NeuroImage 125 (2016) 556–570

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

A hemodynamic model for layered BOLD signals

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ARTICLE INFO

Article history:
Received 29 April 2015
Accepted 10 October 2015
Available online 17 October 2015

Keywords:
fMRI
Cortical layers
Dynamic causal modeling
Bayesian model comparison
Predictive coding

ABSTRACT

High-resolution blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI) at the sub-millimeter scale has become feasible with recent advances in MR technology. In principle, this would enable the study of layered cortical circuits, one of the fundaments of cortical computation. However, the spatial layout of cortical blood supply may become an important confound at such high resolution. In particular, venous blood draining back to the cortical surface perpendicularly to the layered structure is expected to influence the measured responses in different layers. Here, we present an extension of a hemodynamic model commonly used for analyzing fMRI data (in dynamic causal models or biophysical network models) that accounts for such blood draining effects by coupling local hemodynamics across layers. We illustrate the properties of the model and its inversion by a series of simulations and show that it successfully captures layered fMRI data obtained during a simple visual experiment. We conclude that for future studies of the dynamics of layered neuronal circuits with high-resolution fMRI, it will be pivotal to include effects of blood draining, particularly when trying to infer on the layer-specific connections in cortex — a theme of key relevance for brain disorders like schizophrenia and for theories of brain function such as predictive coding.

Introduction

Although only a few millimeters thin, the cerebral cortex is composed of microcircuits whose layered architecture plays a key role in cortical computation (Douglas and Martin, 2007; Heinzle et al., 2007; Bastos et al., 2012). Studying layer-specific computations non-invasively in humans would require two key ingredients: First, non-invasive high-resolution imaging to resolve cortical layers and, second, a modeling approach that explains the measured data as a function of neuronal interactions within and across layers.

Recent advances in high-field functional magnetic resonance imaging (fMRI) have made it feasible to measure blood oxygen level dependent (BOLD) signals from cortical structures with sub-millimeter resolution (Feinberg et al., 2010; Moeller et al., 2010; Poser et al., 2010; Heidemann et al., 2012). At this resolution both columnar architecture (Cheng et al., 2001; Yacoub et al., 2007; Yacoub et al., 2008) as well as cortical layers (Koopmans et al., 2010a; Polimeni et al., 2010; Koopmans et al., 2011; Olman et al., 2012) can be resolved. In rats, a highly specialized fMRI line-scanning method has been used to demonstrate that the layered pattern of temporal onsets of BOLD responses is in line with anatomical cortical connectivity (Yu et al., 2014).

Despite these encouraging technical developments, inferring on neural mechanisms at such high resolution with standard fMRI analysis procedures is complicated. This is due to fact that the strongest signals measured with fMRI depend on blood oxygenation mainly in venous compartments which are not evenly distributed over the cortical depth. Cortical blood supply is organized in a highly regular, layered fashion, similar to the neuroanatomical structure of cortex (Duvernoy et al., 1981; Weber et al., 2008). As illustrated in Fig. 1, arterial blood reaches the layers of cortex via diving arterioles that run perpendicular to cortex, passes the fine capillary bed within individual layers and flows back through ascending venules towards the pial surface (Duvernoy et al., 1981; Weber et al., 2008). This anatomical arrangement of blood flow has been modeled in detail (Boas et al., 2008; Reichold et al., 2009) and poses a fundamental problem for the analysis of layered BOLD activity since draining blood might affect the BOLD signal in lower (close to the white matter) and upper (close to the pial surface) layers differently. Standard hemodynamic models, like the "Balloon model" (Buxton et al., 1998) and subsequent extensions (Friston et al., 2000), assume that the measured BOLD response is driven

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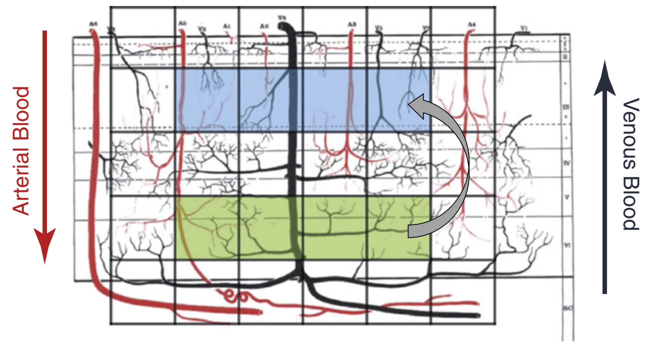
http://dx.doi.org/10.1016/j.neuroimage.2015.10.025
1053-8119/



$$\tau_u \frac{d\nu_u}{dt} = f_u - \nu_u^{\frac{1}{\alpha}} + \lambda_d \nu_l^*$$
$$\tau_u \frac{dq_u}{dt} = f_u \frac{1-(1-E_0)^{1/f_u}}{E_0} - \nu_u^{1/\alpha} \frac{q_u}{\nu_u} + \lambda_d q_l^*$$
$$\tau_l \frac{d\nu_l}{dt} = f_l - \nu_l^{\frac{1}{\alpha}}$$
$$\tau_l \frac{dq_l}{dt} = f_l \frac{1-(1-E_0)^{1/f_l}}{E_0} - \nu_l^{1/\alpha} \frac{q_l}{\nu_l}$$
$$\tau_d \frac{d\nu_l^*}{dt} = -\nu_l^* + (\nu_l - 1)$$
$$\tau_d \frac{dq_l^*}{dt} = -q_l^* + (q_l - 1)$$

Fig. 1. Illustration of blood draining model equations. Top: Schematic visualization of fMRI voxel grid overlaid on an illustration of the layered architecture of blood flow (Duvernoy et al., 1981; reproduced with permission). Arterioles (red) and venules (dark blue) travel perpendicular to the cortical layers. Arrows indicate the directions of arterial and venous blood flow. Shaded voxels correspond to upper (blue) and lower (green) regions of interest whose BOLD signals interact through blood draining effects (gray arrow). Bottom: The local balloon model equations and the newly introduced blood draining (gray) effects.

by changes in relative blood volume and deoxyhemoglobin concentration in the venous blood. However, a fundamental assumption of this model is that the BOLD signal only depends on local neuronal activity. While this assumption seems adequate for conventional fMRI data analyses, it is problematic for high-resolution laminar fMRI since venous blood from deeper layers contributes to the BOLD signal in upper layers as it flows towards the pial surface.

In this work, we address this problem by introducing a novel extension to an established hemodynamic model (Buxton et al., 1998; Friston et al., 2000; Stephan et al., 2007). This extended model takes into account effects of cortical blood flow across layers and considers three different contributions to layer-wise BOLD measures: layer-specific neuronal inputs (e.g., synaptic inputs from remote regions), local neuronal connections across layers, and local blood flow effects across layers. To this end, the model incorporates distinct representations of neuronal connectivity across layers and a phenomenological description of venous blood flow effects perpendicular to the cortical surface; the latter allows BOLD activity in lower layers to contribute to the measured BOLD signal in upper layers via blood inflow, referred to as "blood draining" (BD) for the remainder of the paper. In order to evaluate the utility of this layered hemodynamic model, we use Bayesian model inversion and selection, implemented within the framework of dynamic causal modeling (DCM; Friston et al., 2003).

To prevent any misunderstandings, we would like to emphasize that this study does not present a model of layered BOLD measurements which strives for complete interpretability in physical and physiological terms, as recent models of non-layered BOLD (e.g., Havlicek et al., 2015). Notably, this study pursues a more modest ambition: it introduces a phenomenological description of blood draining effects across layers and examines (i) to what degree this relatively simple model can capture main features of layer-wise BOLD and (ii) the feasibility of model inversion, i.e., how well model parameters and structure can be identified from empirical data. This represents a first step towards establishing a hemodynamic component for models of effective connectivity which can operate on layer-wise BOLD data. Such future models are needed to test predictions from influential theories like predictive coding (Rao and Ballard, 1999; Friston, 2005) which postulate that supragranular and infragranular cortical layers convey different signals via their connections. It is possible that more ambitious and sophisticated biophysical models of blood flow across layers will be beneficial for this endeavor; however, this is an empirical question which will have to be adjudicated by model comparison in future work (see Discussion section).

Following the theoretical derivation of the model, we test the face validity and performance of the proposed model using both simulations and empirical analyses. First, we tested whether adding blood draining from lower to upper layers would reproduce key features of layer-specific BOLD signals as obtained from high-resolution fMRI in humans (e.g. in Siero et al., 2011). Second, we examined whether the model was capable of distinguishing between effects of neuronal connectivity and blood draining across layers, respectively. Third, we illustrate what effect the inclusion or exclusion of blood draining has on inferring the layered input structure from fMRI data. Fourth, we asked how well the parameters of the model could be inferred from simulated data where "ground truth" is known. Finally, we applied the model to fMRI data from a visual paradigm. Here, we used Bayesian model selection (BMS) to investigate which model provided a more convincing explanation for the observed data — the proposed model with blood draining effects across layers or an alternative model that allowed for between-layer differences in local hemodynamics.

Methods

In the following, we describe our novel model for layered hemodynamic responses. Starting from the standard hemodynamic model in DCM of fMRI — an extension of the Balloon model by Buxton et al. (1998) — we outline in detail the assumptions made in order to introduce hemodynamic coupling, from lower to upper layers.

The standard hemodynamic model in DCM

The standard hemodynamic model in DCM has been described in detail in previous work (Stephan et al., 2007). In this model, neurovascular coupling equations relate local changes in blood flow f to local changes in the neuronal activity x:

$$\frac{ds}{dt} = x - \kappa s - \gamma(f-1) \qquad \frac{df}{dt} = s, \tag{1}$$

where s is a vasodilatory signal, and f represents blood flow. x denotes the time course of neural activity, κ is the rate constant of the vasodilatory signal decay and γ specifies the rate constant for autoregulatory feedback by blood flow. These (and all further) hemodynamic states below are time-dependent and normalized to their values at rest. The changes in blood flow lead to local changes in relative blood volume v and in q, deoxygenated hemoglobin (deoxyHB) content of the venous blood. The dynamics of these two quantities are modeled using the Balloon model of Buxton et al. (1998).

$$\tau \frac{dv}{dt} = f - v^{\frac{1}{\alpha}} \qquad \tau \frac{dq}{dt} = f \frac{1-(1-E_0)^{1/f}}{E_0} - v^{1/\alpha} \frac{q}{v}. \tag{2}$$