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On the importance of modeling fMRI transients when estimating effective connectivity: A dynamic causal modeling study using ASL data

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ABSTRACT

Effective connectivity is commonly assessed using blood oxygenation level-dependent (BOLD) signals. In (Havlicek et al., 2015), we presented a novel, physiologically informed dynamic causal model (P-DCM) that extends current generative models. We demonstrated the improvements afforded by P-DCM in terms of the ability to model commonly observed neuronal and vascular transients in single regions. Here, we assess the ability of the novel and previous DCM variants to estimate effective connectivity among a network of five ROIs driven by a visuo-motor task. We demonstrate that connectivity estimates depend sensitively on the DCM used, due to differences in the modeling of hemodynamic response transients; such as the post-stimulus undershoot or adaptation during stimulation. In addition, using a novel DCM for arterial spin labeling (ASL) fMRI that measures BOLD and CBF signals simultaneously, we confirmed our findings (by using the BOLD data alone and in conjunction with CBF). We show that P-DCM provides better estimates of effective connectivity, regardless of whether it is applied to BOLD data alone or to ASL time-series, and that all new aspects of P-DCM (i.e. neuronal, neurovascular, hemodynamic components) constitute an improvement compared to those in the previous DCM variants. In summary, (i) accurate modeling of fMRI response transients is crucial to obtain valid effective connectivity estimates and (ii) any additional hemodynamic data, such as provided by ASL, increases the ability to disambiguate neuronal and vascular effects present in the BOLD signal.

Introduction

Functional neuroimaging is widely used to investigate functional integration in the human brain (Friston, 2011), which is commonly characterized by functional or effective connectivity (Friston, 1994). While functional connectivity describes statistical dependencies among brain activations at the level of observed data, effective connectivity is defined as causal influence that (inferred) neuronal systems exert over another. Thus, determining effective connectivity requires a physically and physiologically motivated (causal) model linking local activation and distributed interactions among neuronal responses to the measured data. The requisite generative models have been proposed for several noninvasive neuroimaging modalities, such as functional magnetic resonance imaging (fMRI) (Friston et al., 2003) and electro- and magneto- encephalography (EEG and MEG) (David et al., 2006; Valdes Sosa et al., 2009) or functional near-infrared spectroscopy (fNIRS) (Tak et al., 2015).

A prominent modeling framework for estimating effective connectivity from BOLD data is dynamic causal modeling (DCM) (Friston et al., 2003). DCM has been extensively used both in healthy subjects and patient studies (see e.g. review by Seghier (2010) and references therein). The generative model of DCM for fMRI data comprises: (i) a neuronal model, in which neuronal activity in one region causes changes in its own activity (via *intrinsic* connections) and neuronal activity in distal regions (via long-range *extrinsic* connections); (ii) a model of neurovascular coupling (NVC) that links region-specific neuronal activity to local changes in cerebral blood flow (CBF); (iii) a hemodynamic model that transforms blood inflow to changes in cerebral blood volume (CBV) and blood oxygenation; and finally (iv) a physical model translating these changes into the measured BOLD signal.

To estimate effective connectivity from fMRI data using DCM, testable hypotheses about how brain areas are connected and how they change with tasks are required. These hypotheses entail assumptions

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about the connectivity architecture, and how it is affected by experimental manipulations (Stephan et al., 2010). Then, using Bayesian inference, DCM fits the BOLD data by tuning the connectivity and hemodynamic parameters so that the discrepancy between modeled and observed fMRI time-courses is minimized under complexity constraints (Penny et al., 2010). This means that the aim of DCM is not only to provide accurate fits to observed data, but also to account for the model complexity, such that more complex models are automatically penalized. The ensuing Bayesian approach enables one not only to estimate model parameters, but also to compare different models in terms of their evidence; i.e. accuracy minus complexity (Penny et al., 2010).

Although Bayesian model selection (BMS) is typically used to choose between different neuronal architectures, it can also be used to identify the most likely physiological or physical mechanism underlying any component of the generative model ((i-iv) above). Examples of this sort of Bayesian model comparison can be found in Stephan et al. (2008, 2007), who compared linear vs. nonlinear neuronal connectivity models and several forms of BOLD generation equations. Furthermore, Marreiros et al. (2008) compared single-state vs. two-state neuronal models, while Rosa et al. (2011) compared different types of electro-physiological models of NVC, using simultaneous EEG and fMRI recordings.

Recently, we introduced a physiologically informed generative model for BOLD DCM (Havlicek et al., 2015), called P-DCM, which extended and updated the standard model used in DCM for fMRI (S-DCM) (Friston et al., 2003) and two-state extension (2S-DCM) (Marreiros et al., 2008) in four key aspects (see also Fig. 1):

1. At the neuronal level, we model local neuronal activity as interacting excitatory and inhibitory (E-I) neuronal populations, allowing fine-tuning of adaptive responses during stimulation and post-stimulation periods – of the sort seen in electrophysiological data. Different brain areas are effectively connected via positive and negative long-range extrinsic connections among excitatory populations.
2. The neurovascular coupling (NVC) – CBF changes evoked by changes in neuronal activity – is strictly feedforward. That is, CBF represents a smoothed version of the neuronal activity.
3. In the hemodynamic model, CBV can be uncoupled from CBF during transient periods due to viscoelastic properties of the post-capillary blood compartments (as in the original balloon model (Buxton et al., 1998)).
4. Finally, sequence-specific parameters of the BOLD signal equation were provided for both GE and SE MRI sequences and for different magnetic field strengths.

In our previous paper (Havlicek et al., 2015), we demonstrated that these extensions allow for a more accurate modeling of single-ROI BOLD responses compared to S-DCM and 2S-DCM, while simultaneously providing higher statistical evidence. This was, in particular, due to the more accurate characterization of the neuronal and vascular origins of the BOLD signal transients; such as response adaptation and post-stimulus undershoot. In the current paper, we evaluate the consequences of model differences when modeling effective connectivity between regions.

The separation of neuronal from hemodynamic parameters in any variant of DCM can be confounded by the fact that the BOLD signal results from a complex interplay between region-specific CBF, CBV and cerebral metabolic rate of oxygen metabolism ($CMRO_2$). That is, even for the same neuronal activity, the BOLD signal time-course can vary between different subjects, brain areas and even voxels in the same brain area due to differences in NVC and CBF-CBV coupling (e.g. see Handwerker et al. (2004), Renvall et al. (2014)). This means that vascular transients can mask or distort neuronal transients. Therefore, any additional experimental data that allows disentangling neuronal and ensuing vascular transients has the potential to increase the validity of the connectivity estimates offered by DCM.

In principle, DCM can also be applied to other fMRI acquisition modalities, such as arterial spin labeling (ASL) (Liu and Brown, 2007), which additionally measures cerebral blood flow (CBF), or vascular occupancy (VASO) (Huber et al., 2014; Lu et al., 2003), which measures cerebral blood volume (CBV). In fact, when considering the causal chain of physiological processes that follows neuronal activation, CBF and CBV signals are more closely related to the neuronal signal

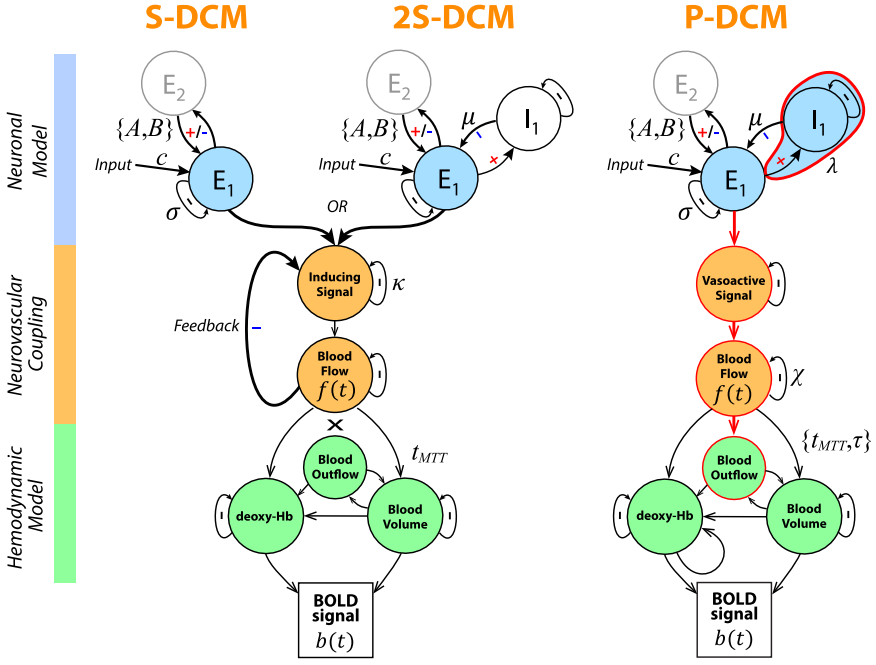

Fig. 1. Scheme illustrating the organization of generative models entailed by S-DCM, 2S-DCM and P-DCM. Three main parts of the generative models; i.e. neuronal model, neurovascular coupling and hemodynamic model, are colored in blue, orange and green, respectively. Main differences in P-DCM with respect to S- and 2S-DCM (see Havlicek (2015)) are highlighted with red color, such as the adaptive part of the two state-neuronal model, feedforward NVC and CBF-CBV uncoupling modeled in the blood outflow. The parameters that are associated with optimization of specific model components during DCM analyzes are displayed.