in all the panels are identical to those representing the structures (c).

Table 2. The estimated dipole orientations (normalized) for each stimulus modality

(The lingual gyri in both hemispheres are very close; therefore, an equivalent dipole (centred in the middle) was used. The SPM t -test (auditory modality) shows no significant values for the left superior temporal gyrus; therefore, a dipole was only used for the right superior temporal gyrus.)

regions	normalized dipole orientations	
	visual	auditory
postcentral gyrus	left: $-0.23, -0.92, -0.32$	right: $0.17, 0.94, 0.31$
precentral gyrus	left: $0.34, 0.82, 0.46$	right: $0.69, 0.67, 0.26$
cerebellum (left)	$0.50, 0.50, -0.70$	$0.12, -0.10, -0.99$
lingual gyrus	average: $-0.48, 0.16, -0.86$	—
superior temp. gyrus	—	right: $-0.54, -0.81, -0.22$

The parameters for each area $\Xi = \{A_k^v, \Phi_k^{vv'}, \varphi_k^v, \kappa_{\alpha}^v, B_k^v, \theta_k^v, \kappa_{\beta}^v\}$ were estimated from the mesostates time-series α_t^v and β_t^v using the least-square estimators (see Appendix C in Riera *et al.* 2004) of the autoregressive model (Brockwell & Davis 1987) with exogenous variables (Appendix B in Riera *et al.* 2004 for a revision of general theory of ARMAx). The main attributes of the impulse response and autocorrelation functions (determined by parameters A_k^v for synaptic activity and B_k^v for haemodynamics) were comparable with previous

results obtained using autoregressive models at the levels of primary currents sources (Yamashita *et al.* 2004) and haemodynamics (Riera *et al.* 2004). Although it is possible to estimate the order of autoregressive models using various criteria for model selection, in our paper it was set up *a priori* in accordance with these previous studies. The haemodynamic was more sensitive to the condition on-off in the stimulus ($\sum_k \theta_k^v \gg \sum_k \varphi_k^v$ for all areas). The estimation of the effective connectivity $\sum_k |\Phi_k^{vv'}|$

Figure 12. The estimated graph of effective connectivity between the areas is summarized using scale of greys (i.e. the connection is stronger for darker greys, white colour symbolizes a very weak connection). The white squares with a cross represent those connections that were *a priori* set to zero (using information obtained from the fibre tract-based atlas). The arrows represent directionality in the connection. The colours are the same as those used in the structures (figure 11).

(figure 12 presents a summary using a grey scale) between the areas constitutes the most relevant result. A more faithful analysis can be performed using the definition of Granger-causality for autoregressive models (Geweke 1984).

4. DISCUSSION

This paper makes a significant contribution in terms of the methodology presented, which is a radical departure from the top-down approaches predominant in recent literature. However, it is inappropriate to make any conclusion based on our experimental results in view of the fact that data from only one subject was available in this study. It is abundantly clear to us that in the near future, the most challenging concern will be the elucidation of crosstalking mechanisms between the neural network and vascular systems. From this study, the complexity of this matter is predictable. Additionally, it is the authors' intent to address the following in the ongoing research:

- (i) What is the consequence of having used a model of multiple dipoles instead of applying optimization strategies that search for locally distributed inverse solutions inside each structure (i.e. Trujillo-Barreto *et al.* 2004)? Such new methodologies will allow the use of multiples areas within a simple structure of the probabilistic atlas.
- (ii) There are doubts as to whether all ballistocardiogram components have been completely removed from the raw EEG, a fact that could dramatically affect the final results. How would the results differ if subjects perform the same experimental paradigm while their EEG signals are recorded outside the MRI scanner?

- (iii) There are doubts about whether a DC shift in the EEG could somehow reflect in the cross talking between synaptic activity and the vasculature. A consistent and reproducible temporal correlation between EEG DC shifts and changes in CBV has been reported (Vanhatalo *et al.* 2003). Unfortunately, in this study, EEG amplifiers and off-line pre-processing have eliminated the DC shifts in the EEG signals.
- (iv) The interactions between brain areas have been modelled linearly in this paper by means of the effective connectivity coefficients $\Phi_k^{vv'}$. In future works of our group, nonlinear types of interactions between brain areas will be considered. For example, in this issue, Robinson *et al.* (2005) presented a detailed neuronal mass model that includes cooperation and competition between cortico-cortico and thalamo-cortico populations via excitatory/inhibitory nonlinear interactions.
- (v) In our model, the geometry of neurons (i.e. pyramidal cells) involved in the genesis of EEG data has not been taken into consideration. In addition, the architectural properties at several levels (i.e. synapses, neurons, networks and neuronal masses) of the multipart brain circuitry have been ignored.
- (vi) Recent questions, for example 'do synchronized neuronal excitatory and inhibitory processes demand more oxygen than the same processes in a desynchronized state?' (Makeig *et al.* 2002), will soon refocus the attention of theoreticians. A model of EEG and fMRI fusion that includes two separate mesostates $\alpha_{\pm}^v(t)$ to distinguish excitatory and inhibitory synaptic activity, as well as to allow for descriptions of their interactions within a neural mass, will be useful to understand the relationship between synchronization and haemodynamics in forthcoming studies. For example, the negative/positive correlations between EEG alpha-band power and fMRI signal found recently (Goldman *et al.* 2002) could be interpreted in this context. The activation seen in functional imaging studies probably results from excitation rather than inhibition (Waldvogel *et al.* 2000), while EEG reflects a competitive balance between them. Some authors, though, have asserted that neuronal inhibitions can raise fMRI and PET measures under certain extreme conditions (Tagamets & Horwitz 2001; Caesar *et al.* 2003). In this issue, Horwitz *et al.* (2005) evaluated the effect on PET and fMRI of using a large-scale excitatory and inhibitory computational model applied to a delayed matched-to-sample task.

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Table 3. Mesoscopic level.

physiological meaning	type	symbol
stimulus (afferent pathways)	input	s_t
stimulus sensitivity factor for the synaptic activity (k th lag and v th area)	parameter	ϕ_k^v
physiological noise at the synaptic activity	input	ζ_t^v
noise variance at the synaptic activity	parameter	κ_α^v
coefficients for the self-dynamics of the synaptic activity (k th lag and v th area)	parameter	A_k^v
synaptic activity at the v th area	variable	α_t^v
effective connectivity coefficients (k th lag, $v \rightarrow v'$)	parameter	$\Phi_k^{vv'}$
evoked transient at the v th area	variable	e_t^v
stimulus sensitivity factor for the synaptic activity (k th lag and v th area)	parameter	θ_k^v
stimulus delay (haemodynamics)	parameter	d
physiological noise at the haemodynamics	input	ζ_t^v
noise variance at the haemodynamics	parameter	κ_β^v
coefficients for the self-dynamics of the haemodynamics (k th lag and v th area)	parameter	B_k^v
haemodynamics at the v th area	variable	β_t^v
flow-inducing signal	variable	η_t^v
the low-pass vascular filter (coefficient of the k th lag)	parameter	χ_k
scaling factor (synaptic activity $\rightarrow$ haemodynamics)	parameter	ρ_v
flow-inducing signal susceptibility	parameter	ω_v

APPENDIX A: MESOSTATES IDENTIFICATION

The estimation of mesostates from the fused EEG (T_e samples) and fMRI (T_v scans) data is performed by solving recursively the equations (A 1)–(A 8). Note that $\mathbf{K}_{ev} = \mathbf{K}_e(\mathbf{r}_v)$.

(a) The mesostates α_t^v and β_t^v for the v th area

$$\begin{aligned} \hat{\alpha}_t^v &= \left(\sum_{e=1}^{N_e} (\mathbf{K}_{ev} \cdot \hat{\mathbf{m}}_v)^2 \right)^{-1} \sum_{e=1}^{N_e} (\mathbf{K}_{ev} \cdot \hat{\mathbf{m}}_v) \\ &\quad \times \left(V_t^e - \hat{\mu}_t^e - \sum_{v' \neq v} \mathbf{K}_{ev'} \cdot \hat{\mathbf{m}}_{v'} \hat{\alpha}_t^{v'} \right), \quad (\text{A } 1) \\ \hat{\mathbf{m}}_v &= \left(\sum_{e=1}^{N_e} (\mathbf{K}_{ev} \mathbf{K}_{ev}') \sum_t (\hat{\alpha}_t^v)^2 + \hat{\lambda}_v^2 I_3 \right)^{-1} \\ &\quad \times \sum_{e=1}^{N_e} \sum_{t=1}^{T_e} \hat{\alpha}_t^v \mathbf{K}_{ev} \left(V_t^e - \hat{\mu}_t^e - \sum_{v' \neq v} \mathbf{K}_{ev'} \cdot \hat{\mathbf{m}}_{v'} \hat{\alpha}_t^{v'} \right). \quad (\text{A } 2) \end{aligned}$$

The Lagrange multipliers λ_v^2 are used to constrain the dipole orientation to have unitary norm. These factors are determined by solving a small nonlinear optimization problem:

$$\begin{aligned} \min_{\lambda_v} &\left\{ \sum_k \left[\mathbf{u}_k^v \cdot \sum_{e=1}^{N_e} \sum_{t=1}^{T_e} \hat{\alpha}_t^v \mathbf{K}_{ev} \right. \right. \\ &\quad \left. \left. \times \frac{\left(V_t^e - \hat{\mu}_t^e - \sum_{v' \neq v} \mathbf{K}_{ev'} \cdot \hat{\mathbf{m}}_{v'} \hat{\alpha}_t^{v'} \right)}{d_k^v + \lambda_v^2} \right]^2 - 1 \right\}. \quad (\text{A } 3) \end{aligned}$$

The magnitudes $\mathbf{u}_k^v$ and d_k^v are the eigenvector and eigenvalue of the (3×3) matrix

$$\sum_{e=1}^{N_e} (\mathbf{K}_{ev} \mathbf{K}_{ev}') \sum_{t=1}^{T_e} (\hat{\alpha}_t^v)^2,$$

respectively.

$$\hat{\beta}_t^v = \frac{1}{n^v} \sum_{v_i=1}^{n^v} (y_{t_i}^{v_i} - \hat{\mu}_{t_i}^{v_i}). \quad (\text{A } 4)$$

The number of voxel inside the v th region is denoted by n^v .

(b) The estimator of nuisance effects μ_t^e and $\mu_t^{v_i}$

For the EEG: $\hat{\mu}_t^e = \mathbf{K}_{eo} \cdot \hat{\mathbf{m}}_0 \hat{b}_t + \hat{c}^e$, where:

$$\begin{aligned} \hat{b}_t &= \left(\sum_{e=1}^{N_e} (\mathbf{K}_{eo} \cdot \hat{\mathbf{m}}_0)^2 \right)^{-1} \sum_{e=1}^{N_e} (\mathbf{K}_{eo} \cdot \hat{\mathbf{m}}_0) \\ &\quad \times \left(V_t^e - \hat{c}^e - \sum_{v=1}^{N_v} \mathbf{K}_{ev} \cdot \hat{\mathbf{m}}_v \hat{\alpha}_t^v \right), \quad (\text{A } 5) \\ \hat{\mathbf{m}}_0 &= \left(\sum_{e=1}^{N_e} (\mathbf{K}_{eo} \mathbf{K}_{eo}') \sum_{t=1}^{T_e} (\hat{b}_t)^2 + \hat{\lambda}_0^2 I_3 \right)^{-1} \\ &\quad \times \sum_{e=1}^{N_e} \sum_{t=1}^{T_e} \hat{b}_t \mathbf{K}_{eo} \left(V_t^e - \hat{c}^e - \sum_{v=1}^{N_v} \mathbf{K}_{ev} \cdot \hat{\mathbf{m}}_v \hat{\alpha}_t^v \right). \quad (\text{A } 6) \end{aligned}$$

Similarly, the factor λ_0 will warrant that dipole orientation has unitary norm, and it can be estimated from

$$\begin{aligned} \min_{\lambda_0} &\left\{ \sum_k \left[\mathbf{u}_k^0 \cdot \sum_{e=1}^{N_e} \sum_{t=1}^{T_e} \hat{b}_t \mathbf{K}_{eo} \right. \right. \\ &\quad \left. \left. \times \frac{\left(V_t^e - \sum_{v=1}^{N_v} \mathbf{K}_{ev} \cdot \hat{\mathbf{m}}_v \hat{\alpha}_t^v \right)}{d_k^0 + \lambda_0^2} \right]^2 - 1 \right\}, \end{aligned}$$

with magnitudes $\mathbf{u}_k^0$ and d_k^0 being the eigenvector and eigenvalues of matrix

$$\sum_{e=1}^{N_e} (\mathbf{K}_{eo} \mathbf{K}_{eo}') \sum_{t=1}^{T_e} (\hat{b}_t)^2,$$

$$\hat{c}^e = \frac{1}{T_e} \sum_{t=1}^{T_e} \left(V_t^e - \mathbf{K}_{eo} \cdot \hat{\mathbf{m}}_0 \hat{b}_t - \sum_{v=1}^{N_v} \mathbf{K}_{ev} \cdot \hat{\mathbf{m}}_v \hat{\alpha}_t^v \right).$$

(A 7)

Table 4. Echo/macrosscopic level.

meaning	type	symbol
dipole location (centre of v th area)	parameter	$\mathbf{r}_v$
normalized dipole orientation (v th area)	parameter	$\mathbf{m}_v$
instrumental error (EEG, e th lead electrode)	input	ε_t^e
standard deviation of the instrumental error EEG ' e th lead electrode'	parameter	σ_e
dipole location (ballistocardiogram)	parameter	$\mathbf{r}_o$
normalized dipole orientation (ballistocardiogram)	parameter	$\mathbf{m}_o$
time-varying amplitude of the dipole (ballistocardiogram)	variable	b_t
EEG temporal DC (e th lead electrode)	parameter	c^e
nuisance global effect of ballistocardiogram ' e th lead electrode'	variable	μ_t^e
EEG data (e th lead electrode)	data	V_t^e
instrumental error (BOLD signal, v_i th voxel)	input	$\varepsilon_t^{v_i}$
standard deviation of the instrumental error fMRI ' v th area'	parameter	σ_{v_i}
nuisance potential drift ' v_i th voxel'	variable	$\mu_t^{v_i}$
k th coefficient of the nonlinear polynomial series ' v_i th voxel'	parameter	$\gamma_k^{v_i}$
fMRI data (v_i th voxel)	data	$y_t^{v_i}$

For the fMRI: $\hat{\mu}_t^{v_i} = \hat{\gamma}^{v_i} \cdot \mathbf{T}_t$

$$\hat{\gamma}^{v_i} = \left(\sum_t \mathbf{T}_t \mathbf{T}_t' \right)^{-1} \sum_{t=1}^{T_v} (y_t^{v_i} - \hat{\beta}_t^{v_i}) \mathbf{T}_t. \quad (\text{A } 8)$$

The vector notation $\gamma^{v_i} = (\gamma_0^{v_i}, \dots, \gamma_\delta^{v_i})'$ and $\mathbf{T}_t = (1, t, t^2, \dots, t^\delta)'$ has been used.

APPENDIX B: SUMMARY OF THE DATA, INPUTS, VARIABLE AND PARAMETERS OF THE MODEL

See tables 3 and 4.

ENDNOTE

¹QRS represents a complexes wave constituted by three components: Q, R and S. The Q wave, when present, represents the small horizontal (left to right) current as the action potential travels through the interventricular septum. Very wide and deep Q waves do not have a septal origin, but indicate myocardial infarction. The R and S waves indicate contraction of the myocardium.

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