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Technical Note

Hemodynamic correlates of EEG: A heuristic

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In this note we describe a heuristic, starting with a dimensional analysis, which relates hemodynamic changes to the spectral profile of ongoing EEG activity. In brief, this analysis suggests that 'activation', as indexed by increases in hemodynamic signals, should be associated with a loss of power in lower EEG frequencies, relative to higher frequencies. The fact that activation is expressed in terms of frequency (i.e., per second) is consistent with a dimensional analysis in the sense that activations reflect the rate of energy dissipation (per second). In this heuristic, activation causes an acceleration of temporal dynamics leading to (i) increased energy dissipation; (ii) decreased effective membrane time constants; (iii) increased effective coupling among neuronal ensembles; and (iv) a shift in the EEG spectral profile to higher frequencies. These predictions are consistent with empirical observations of how changes in the EEG spectrum are expressed hemodynamically. Furthermore, the heuristic provides a simple measure of neuronal activation based on spectral analyses of EEG.

Keywords: EEG; MRI; Oscillations; Alpha; Synchrony

Introduction

It is now generally accepted that the integration of fMRI and electromagnetic measures of brain activity has an important role in characterizing evoked brain responses (Goldman et al., 2002; Laufs et al., 2003a,b; Martinez-Montes et al., 2004; Salek-Haddadi et al., 2003). The possibility of integrating these two measures in humans is supported by the results of the study of Logothetis et al. (2001). In this study the authors demonstrated that within the macaque monkey visual cortex intracortical recordings of the local field potential (LFP) and the BOLD signal were linearly correlated. Approaches to integration can be classified into three schemes: integration through prediction; integration through constraints; and integration through fusion. These are depicted schematically in Fig. 1. Integration through prediction (Fig. 1 dotted line) uses temporally resolved EEG signal as a predictor of changes in concurrently recorded fMRI. The ensuing region-specific hemodynamic correlates can then be characterized with high spatial resolution with conventional imaging methodology (Lovblad et al., 1999; Lemieux et al., 2001; Czisch et al., 2004). Several studies of this type (Goldman et al., 2002; Laufs et al., 2003a,b; Martinez-Montes et al., 2004) have focussed on correlating modulations in ongoing oscillatory activity measured by EEG with the hemodynamic signal. They have demonstrated that modulations in alpha rhythms (oscillations at ~10 Hz) are negatively correlated with modulations in the BOLD signal—i.e., an increase in alpha power is associated with a decrease in the BOLD signal. Studies employing integration through constraints (Fig. 1 dashed line) have used the spatial resolution of focal fMRI activations to constrain equivalent dipole or distributed estimates of EEG or MEG sources (Dale et al., 2000; Phillips et al., 2002). However, neither of these schemes can be considered as true integration of multimodal data in the sense that there is no common temporal forward model that links the underlying neuronal dynamics of interest to measured hemodynamic and electrical responses (Fig. 1, solid black lines).

The characterization of the relationship between the electrophysiology of neuronal systems and their slower hemodynamics in terms of their respective forward models is therefore crucial from a number of perspectives: Not only for forward models of electrical and hemodynamic data, but also for the utility of spatial priors, derived from fMRI, in the inverse EEG/MEG source reconstruction problem, and for the disambiguation of induced, relative to evoked, brain responses using both modalities.

In this note, we describe perhaps the simplest of all models, so simple that we call it a heuristic, which helps to explain some empirical observations of EEG/fMRI integration using a dimensional analysis and a biophysical model. In brief, this heuristic suggests that a shift in the spectral mass from low to high frequencies will be associated with increases in fMRI measures.

Theory

Dimensional analysis

Given the tenable assumption that hemodynamics reflect the energetics of underlying neuronal changes (Jueptner and Weiller, 1995; Shulman and Rothman, 1998; Hoge et al., 1999; Magistretti et al., 1999; Magistretti and Pellerin, 1999; Shin, 2000), we assume here that the BOLD signal b, at any point in time, is proportional to

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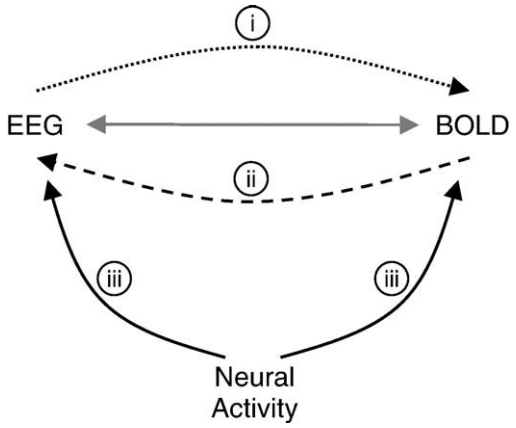

Fig. 1. Schematic showing the approaches to EEG/fMRI integration. (i) Integration through prediction. (ii) Integration through constraints. (iii) Integration through fusion with forward models.

the rate of energy dissipation, induced by transmembrane currents. Note that we are not assuming here that the increase in blood flow, which is the major contributor to the BOLD signal, is a direct consequence of the rate of energy dissipation, but rather that these two measures are proportional (see Hoge et al., 1999). Although recent work has suggested that the neurovascular coupling is driven by glutamate release (see Lauritzen, 2001; Attwell and Iadecola, 2002), in practice the measures of glutamate release, BOLD, and energy usage are correlated and therefore the assumption here that the BOLD signal is proportional to the rate of energy dissipation is valid. This dissipation is expressed in terms of Joules per second and corresponds to the product of transmembrane potential (v, Joules per Coulomb) and transmembrane current (i, Coulombs per second).

$$b \propto \langle v^T i \rangle \tag{1}$$

Where the expectation is over time and $v = [v_1, \ldots v_k]^T$ corresponds to a [large] column vector of potentials for each neuronal compartment k within a voxel, similarly for i. Clearly, Eq. (1) will not be true instantaneously because it may take some time for the energy cost to be expressed in terms of increased oxygen delivery, extraction, and perfusion. However, over a suitable time scale, of order seconds, Eq. (1) will be approximately correct. Assuming a single-compartment model, currents are related to changes in membrane potential though their capacitance c, which we will assume is constant (see Dayan and Abbot, 2001, p. 156). By convention, the membrane current is defined as positive when positive ions leave the neuron and negative when positive ions enter the neuron.

$$i = -c\dot{v} \tag{2}$$

then

$$b \propto c\langle v^T \dot{v} \rangle \tag{3}$$

A neuronal model

To relate changes in membrane potential to the BOLD signal we need to adopt some model of a neuronal system and how it activates. A simple integrate and fire model of autonomous neuronal dynamics can be expressed in the form

$$\begin{aligned} \dot{v}_k &= -v_k/\tau_k + u_k \\ &= f_k(v) \end{aligned} \tag{4}$$

for the kth compartment or unit. We have assumed here that synaptic currents are caused by some nonlinear function of the depolarization status of all units in the population: i.e., $u_k = g_k(v)$. For a system of this form we can approximate the dynamics of perturbations with the first-order system.

$$\begin{aligned} \dot{v}(t) &= -Jv \\ J &= \frac{\partial f}{\partial v} \end{aligned} \tag{5}$$

The Jacobian J summarizes the functional or causal architecture of the neuronal system. The leading diagonal elements of J correspond to self-inhibition and play the role of effective membrane rates or conductances. In the absence of influences from any other units the kth potential will decay exponentially to the equilibrium or resting potential $v = 0$.

$$\dot{v}_k = -J_{kk} v_k \tag{6}$$

It can be seen that $J_{kk} = 1/\tau_k$ has units of per second and is the inverse of the effective membrane time constant. In fact, in most biophysical models of neuronal dynamics, this 'rate' is usually considered as the ratio of the membrane's conductance to its capacitance. Conductivity will reflect the configuration of various ion channels and the ongoing post-synaptic receptor occupancy. In a similar way, the off-diagonal elements of the Jacobian characterize the effective connectivity or intrinsic coupling among units, where $J_{kj} = \partial f_k/\partial v_j = \partial \dot{v}_k/\partial v_j$. Effective connectivity is simply the influence one neuronal system exerts over another. It is interesting to note that plausible neuronal models of ensemble dynamics suggest a tight coupling between average spiking rate and decreases in effective membrane time constants (e.g., Chawla et al., 2000). However, as we will see below, we do not need to consider spikes to close the link between BOLD and frequency profiles of ongoing EEG or MEG dynamics.

From Eqs. (3) and (5) we have

$$\begin{aligned} b &\propto c < v^T J v > \\ &\propto ctr\left(J < vv^T >\right) \\ &\propto ctr(J\mathrm{Cov}\{v\}) \end{aligned} \tag{7}$$

This means that the metabolic response is proportional to the trace of the product of the Jacobian (i.e., effective connectivity) and the temporal covariance of the transmembrane potentials.

Modeling activations

At this point we have to consider how 'activation' is mediated. In other words, how the dynamics over an extended period of time could change. If we treat the units within any voxel as an autonomous system then any extrinsic influence must be mediated by changes in the Jacobian; e.g., changes in conductance or coupling among neurons induced by afferent input. The attending changes in potential are secondary to these changes in the functional architecture of the system and may, or may not, change their covariances $\mathrm{Cov}\{v\}$. According to Eq. (7), a metabolic cost is induced through changes in J, even in the absence of changes in the covariance. To link BOLD and EEG responses we need to model the underlying changes in the Jacobian that generate them. This is accomplished in a parsimonious way by introducing an activation variable, α, that changes J. Here α is a parameter that

changes the effective connectivity (i.e., synaptic efficacies) and, implicitly, the dynamics of neuronal activity. In this model different modes of brain activity are associated with the Jacobian.

$$J(\alpha) = J(0) + \alpha \partial J / \partial \alpha \tag{8}$$

We will assume that $\partial J/\partial \alpha = J(0)$. In other words, the change in intrinsic coupling (including self-inhibition), induced by activation, is proportional to the coupling in the 'resting' state when $\alpha = 0$. The motivations for this assumption include the following:

- Its simplicity.
- Guaranteed stability, in the sense that if $J(0)$ has no unstable modes (positive eigenvalues) then neither will $J(\alpha)$. For example, it ensures that activation does not violate the 'no-strong-loops hypothesis' (Crick and Koch, 1998).
- It ensures the intrinsic balance between inhibitory and excitatory influences that underpins 'cortical gain control' (Abbot et al., 1997).
- It models the increases in membrane conductance associated with short-term increases in synaptic efficacy.

Effect of neuronal activation on BOLD

These considerations suggest that the coupling J_{kj} among neurons (positive and negative) will scale in a similar way and that these changes will be reflected in changes to effective membrane time constants J_{kk}. Under this model for activation the effect of α is to accelerate the dynamics and increase the system's energy dissipation. This acceleration can be seen most easily by considering the responses to perturbations around v_0 under $J = J(0)$ and $\tilde{J} = J(\alpha) = (1 + \alpha)\, J$

$$v(t) = e^{-Jt} v_0$$

$$\tilde{v}(t) = e^{-\tilde{J}t} v_0 = v((1+\alpha)t) \tag{9}$$

In other words, the perturbation under $J(\alpha)$ at time t is exactly the same as that under $J(0)$ at $(1 + \alpha)t$. This acceleration will only make dynamics faster; it will not change their form. Consequently there will be no change in the covariation of membrane potentials and the impact on the fMRI responses is mediated by, and only by changes in J.

$$\frac{\tilde{b}}{b} \propto \frac{tr(\tilde{J}\mathrm{Cov}\{v\})}{tr(J\mathrm{Cov}\{v\})} = (1+\alpha) \tag{10}$$

In other words, the activation, α, is proportional to the relative increase in metabolic demands. This is intuitive from the perspective of fMRI but what does an activation look like in terms of the EEG?

Effect of neuronal activation on EEG

From the point of view of the fast temporal activity reflected in the EEG, activation will cause an acceleration of the dynamics, leading to a 'rougher' looking signal with loss of lower frequencies, relative to higher frequencies. A simple way to measure this effect is in terms of the roughness r, which is the normalized variance of the first temporal derivative of the EEG. From the theory of stationary processes (Cox and Miller, 1965), this is mathematically the same as the negative curvature of the EEGs autocorrelation function evaluated at zero lag. Thus, for an EEG signal, e:

$$r = \frac{\mathrm{Var}(\dot{e})}{\mathrm{Var}(e)} = -\rho(0)''$$

Assuming e (measured at a single site) is a linear mixture of potentials, i.e., $e = lv$, where l is a lead-field row vector, its autocorrelation at lag h is:

$$\rho(h) = <v(t)^T l^T l v(t+h)> \tag{11}$$

From Eqs. (9) and (11) we have

$$\tilde{\rho}(h) = \rho((1+\alpha)h)$$

$$\tilde{\rho}(h)'' = (1+\alpha)^2 \rho(h)'' \tag{12}$$

It follows that the change in r is related to neuronal activation by

$$\frac{\tilde{r}}{r} = \frac{\tilde{\rho}(0)''}{\rho(0)''} = (1+\alpha)^2 \tag{13}$$

As the spectral density of a random process is defined to be the Fourier transform of its autocorrelation function, $g(\omega) = \int \rho(h) e^{-\mathrm{iwh}} dh$, the equivalent relationship in the frequency domain obtains from the 'roughness' expressed in terms of spectral density $g(\omega)$ is

$$r = \frac{\int \omega^2 g(\omega) d\omega}{\int g(\omega) d\omega}$$

From Eq. (12) the equivalent of the activated case in terms of the spectral density is:

$$\tilde{g}(\omega) = \frac{g((1+\alpha)\omega)}{(1+\alpha)} \tag{14}$$

Here, the effect of activation is to shift the spectral profile toward higher frequencies with a reduction in amplitude (see Fig. 2). The activation can be expressed in terms of the 'normalized' spectral density.

$$\frac{\tilde{r}}{r} = \frac{\int \omega^2 \tilde{p}(\omega) d\omega}{\int \omega^2 p(\omega) d\omega} = (1+\alpha)^2$$

$$p(\omega) = \frac{g(\omega)}{\int g(\omega) d\omega} \tag{15}$$

$p(\omega)$ could be treated as an empirical estimate of probability, rendering roughness equivalent to the expected or mean square

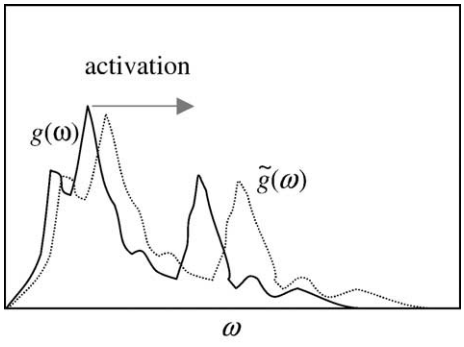

Fig. 2. Schematic showing the effect of activation on the spectral profile.

frequency. Gathering together the above equalities, we can express relative values of fMRI and spectral measures in terms of each other.

$$\left[\frac{\tilde{b}}{b}\right]^2 \propto (1+\alpha)^2 \propto \frac{\int \omega^2 \tilde{p}(\omega) d\omega}{\int \omega^2 p(\omega) d\omega} \quad (16)$$

Summary

Eq. (14) means that as neuronal activation increases, there is a concomitant increase in BOLD signal and a shift in the spectral profile to higher frequencies. High-frequency dynamics are associated with small effective membrane time constants and high [leaky] transmembrane conductances. The ensuing currents and fast changes in potential incur an energy cost to which the BOLD signal is sensitive. Such high-frequency dynamics have also been shown to be dependent upon the firing patterns of inhibitory interneurons (Traub et al., 1996; Whittington and Traub, 2003). The conjoint effect of inhibitory and excitatory synaptic input is to open ion channels, rendering the post-synaptic membrane leaky with high rate constants. The effect is captured in the model by the scaling of the leading diagonal elements of the Jacobian. This suggests that the changes in the temporal dynamics to which the BOLD signal is sensitive are mediated by changes in the firing patterns of both excitatory and inhibitory subpopulations.

Critically however, the predicted BOLD signal is a function of the frequency profile as opposed to any particular frequency. For example, an increase in alpha (low frequency), without a change in total power, would reduce the mean square frequency and suggest de-activation. Conversely an increase in gamma (high frequency) would increase the mean square frequency and speak to activation (see Fig. 3).

In brief, activation corresponds to a decrease in low frequencies relative to high frequencies or, conversely, an increase in high frequencies relative to low frequencies. We have deliberately used the term 'activation' here because it fits comfortably with the notion of EEG activation that is typically associated with a loss of low frequencies and the expression of an irregular de-synchronized trace, comprising high frequencies. It will also be noted that activation is synonymous with de-synchronization (i.e., a loss of alpha frequencies). However, the use of '[de-]synchronization' in an event-related sense is a little unfortunate, as discussed below.

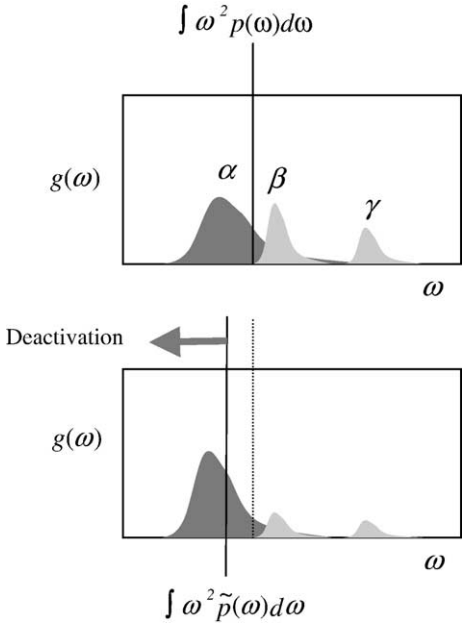

Fig. 3. Schematic showing the effect of de-activation on mean square frequency.

Discussion

The above heuristic was based on a generative model of how neuronal dynamics activate. The heuristic was partly inspired by the results of EEG-fMRI integration in the study of epilepsy. In this field, increased slow wave activity has been shown to be associated with decreased BOLD (Archer et al., 2003) while spikes and wave discharges (with high-frequency components) have been shown to cause BOLD activations (Krakow et al., 2001; Hamandi et al., 2004). The model outlined here ties together expected changes in BOLD and EEG measures and makes a clear prediction about the relationship between the different frequency components of ongoing EEG or MEG activity and the expected BOLD response. According to the model any modulations in the degree of low-frequency relative to the high-frequency components in the EEG signal will be inversely correlated with the BOLD signal. This is largely in agreement with the empirical data available. It is now generally accepted that modulations in the on-going alpha rhythm, 8–12 Hz, when the eyes are shut, are inversely correlated with the BOLD signal at voxels within the parietal, parieto-occipital, and frontal cortices (Goldman et al., 2002; Laufs et al., 2003a,b; Moosmann et al., 2003; Martinez-Montes et al., 2004). Furthermore, during low-frequency visual entrainment, using a periodic checkerboard stimulus, the BOLD signal is reduced compared to an aperiodic stimulus (Parkes et al., 2004). The model presented here also predicts that a shift in the frequency profile of the EEG to high-frequency components should be correlated with an increase in the BOLD signal. Although there is a much smaller literature on high-frequency EEG-BOLD correlations, what has been published is broadly in agreement with this prediction. Laufs et al. (2003b) report predominantly positive correlations between the BOLD signal and the EEG power in the 17- to 23-Hz and the 24- to 30-Hz band width and Parkes et al. (2004) demonstrate that an aperiodic checkerboard stimulus induces a greater BOLD signal than a low-frequency periodic stimulus.

However, there are a number of observations that are not captured by the model. Firstly, the model does not address very slow changes in potentials, <0.1 Hz, that are unlikely to contribute to the event-related response. As such it does not capture the very slow modulations in LFP that have previously been shown to be related to the BOLD response (Leopold et al., 2003). Secondly, and most notably, it does not explain the positive correlation of the BOLD signal with alpha oscillations in the thalamus (Goldman et al., 2002; Martinez-Montes et al., 2004). This discrepancy could reflect the unique neuronal dynamics of the thalamus. Thalamic neurons are characterized by complex intrinsic firing properties, which may range from the genesis of high-frequency bursts of action potential to tonic firing (Steriade et al., 1993). However, it could also reflect the fact that the model is based on several assumptions that are wrong:

- The first assumption is that the dynamics of transmembrane potentials conform to an autonomous ordinary differential

equation. The shortcomings of this assumption are that there is no opportunity for deterministic noise. However, this is a fairly mild restriction in relation to the autonomy, which precludes extrinsic input. This enforces afferent inputs outside the voxel or source to exert their influence vicariously though changes in the systems parameters, encoded by the Jacobian. This can be seen as a limitation, given the driving nature of [forward] extrinsic connections in sensory cortex, but does fit comfortably with other perspectives on functional integration in the brain (see below).

- The use of an autonomous ODE precludes hidden states that mediate changes in conductance and limits the model to a simple integrate- and fire-like summary of neuronal behavior. A more general form for Eq. (2) would require.

$$\dot{v} = f_v(v,x)$$
$$\dot{x} = f_x(v,x) \tag{17}$$

where, other hidden states x might correspond to conductances and channel gating terms as in more detailed biophysical models of neurons (Dayan and Abbot, 2001). The only argument that can be offered in defense of Eq. (2) is that it may be sufficient to capture important behaviors by appeal to neuronal mass and mean field approximations.

- The activation is modeled effectively by a scaling of the Jacobian. Functionally, this is a severe assumption because it precludes the selective enabling of particular connections. The consequence of this assumption is that any neuronal system can vary its rate or speed of computation, but can only do one thing. In reality, a better approximation would be bilinear with a multidimensional activation denoted by the vector $\alpha = [\alpha_1, \ldots]$

$$\tilde{J} = J + \sum_i \alpha_k B_k$$
$$B_k = \frac{\partial J}{\partial \alpha_k} \tag{18}$$

However, this model is too unconstrained to make any generic comments, without assuming a particular form for the bilinear terms B_k.

There are other shortcomings that could be invoked and that would have to be considered if the model failed to predict BOLD-EEG relationships. Having briefly deconstructed the model it is worth noting that it highlights some conceptual issues that might be useful. These include:

- First, it re-frames the notion of 'activation' in dynamic terms, suggesting that activation is not simply an excess of spikes, or greater power in any particular EEG frequency band. Activation may correspond to an acceleration of dynamics, subserving more rapid computations. This sort of activation can manifest with no overall change in power but a change in the frequencies at which power is expressed. Because more rapid or dissipative dynamics are energetically more expensive, it may be that they are reserved for 'functionally' adaptive or necessary neuronal processing.
- Second, under the generative model of activation, a speeding up of the dynamics corresponds to a decrease in the width of the cross-correlation functions between all pairs of units in the population. (At the macroscopic level of EEG recordings, considered here, the synchronization between pairs of units, as measured by the cross-correlation function, is captured in the width of the autocorrelation of the EEG signal, because the EEG signal is a measure of synchronous neural activity). This width is a ubiquitous measure of synchronization that transcends any frequency-specific changes in coherence. In short, activation as measured by fMRI is caused, in this model, by increased synchronization and, implicitly, a change in the temporal structure of neuronal dynamics.
- Third, our analysis suggests that the underlying 'activation' status of neuronal systems is not expressed in any single frequency but is exhibited across the spectral profile. This has implications for use of classical terms like 'event-related de-synchronization'. If one only considered modulations in spectral density at one frequency, as in the classical use of the term de-synchronization, one would conclude that the effect of activation was a de-synchronization of low-frequency components. According to the heuristic, however, the effect of activation is a shift in the entire spectral profile to higher frequencies with a concomitant attenuation in amplitude of all frequencies. This general conclusion does not preclude the selective expression of certain frequencies during specific cognitive operations (e.g., increases in theta oscillations during mental arithmetic; e.g., Mizuhara et al., 2004). However, the heuristic suggests that the context in which these frequencies are expressed is an important determinant of the BOLD response. In other words, it is not the absolute power of any frequency but the profile which determines expected metabolic cost.
- Fourth, as introduced above, one of the assumptions treats neuronal systems as autonomous, such that the evolution of their states is determined in an autonomous fashion. This translates into the assumption that the pre-synaptic influence of intrinsic connections completely overshadows extrinsic inputs. This may seem an odd assumption. However, it is the basis of nonlinear coupling in the brain and may represent, quantitatively, a much more important form of integration than simple linear coupling. We have addressed this issue both empirically and theoretically in Friston (2000). In brief, if extrinsic inputs affect the excitability of neurons, as apposed to simply driving a response, the coupling can be understood in terms of changes in the system parameters, namely the Jacobian. This means the response to input will be nonlinear. Quantitative analyses (a simple form of bi-coherence analysis) of MEG data suggest this form of nonlinear coupling can account for much more variation in power than linear coupling, i.e., coherence (Friston, 2000).

Conclusion

The integration of EEG and fMRI data is likely to play an important role in our understanding of brain function. Through such multimodal fusion it should be possible to harness the temporal resolution of EEG and the spatial resolution of fMRI in characterizing neural activity. The majority of the studies integrating EEG and fMRI to date have focussed on directly correlating the two measures, after first transforming the data so that they are on the same temporal scale (usually by convolution of the EEG time series with a canonical hemodynamic response function). This

approach has proved successful in demonstrating that multimodal fusion is feasible and that regionally specific dependencies between the two measures exist. However, this approach to characterizing the relationship between the EEG and the fMRI is limited as it does not characterize the integration in terms of the underlying neuronal activity. We will only be able to fully harness the benefits of EEG/fMRI integration by understanding the relationship between the underlying neuronal activity and the BOLD and EEG signals through their respective forward models. Although the current heuristic falls a long way short of this, it can explain the nature of some of the previously reported correlations between EEG and fMRI by considering the integration in terms of the underlying neuronal dynamics.

We have proposed a simple model that relates BOLD changes to the relative spectral density of an EEG trace and the roughness of the EEG time series. Neuronal activation affects the relative contribution of high and low EEG frequencies. This model accommodates the observations that BOLD signal correlates negatively with the expression of alpha power and positively with the expression of higher frequencies. This model would be simple to test empirically using concurrent EEG and fMRI recordings and a time frequency analysis of the ensuing source reconstructed EEG data. It rests on classical Maxwellian arguments and a simple model of activation. Clearly, many of the assumptions are not correct in detail, but the overall picture afforded may provide a new perspective on some important issues in neuroimaging.

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