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Biophysical models of fMRI responses

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Functional magnetic resonance imaging (fMRI) is used to investigate where the neural implementation of specific cognitive processes occurs. The standard approach uses linear convolution models that relate experimentally designed inputs, through a haemodynamic response function, to observed blood oxygen level dependent (BOLD) signals. Such models are, however, blind to the causal mechanisms that underlie observed BOLD responses. Recent developments have focused on how BOLD responses are generated and include biophysical input-state–output models with neural and haemodynamic state equations and models of functional integration that explain local dynamics through interactions with remote areas. Forward models with parameters at the neural level, such as dynamic causal modelling, combine both approaches, modelling the whole causal chain from external stimuli, via induced neural dynamics, to observed BOLD responses.

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Abbreviations

BOLD	blood oxygen level dependent
DCM	dynamic causal modeling
fMRI	functional magnetic resonance imaging
HRF	haemodynamic response function
MAR	multivariate autoregressive

Introduction

Functional magnetic resonance imaging (fMRI) has become the most commonly used method for investigating human brain function. Historically, neuroimaging has been concerned predominantly with the localization of function — that is, where in the brain neural computations mediate a cognitive process of interest. This approach rests on linear time-invariant models that relate the time course of experimentally controlled manipulations (e.g. changes in sensory stimuli or cognitive set) to observed blood oxygen level dependent (BOLD) signals in a voxel-specific fashion. Although different statistical models have been suggested (see [1,2] for recent reviews of different approaches), these standard models treat all voxels throughout the brain as isolated black boxes, whose input–output functions are characterized by BOLD responses evoked by various experimental conditions.

In this article, we briefly review current developments in causal models of how BOLD responses are generated. We focus specifically on the following two issues. First, what are the mechanisms that translate local neural dynamics into observed BOLD signals? This question relates to biophysical models of the neurovascular coupling. Second, how do local responses result from neural interactions with other brain regions? Answering this question requires models of functional integration that consider context-dependent causal interactions among remote areas or, in other words, in terms of effective connectivity.

Below, we briefly summarize standard convolution models for fMRI analysis that are blind to the causal mechanisms underlying the BOLD signal. We then present current biophysical models of regionally specific responses. Finally, we discuss progress in the field of effective connectivity. Particular emphasis will be given to dynamic causal modelling (DCM) [3••], which is the first example of an emerging class of model that combines the biophysics of local responses and effective connectivity.

Convolution models and the haemodynamic response function

Most current approaches to fMRI analysis are implemented in the context of the general linear model:

$$y = X\beta + e \quad (1)$$

which models the voxel-specific BOLD responses (y) in terms of a linear combination of explanatory variables in the design matrix (X) plus a Gaussian error term (e). The design matrix is based on stimulus functions that encode evoked neural responses. The relationship between neural and BOLD responses is modelled by the haemodynamic impulse response function (HRF). This function describes the characteristic haemodynamic response to a brief neural event and thus characterizes the input–output behaviour of a given voxel. The standard convolution model for fMRI treats each voxel as an independent linear time-invariant system, convolving the stimulus functions with an HRF to give predicted haemodynamic responses that enter the design matrix as regressors [4].

The HRF can vary from voxel to voxel and from subject to subject [5], and this variation has to be accommodated in the general linear model. To allow for voxel-specific HRFs, temporal basis functions can be used to express the predicted BOLD response as the linear combination of several functions of peristimulus time [2,6]. An alternative approach is to estimate the HRF directly from the data by using parametric [5] or non-parametric [7,8] models.

In summary, regardless of whether the HRF is modelled by temporal basis functions or estimated from the data, the issue being addressed is 'where' in the brain a given experimental manipulation leads to changes in BOLD signal; such approaches are blind to the mechanisms that underlie these changes.

Biophysical models of regional BOLD responses

By adopting a convolution model of brain responses in fMRI, we are implicitly positing the existence of an underlying dynamic system that converts neuronal responses into observed haemodynamic responses. In pioneering work by Buxton *et al.* [9,10] (the 'balloon model') and Mandeville *et al.* [11] (the 'Windkessel model'), detailed biophysical models of the neurovascular coupling have been validated by physiological experiments. These models predict how increases in regional blood flow (f) dilate a venous balloon, increase its volume (v) and dilute venous blood to decrease deoxyhaemoglobin content (q). The resulting BOLD signal is a nonlinear function of v and q and follows the flow dynamics with a delay of about 1 s.

This model has been extended by Friston *et al.* [12,13] to include the effects of external inputs (u) on an autoregulated vasodilatory signal (s), assuming that the relationship between evoked neural activity and blood flow is linear. This linear relationship had been demonstrated directly in elegant animal studies combining optical imaging, laser Doppler flowmetry and multielectrode recordings [14•,15], and indirectly in perfusion studies of the human brain [16].

As detailed in Figure 1, the extended input-state-output model of Friston [13] comprises four haemodynamic state variables, combined into a vector **x**, whose interactions are described by differential equations with five haemodynamic parameters (θ^h). These parameters have an explicit biophysical meaning (see the legend to Figure 1). At the beginning of the haemodynamic cascade, a flow-inducing signal is triggered by neural responses to experimental inputs, which are weighted by different efficacies ($\varepsilon_1 \ldots \varepsilon_m$ in Figure 1). These input-specific efficacies represent the neural parameters of the model (θ^n). The model represents a deterministic forward model with hidden states: for any given combination of neural and haemodynamic parameters θ and inputs u, the state equation $\dot{x} = f(x,u,\theta)$ can be integrated and passed through the output nonlinearity λ to give a predicted BOLD response y (see Figure 1 for details).

$$\dot{x} = f(x,u,\theta)$$
$$y = \lambda(x) \quad (2)$$

This approach can be extended to an observation model, in which the observed output y is a function of the inputs and parameters plus some measurement error e, but without reference to the hidden states x:

$$y = h(u,\theta) + e \quad (3)$$

This formulation forms the basis for estimating parameters from measured data. For example, the distributions of the biophysical parameters θ^h have been estimated from fMRI data by a Volterra series expansion [12]. The means and variances of these distributions were then used as empirical priors in a fully Bayesian scheme with an iterative expectation maximization algorithm [13], by using a bilinear approximation of the state equations. The latter scheme is also used in DCM (see below).

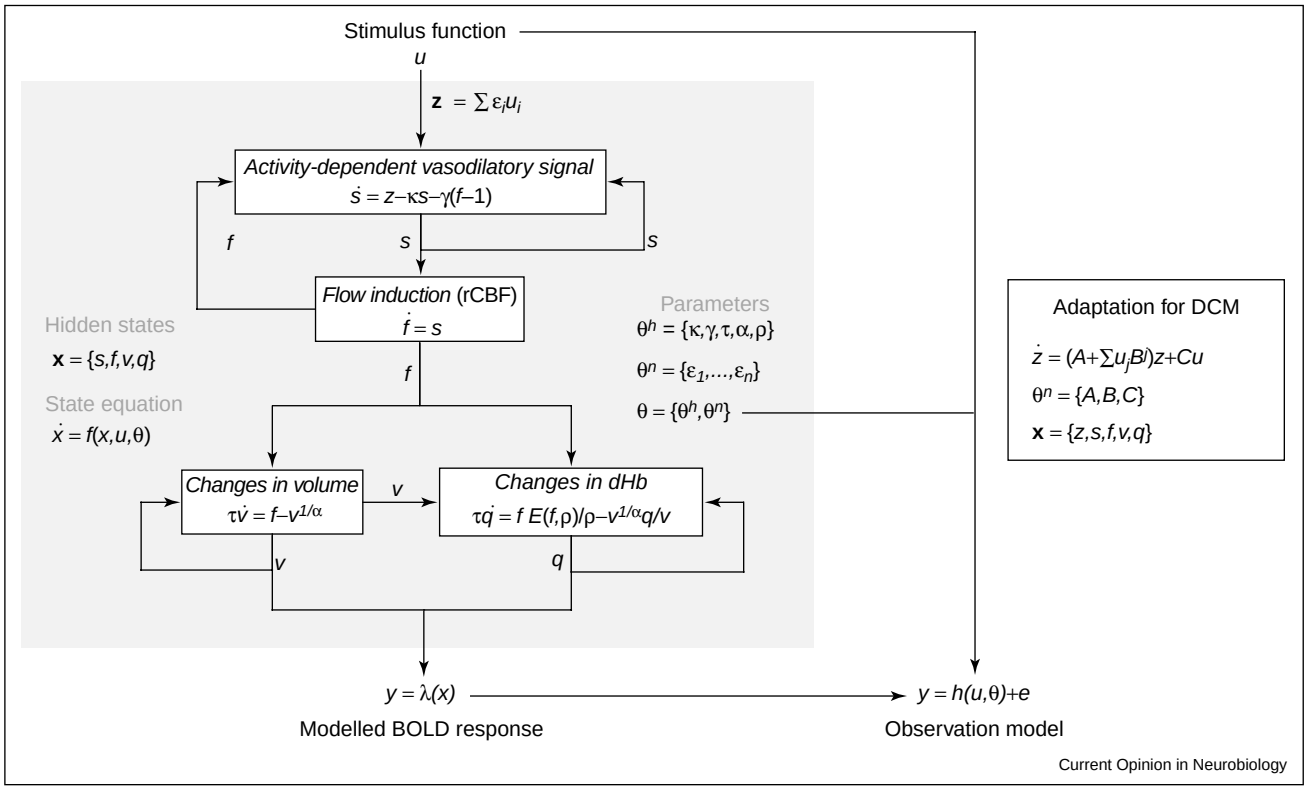
A limitation of this model is that it can deal only with measurement noise (see Equations 2 and 3). An extended model that considers also physiological noise has been proposed by Riera *et al.* [17••], who augmented the state equation (Equation 2) with an innovation term, resulting in the stochastic differential equation:

$$\dot{x} = f(x,u,\theta) + \mathrm{g}\omega \quad (4)$$

where ω is a scalar Wiener process representing physiological noise, and **g** is a vector defining the degree of randomness for each state variable. Equation 4 was then transformed into a nonlinear state space model, from which parameters were estimated by using a recursive local linearization filter [18]. This method has two advantages: first, the parameter estimates converge to the true values, not to the values of a bilinear approximation; and second, the fit of the model can be evaluated easily by testing whether the distribution of the innovation terms deviates from a Gaussian distribution. In Figure 2, for example, a BOLD signal that was generated from simulated state trajectories is reconstructed precisely from the estimated states despite the presence of both physiological and measurement noise.

A limitation of the above models is that they assume a tissue oxygen concentration of zero. Consequently, the capillary oxygen extraction rate depends entirely on oxygen delivery and thus on blood flow (see Equation 6 in [10]). Although this coupling between oxygen extraction and flow is supported by earlier studies [19], recent

Figure 1



Summary of the haemodynamic model of Friston [13] and its adaptation for DCM [3••]. A series of experimentally controlled inputs (u) evoke neural responses (z) that trigger a haemodynamic cascade, which is modelled by four state equations with five parameters. These haemodynamic parameters comprise the rate constant for vasodilatory signal decay (κ), the rate constant for autoregulatory feedback by blood flow (γ), transit time (τ), Grubb's vessel stiffness exponent (α), and capillary resting net oxygen extraction (ρ). Integrating the haemodynamic state equations for a given set of inputs and parameters and passing the result through the output non-linearity λ produces a predicted blood oxygen level dependent (BOLD) response (see Equation 5 in [13] for a detailed definition of λ). For parameter estimation, an observation model is used that treats the observed BOLD response as a function h of inputs and parameters plus some observation error e. Abbreviation: dHb, deoxyhaemoglobin; rCBF, regional cerebral blood flow.

experiments indicate that it may be an oversimplification [20]. Thus, more sophisticated models of oxygen extraction might be useful. For example, Zheng *et al.* [21] have extended the Friston model [13] by incorporating three new state variables that enable precise dynamic modelling of intracapillary oxygen transport to tissue. Similarly, Obata *et al.* [22•] have provided a generalized version of the original balloon model of Buxton *et al.* [10] that considers both intra- and extravascular signal changes.

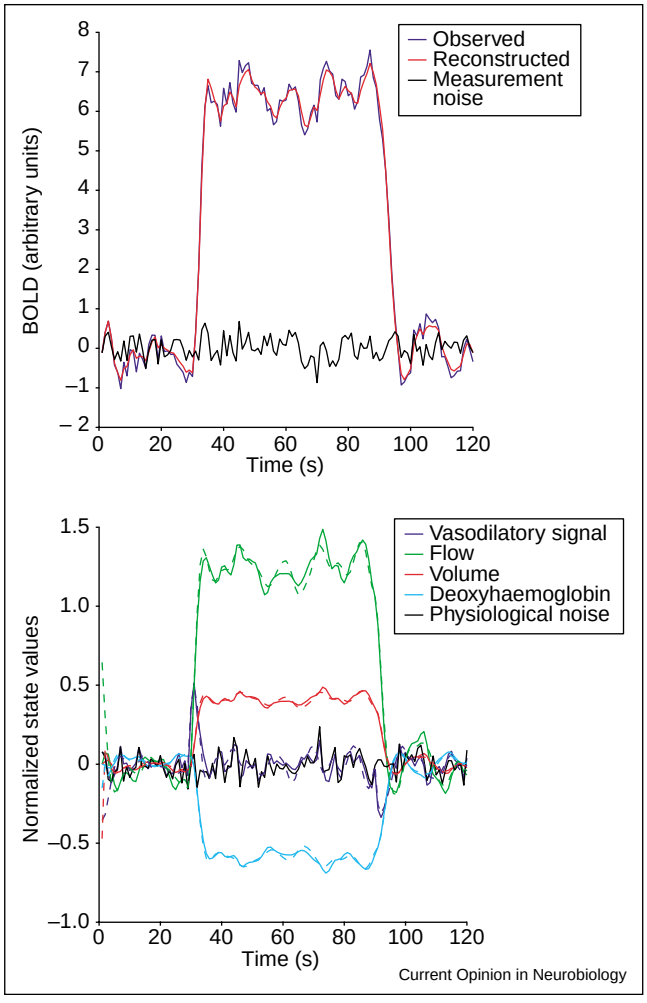
It should be noted that none of the biophysical models discussed in this section specifies precisely what is meant by neural activity; therefore, these models cannot tell us what aspect of neural information processing is reflected by the BOLD signal. Neural information processing within a given cortical unit can be described along many different dimensions, and the relationship between a neurophysiological process and the resulting BOLD response can be characterized on different scales, for example, local field potentials versus spiking activity, excitatory versus inhibitory postsynaptic potentials or different types of receptor at synapses.

Sophisticated animal studies that combine multi-electrode recordings with fMRI [23,24••] or with optical imaging techniques [14•,15] have started to address these issues. The next step is to transform the current biophysical models of the BOLD response into comprehensive forward models with parameters at the neural level, thereby modelling the whole causal chain from external stimuli, via induced neural dynamics, to observed BOLD responses. Such models must be parameterized in a neurophysiologically meaningful, yet parsimonious and estimable fashion. DCM [3••], as we discuss below, is a first step in this direction.

Models of functional integration: effective connectivity

Integration within distributed neural systems is usually best understood in terms of 'effective connectivity': that

Figure 2



Reconstruction of a blood oxygen level dependent (BOLD) signal from estimated states. The figure demonstrates how a BOLD signal (top, blue line) generated from simulated haemodynamic state trajectories (bottom, unbroken lines) can be reconstructed (top, red line) from the estimated states (bottom, broken lines), despite the presence of both physiological noise (bottom, black line) and measurement noise (top, black line). This example used the model by Riera *et al*. [17••] with an additional Kalman smoothing step.

is, the influence that one neural system exerts over another. Aertsen and Preißl [25] have proposed that ''effective connectivity should be understood as the experiment- and time-dependent, simplest possible circuit diagram that would replicate the observed timing relationships between the recorded neurons''. This explanation relates to two important points: first, effective connectivity is dynamic and context-dependent; and second, it depends on a causal model of the neural interactions. Classical estimation procedures, used in functional neuroimaging, were based initially on variants of linear regression models, such as structural equation modelling [26,27]. Below, we briefly review current developments that have a focus on multivariate autoregressive (MAR) models and dynamic causal models.

Multivariate autoregressive models

Autoregressive models of fMRI data are usually not concerned with causality in a biophysical sense — that is, how an observed BOLD series results from underlying neural processes; instead, they address the temporal aspect of causality in a BOLD time series, focusing on the causal dependence of the present on the past: each data point of a time series is explained as a linear combination of past data points. This approach contrasts with regression-based models of effective connectivity in which the time series can be permuted without changing the results. MAR models extend the autoregressive approach to multiple brain regions, modelling the vector of regional BOLD signals at time t ($\mathbf{y}_t$) as a linear combination of p past data vectors, whose contributions are weighted by the parameter matrices A_i, plus an error term e_t:

$$y_t = \sum_{i=1}^{p} y_{t-i} \mathrm{A}_i + e_t \qquad (5)$$

MAR models contain directed influences among a set of regions whose causal interactions, expressed at the BOLD level, are inferred via their mutual predictability from past time points. Although MAR modelling is an established statistical technique, specific implementations for fMRI have been suggested only very recently. Harrison *et al*. [28•] have presented a MAR model that allows for bilinear variables representing modulatory effects on connections and uses a Bayesian parameter estimation scheme suggested by Penny and Roberts [29]. This Bayesian scheme also determines the optimal model order, that is, the number of past time points (p) to be considered by the model.

A complementary MAR approach, based on the idea of 'Granger causality' [30], has been proposed by Goebel *et al*. [31•]. These researchers computed whole-brain connectivity maps by evaluating voxel-specific two-dimensional MAR models of the interactions between the current voxel and a reference voxel and introduced a statistical framework for distinguishing different types of interaction.

A logical extension of MAR models is to augment them with a biophysical forward model to enable inferences about neural parameters. So far, this type of model has been introduced only for electroencephalographic data [32]. For fMRI data, DCM is so far the only approach that marries biophysical and functional integration models.

Dynamic causal modelling

The general idea behind DCM is to construct a reasonably realistic neuronal model of interacting cortical

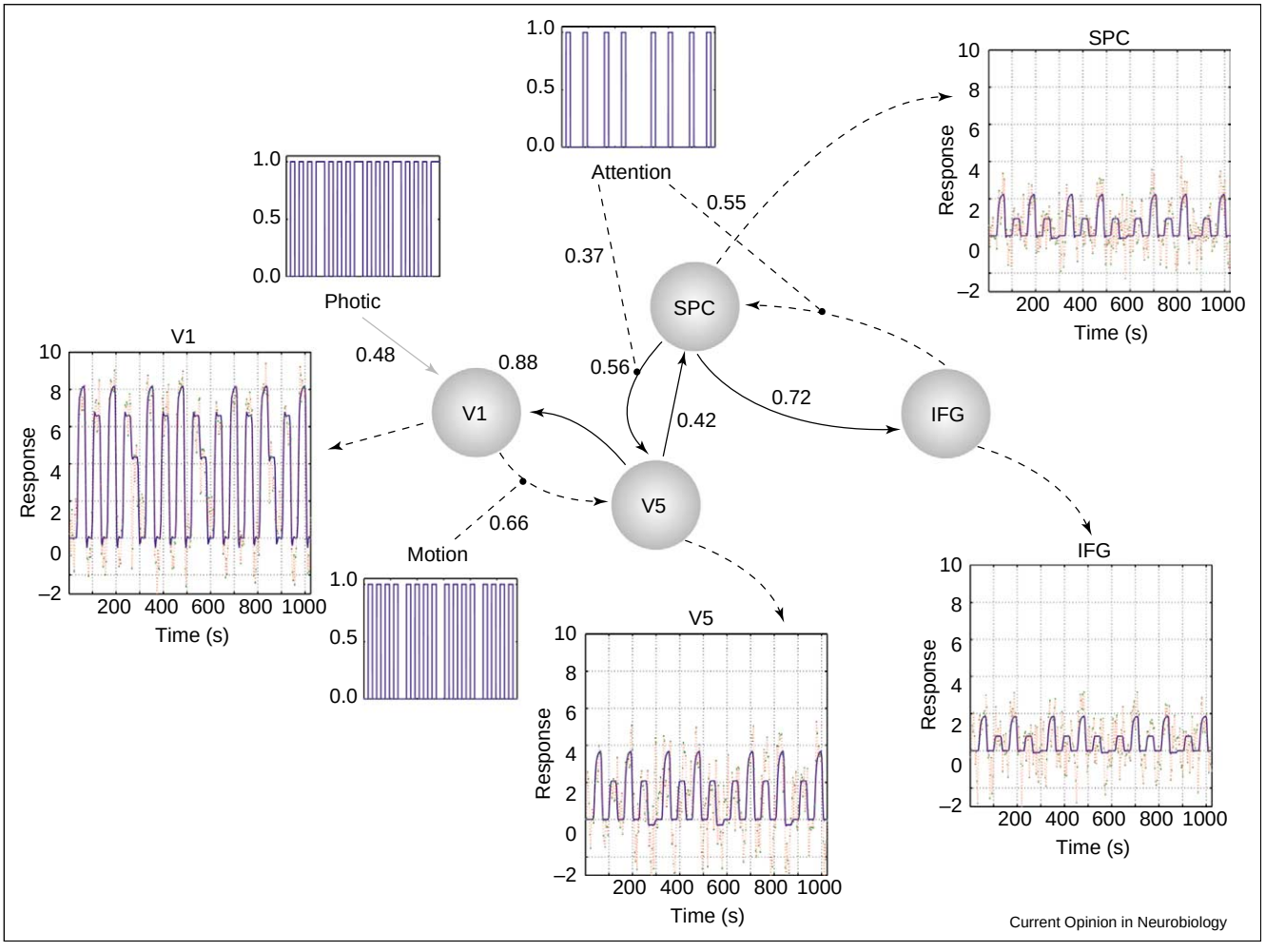
regions with neurophysiologically meaningful parameters. These parameters are estimated such that the predicted BOLD time series, which results from converting the neural dynamics into haemodynamics, corresponds as closely as possible to the observed BOLD series [3••]. In DCM, neural dynamics in several regions (represented by a neural state vector **z** with one state per region) are driven by experimentally designed inputs that enter the model in two distinct ways: they can elicit responses through direct influences on specific anatomical nodes (e.g. evoked responses in early sensory cortices) or they can modulate the coupling among nodes (e.g. during learning or attention). DCM models the change in neural states as a nonlinear function of the states (z), the inputs (u) and the neural parameters (θ^n):

$$\dot{z} = F(z, u, \theta^n) \tag{6}$$

The parameters are the connectivity matrices, $\theta^n = \{A,B,C\}$, that define the functional architecture and interactions among brain regions at a neuronal level. The bilinear approximation of Equation 6 is given by:

$$\dot{z} = Az + \sum u_j B^j z + Cu \tag{7}$$

Figure 3



DCM analysis of a single subject fMRI data set on attention to visual motion. The fMRI data were from a study in which subjects viewed identical stimuli (radially moving dots) under different attentional manipulations of the task (detection of velocity changes) [26]. Only those conditional estimates for which there was at least 90% confidence that they exceeded the chosen threshold of 0.17 Hz are shown alongside their connections (corresponding to neural transients with a half-life shorter than 4 seconds). The shown values result from a re-analysis with the current developer version of SPM2 (May 2004) and therefore marginally diverge from those reported previously [3••]. The temporal structure of the inputs is shown by box-car plots (blue). Note that motion and attention exert bilinear effects: motion modulates the connection from V1 to the motion-sensitive area V5, whereas attention modulates the backward connections from the inferior frontal gyrus (IFG) to the superior parietal cortex (SPC) and from SPC to V5. Dashed arrows connecting regions represent significant bilinear effects in the absence of a significant intrinsic coupling. Fitted responses that are based upon the conditional estimates and the adjusted data are shown in the panels connected to the areas by dotted lines.

in which coupling parameters correspond to partial derivatives of F:

$$A = \frac{\partial F}{\partial z} = \frac{\partial \dot{z}}{\partial z}$$
$$B^j = \frac{\partial^2 F}{\partial z \partial u_j} = \frac{\partial}{\partial u_j}\frac{\partial \dot{z}}{\partial z} \quad (8)$$
$$C = \frac{\partial F}{\partial u}$$

The matrix A represents the effective connectivity among the regions in the absence of modulatory input, the matrices B^j encode the change in effective connectivity induced by the jth input u_j, and C embodies the strength of direct influences of inputs on neuronal activity.

DCM combines this neural model with the biophysical forward model of Friston [13], which describes how neuronal activity translates into a BOLD response (Figure 1). This enables the parameters and time constants of the neuronal model to be estimated from measured data, by using a fully Bayesian approach with empirical priors for the biophysical parameters and conservative shrinkage priors for the coupling parameters. The posterior distributions of the parameter estimates can then be used to test hypotheses about the size and nature of the modelled effects. Usually, these hypotheses concern context-dependent changes in coupling that are represented by the bilinear terms of the model.

For example, applications of DCM have addressed the modulatory effects of object category [33] and attention to motion [3••] (see also Figure 3) on connections in the visual system. If there is uncertainty about which connections should be included in a model, or if competing hypotheses (represented by different DCMs) require comparison, a Bayesian model selection procedure can be used to find the DCM that shows an optimal balance between model fit and model complexity [34].

Conclusions

As a complement to existing models of 'where' evoked brain responses are expressed, current effort is being invested in developing models of 'how' neuronal responses are caused. Here, we have reviewed several models that address this causality in different ways. A promising strategy is to use comprehensive forward models with meaningful neurophysiological parameters that link experimental manipulations, via induced neural dynamics, to observed BOLD responses. We expect that such models will greatly enhance our ability to investigate and to understand the neural systems that mediate specific cognitive processes.

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