

On the importance of modeling fMRI response transients for effective connectivity: a Dynamic causal modeling of ASL data

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Abstract

Effective connectivity is commonly assessed using the blood oxygenation level-dependent (BOLD) signal. In (Havlicek et al., 2015), we presented a novel, physiologically informed dynamic causal model (P-DCM) that extends current generative models with: a) an adaptive two-state neuronal model; b) a purely feedforward neurovascular coupling (NVC); and c) uncoupling between cerebral blood volume (CBV) and cerebral blood flow (CBF). We demonstrated the improvement afforded by P-DCM in relation to current models in terms of the ability to capture commonly observed neuronal and vascular transients in single regions. Here, we assess the ability of the novel and previous DCM models to estimate effective connectivity among a network of five ROIs driven by a visuo-motor task. Furthermore, we implement DCM for arterial spin labeling (ASL) fMRI that simultaneously measures both BOLD and CBF signals – therefore providing additional information about neurovascular coupling. Using experimental data acquired with ASL, it is shown that P-DCM is statistically superior to other models in estimating effective connectivity, regardless when applied to BOLD data alone or to combined BOLD/CBF time-series. In addition, we demonstrate that connectivity estimates depend sensitively on the DCM used. In other words, incorrect modeling of hemodynamic response transients, such as the post-stimulus undershoot or adaptation during stimulation, might result in spurious (e.g. inhibitory, feedback) connections between areas. Finally, we demonstrate the added benefits of using ASL data, especially under the physiologically informed generative model (P-DCM).

Keywords:

DCM, effective connectivity, ASL, BOLD signal, hemodynamic transients

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 used extensively 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 (that is, experiment- and time-dependent directed connectivity among different brain areas) from fMRI data using DCM, testable hypotheses about how brain areas are connected (and how connections change with task) are required. These hypotheses entail assumptions 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 (for a given set of connectivity

hypotheses) 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 Figure 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 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 the single-ROI BOLD response compared to S-DCM and 2S-DCM while simultaneously providing higher statistical evidence. This was, in particular, due to the characterization of the neuronal and vascular origins of BOLD signal transients, such as response adaptation and post-stimulus undershoot.

However, the separation of neuronal from hemodynamic parameters in any variant of DCM can be hampered by the fact that the BOLD signal results from a complex interplay between region-specific CBF, CBV and cerebral metabolic rate of oxygen metabolism (CMRO₂). 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 estimated neuronal transients. Thus, any additional experimental data that allows disentangling active neuronal and passive vascular transients has the potential to increase the validity of the inferences made 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 the current paper, we extend the DCM models, described above, for BOLD fMRI to model ASL signals, where we jointly model both CBF and BOLD responses to stimulus-induced neuronal activations. 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 compared to the BOLD signal. Since ASL simultaneously acquires BOLD signal and CBF, it affords the unique opportunity to compare connectivity estimates as a function of fMRI data (BOLD signal alone or BOLD signal together with CBF) and to evaluate the impact of physiological mechanisms embedded within different DCM variants (S-, 2S and P-DCM) on connectivity estimates. To the best of our knowledge, this is the first fMRI study systematically investigating the dependency of estimated effective connectivity on physiological assumptions of the generative model and on the type of fMRI data.

Materials and methods

Experimental data

Data acquisition and experimental task

MR images were acquired on 3T Siemens Prisma scanner (Siemens Medical Solutions, Erlangen, Germany) from five healthy subjects (right-handed females; age range: 24–31). The subjects gave informed consent prior to scanning, according to the guidelines of the local ethics committee of the Faculty of Psychology & Neuroscience, Maastricht University. Following a localizer scan, MPRAGE T1-weighted anatomical images with 1 mm isotropic voxel size were acquired. Functional CBF and BOLD signals were measured using a PICORE-Q2TIPS ASL (Wong et al., 1997) sequence with the following parameters: TR = 2200 ms; TE = 17 ms; flip-angle = 80°; FOV = 256×256 mm²; voxel size = 3×3×3 mm³; TI1 = 900 ms; TI2 = 1600 ms. Ten oblique slices covering early visual and motor areas were acquired in descending order. A descending order of slice acquisition was chosen to acquire the motor cortex first, which is known to have slightly shorter arterial arrival time (~800 ms) compared to the visual cortex (~900 ms) (Donahue et al., 2014). The tag was 10 cm in width positioned at a 1 cm gap inferior to the imaging slices.

Each subject performed 4 runs (each 382 TRs long) of a visuo-motor task consisting of 4 conditions arranged in blocks interspersed with resting fixation baseline periods (see Figure 3A). During the entire experiment, subjects fixated a white cross in the middle of the projected screen. The grey background was isoluminant with a 150° checkerboard wedge (black and white) stimulus presented either on the left or right visual field. During the two ipsilateral conditions (either left or right), subjects were instructed to respond to the visual stimulation (appearing for 200 ms) with sequential ipsilateral finger tapping (thumb-index, thumb-middle and thumb-index finger). During the two contralateral conditions (either left or right), subjects were instructed to respond to visual stimulation with contralateral hand. Ipsilateral and contralateral conditions were indicated by a color change of the white fixation cross – blue for the ipsilateral conditions and red for the contralateral conditions. During the resting periods, subjects were instructed to

continue fixating the white cross. Visual stimuli for each condition were organized into 14 sec blocks (each included 11 events with randomized ISI lasting at least 1 sec) followed by 26 sec resting period. The initial and final rest conditions were 37 and 38 sec in duration, respectively. Blocks of ipsilateral and contralateral conditions (20 blocks in each run) were pseudo-randomized within and between runs.

Preprocessing and ROI selection

The data were preprocessed using SPM12 (R6470) package (<http://www.fil.ion.ucl.ac.uk/spm>). Functional data from each subject were realigned to the first volume of the first run to correct for head motion. This was performed separately for control and labeled images obtained with the ASL sequence. The mean labeled image was then coregistered to the mean control image and the transformation matrix was applied to all the labeled images. The mean of the realigned functional time-series was coregistered to the anatomical image and the latter was used to segment gray matter, white matter and CSF. The spatial transformation parameters from the segmentation were used to spatially normalize the anatomical and functional images into MNI space, and the latter were further smoothed with a 4 mm FWHM isotropic Gaussian kernel.

The data were then modeled using a general linear model (GLM) that included the tasks (two ipsilateral and two contralateral conditions) in all four runs. In particular, a GLM of ASL signal was constructed to reflect the simultaneous contributions of CBF and BOLD signal changes (see Figure 2A, for details on this ASL model see (Mumford et al., 2006)):

$$y = \beta_0 + x_{CBF_0} \cdot \beta_1 + x_{BOLD} \cdot \beta_2 + x_{CBF_0} \cdot x_{BOLD} \cdot \beta_3 + H_0 \cdot \gamma_{1:K} + \varepsilon, \quad (1)$$

where y is a vector that contains the voxels' time-courses. Besides the standard intercept representing the baseline of static MR signal (β_0), we included an explanatory variable representing baseline CBF (x_{CBF_0}) that simulates the alternation of tagged and control signals ($x_{CBF_0}(t) = (-1)^t$; i.e. -1 associated with tagged time points and $+1$ with control time points). The parameter β_1 is then proportional to the tag and control MRI signal magnitude difference and, hence, is proportional to the amount of tagged blood delivered to the local tissue. Each task

condition was modeled with two explanatory variables: The first predictor represents the BOLD response (x_{BOLD}) generated by convolution of the stimulus function with a double-gamma hemodynamic response function. As in previous studies (Hernandez-Garcia et al., 2010; Mumford et al., 2006), the second predictor represents CBF response that was approximated using the same BOLD response model (x_{BOLD}) but modulated by CBF baseline (x_{CBF_0}); i.e. yielding an interaction term $x_{CBF_0} \cdot x_{BOLD}$. The parameters β_2 and β_3 are therefore proportional to the relative contributions of BOLD and CBF responses to the ASL signal¹. Additionally, low-frequency signal drifts (with cutoff period of 180 sec) were modeled in matrix H_0 using discrete cosine transform basis functions. The error vector $\varepsilon = \mathcal{N}(0, \sigma^2 V)$ models colored noise using a first-order autoregressive model with intrinsic autocorrelation matrix V . This GLM was estimated using standard estimation routines in SPM12 software. Contrast images were created for each condition, assuming ('global') conjunction of CBF and BOLD model estimates (Friston et al., 2005). The statistical threshold was set at $p < 0.05$, corrected for family-wise errors (FWE).

Finally, five regions of interests (ROIs) were defined from significant responses to the visuo-motor task in both CBF and the BOLD signal. In particular, ROIs centered in left and right V1, left and right M1 and SMA were selected. Voxel contributions from left and right SMA were considered together as their time-courses looked almost identical. Additionally, regions labeled as V1 and M1 most likely include partial contributions from V2 and S1 and PMC, respectively. The ASL signals (corrected for the low frequency fluctuations; cut-off = 1/180 sec) were extracted from a sphere (radius 10 mm) centered at the peak T-value within each contrast image, and only voxels from grey matter (considering intersection of contrast images with the grey matter mask) were included. BOLD signals were derived from the ASL time-series using surround averaging (Mumford et al., 2006). Finally, the signal baselines of the BOLD timeseries were identified from the initial and the last resting periods of each run and adjusted to zero².

¹ Note that we initially also included second and third temporal derivatives of the hemodynamic response to account for variability in response shape between brain areas in both CBF and BOLD signal component. However, we did not observe any significant differences in activation locations; therefore, we only report the results using the basic model.

² This is an important step if one wants to compare different DCMs, as these models are designed to model activity changes with respect to resting baseline.

Dynamic causal modeling

In this paper, we evaluate three DCM variants: standard, two-state and physiologically-informed DCM (S-, 2S- and P-DCM, respectively; please see (Havlicek et al., 2015) and Supplementary Material 1 for details). In the following, we also introduce DCM for ASL that allows one to perform model comparison for BOLD data alone or BOLD signal together with CBF. Hereafter, by stating “BOLD-data-alone”, we refer to the analysis based only on the BOLD signal derived from ASL data. In contrast, by stating “ASL-data”, we refer to the analysis performed directly on ASL data that includes both CBF and BOLD signal changes.

DCM of arterial spin labeling

ASL is an MRI approach that simultaneously measures CBF and BOLD signals (see Figure 2A). Thus, ASL – in contrast to BOLD signal alone – may provide additional information for studying neuronal dynamics and effective connectivity. We propose a full generative model of ASL data that extends the standard applications of DCMs for fMRI. In this model, we combine the abobe described GLM model of ASL signal (Hernandez-Garcia et al., 2010; Mumford et al., 2006; Woolrich et al., 2006), which has been shown to have reduced artifacts as compared to interpolation approaches, with physiological variables defined in hemodynamic models (Havlicek et al. 2015):

$$y_{ASL}(t) = l_0 + l_1 \cdot x_{CBF_0}(t) + b(t) + l_2 \cdot x_{CBF_0}(t) \cdot (f(t) - 1) + \varepsilon(t). \quad (1)$$

As in the ASL-GLM (see equation (1)), we model both MR and CBF signal baselines, whose effects are scaled by parameters l_0 and l_1 , respectively. The CBF baseline has the same form as in ASL-GLM. In contrast to ASL-GLM, the BOLD contribution in the ASL signal is modeled using BOLD signal generated by the hemodynamic model $b(t)$. Therefore, changes in the BOLD signal are caused by the neuronal signal via input and connectivity parameters (see below). The CBF contribution in the ASL signal is modeled directly using the output of neurovascular coupling (NVC); i.e., the blood flow state ($f(t) - 1$) that is driven by the same neuronal activity as the BOLD signal – and is modulated by the CBF baseline due to the alternating tag and control image acquisition in ASL. Since the contribution of CBF to the ASL signal varies as a function of MR acquisition parameters, the CBF component is additionally scaled by the parameter l_2 . Note for l_1 and l_2 values equal zero – that is no blood flow tagging and therefore no direct contribution of CBF to the measured signal – we obtain the standard BOLD model of DCM. In line with GLM (Friston et al., 1995), the error term $\varepsilon = \mathcal{N}(0, C_\varepsilon)$ models serially correlated noise by assuming an AR(1) plus white noise process encoded in the inverse covariance matrix $C_\varepsilon^{-1} = \sum \lambda_i Q_i$, where Q_i are known precision basis functions scaled by hyperparameters λ_i . An illustration of the ASL model for DCM is provided in Figure 2B.

Figure 2

DCM analysis

We chose visuo-motor experiment as an exemplary data-set to compare different DCM models and their physiological components. Note that the main aim of this paper is not to evaluate the best structural connectivity model for this task, but rather to identify relevant parts of neuronal and hemodynamic models and their impact on connectivity estimates. That is, the experimental data serve merely as an illustration on how different DCM variants can account for neuronal and hemodynamic transients and on the influence of these transients on connectivity estimates. Therefore, we chose only a single candidate of connectivity structure that is common for all different DCMs that are being compared on the basis of their physiological mechanisms (see below). This connectivity model was selected over other plausible candidates based on initial BMS procedure; i.e. it represents connectivity structure that is well supported by the

experimental data and all three DCMs (S-DCM, 2S-DCM and P-DCM). Additional details about this pre-selection are provided in the Discussion section.

Connectivity structure specification

A network of five brain regions as illustrated in Figure 3A was considered in our DCM analyses. For all DCMs, we used the bilinear form of neuronal connectivity model³:

$$\frac{dx_E(t)}{dt} = (A + \sum_{m=1}^M B^{(m)} \cdot u_m(t)) \cdot x_E(t) + C \cdot u(t). \quad (3)$$

The network received driving inputs to the left or right V1, representing stimulations presented on the right or left visual fields, respectively (depicted in Figure 3 with red and blue colors). The strengths of these inputs were encoded in matrix C. Since we are interested in evaluating connectivity changes only between ipsilateral and contralateral conditions (see Discussion section for justification), we can describe an average connectivity during the ipsilateral condition as the endogenous connectivity encoded in matrix A. The regions are fully interconnected (depicted with black arrows) except for the two inter-hemispheric connections between right V1 and left M1 and between left V1 and right M1, which were excluded in both directions. Next, to introduce changes in endogenous connectivity during contralateral conditions, we assume that all extrinsic connections in matrix A, except connections between left and right V1, can be modulated (depicted with green and orange dots). Note that exclusion of modulatory connection weights between left and right V1 is strictly based on prior BMS, where we compared models with and without these connections (further explained in Discussion section). Modulatory connection weights were encoded in B matrix with two levels ($M = 2$): $B^{(1)}$ for visual stimulation in the left visual field and $B^{(2)}$ for visual stimulation in the right visual field. Therefore, the matrices B express the additive contextual changes in connectivity due to switching motor output with respect to lateralized visual input. Modulation of extrinsic connections in matrix A by B matrices was controlled via modulatory inputs represented by simple box-car functions that are ON during stimulation intervals (see Figure 3). This means that

³ Note that Equation (3) is displayed here in its general form, which lacks contribution of inhibitory neuronal populations that are modeled in 2S-DCM and P-DCM. For a complete description of these models see Table S1.1 in the Supplementary Material 1.

average connectivity during contralateral conditions is given by $A + \sum_{m=1}^2 B^{(m)}$. Next to the connectivity parameters, some region-specific parameters of hemodynamic models are optimized during the model inversion as well – their specification is provided in the Supplementary Material 1.

Figure 3

Model inversion

All models (described in detail below) were inverted using Variational Laplace (VL), implemented for DCM in SPM12 (update R6470, (Friston et al., 2007)). This iteratively updates the moments of a conditional density over model parameters $q(\theta) = \mathcal{N}(\eta, C)$, to maximize a lower bound on the log model evidence:

$$\log p(y|m) = F(m) + KL(q(\theta)||p(\theta|y, m)). \quad (4)$$

The model evidence is the probability of obtaining observed data, y , given model, m , and is the cornerstone of Bayesian model selection (BMS). The first term, $F(m)$, is the lower bound (also called the negative free energy) and the second term represents the Kullback-Leibler (KL) divergence between the approximate posterior density, $q(\theta)$, and the true posterior, $p(\theta|y, m)$. During the model inversion, the KL divergence is minimized and $F(m)$ becomes an approximation to the model log-evidence.

Model inversions were performed individually for each subject and functional run, and separately for BOLD-data-alone and for ASL-data using the same prior distributions over model parameters (see Table S1.2). They all converged within 128 iterations.

Analysis of the dependency of connectivity on model and data

To determine the dependency of connectivity strengths on the physiological assumptions of the three DCM models, we employed conditional parameter estimates (i.e. conditional means and (co)variances) to calculate group connectivity patterns provided by S-DCM, 2S-DCM and P-DCM. In particular, these were obtained using Bayesian model and parameter averaging (BMA and BPA) of extrinsic and intrinsic connectivity parameters, under FFX assumptions (Penny, 2012). Differences in averaged connectivity estimates were assessed between models for both ipsilateral and contralateral conditions.

To assess the similarity of the group connectivity estimates between BOLD and ASL-data for each DCM model, Pearson correlation coefficients were calculated between the average extrinsic connection strengths of BOLD-data-alone and ASL-data, respectively. Furthermore, to evaluate which data (BOLD-data-alone or ASL) provides more informed constraints on the underlying effective connectivity, we used the conditional posterior estimates of the three DCM models. Note that ASL-DCM cannot be directly compared with BOLD-DCM using BMS in terms of model log-evidence, because these two models are not fitted to the same data. However, posterior distributions of model parameters can be compared in terms of KL divergence between prior and posterior distributions. This KL divergence represents the part of model evidence that is directly related to model complexity (Penny, 2012). Hypothetically, one expects the prior and posterior distributions to diverge in a non-trivial fashion if there is sufficient information in the observed data to support the implicit increase in complexity. We restricted ourselves to prior and posterior distributions of extrinsic connectivity parameters – these are present in all DCMs for both BOLD-data-alone and ASL-data. Additionally, to address the same question from a different perspective, we used the KL divergence to calculate the number of effectively estimated parameters (NEP) (Penny, 2012) and to relate it to the actual number of free parameters (there are 44 parameters corresponding to the weights of extrinsic connections in each model).

Evaluating hemodynamic response fits

We calculated a subject-specific average BOLD response for each region and each condition in both measured and predicted BOLD time-courses. Further, using these averages, the percentage of explained response variance (PVE, also called coefficient of determination) for

each brain region was determined. These PVE values were calculated at both the subject and group level. These constitute measures of accuracy that complement the KL complexity measures, described above.

For full ASL-data, the average CBF and BOLD responses were calculated from a predicted ASL time-series by applying surround averaging and surround subtraction (Liu and Wong, 2005; Mumford et al., 2006) in order to mimic the same processing of measured ASL-data. For ASL, we also calculated PVE for both CBF and BOLD responses in each brain region.

Comparing model families

The above analysis focuses only on evaluating qualitative and quantitative differences between connectivity weights provided by the different models and their fits to the data. Here, we performed Bayesian model selection (BMS) (Penny et al., 2010) to compare S-, 2S- and P-DCM. In particular, we aimed to identify the relative importance of three new model components in P-DCM over their previous variants in S- and 2S-DCM (see (Havlicek et al., 2015)). Therefore, three families within the space of model components were considered (see Table 1): the first family compared neuronal models, i.e. single-state vs. two-state vs. adaptive two-state neuronal model; the second family compared models of neurovascular coupling (NVC), i.e. feedback based NVC vs. feedforward NVC; and the third family compared vascular mechanisms within hemodynamic models, i.e. coupled vs. uncoupled CBF-CBV relationship. This resulted in twelve different combinations of DCMs, where the Model 1 corresponds to S-DCM, Model 5 to 2S-DCM and Model 12 to P-DCM (see Table 1).

Table 1. Families of physiological model components.

Model	Neuronal family			NVC family		Hemodynamic family	
	1-state	2-state	Adaptive 2-state	Feedback based NVC	Feedforward NVC	Coupled CBF-CBV	Uncoupled CBF-CBV
Model 1	●	-	-	●	-	●	-

Model 2	●	-	-	●	-	-	●
Model 3	●	-	-	-	●	●	-
Model 4	●	-	-	-	●	-	●
Model 5	-	●	-	●	-	●	-
Model 6	-	●	-	●	-	-	●
Model 7	-	●	-	-	●	●	-
Model 8	-	●	-	-	●	-	●
Model 9	-	-	●	●	-	●	-
Model 10	-	-	●	●	-	-	●
Model 11	-	-	●	-	●	●	-
Model 12	-	-	●	-	●	-	●

Based on the group log-evidence (i.e. log-evidence summed up over individual runs and subjects under fixed effects assumptions), the model with the lowest log-evidence was identified and then the relative log-evidences were determined among all twelve models listed in Table 1 (Penny et al., 2010). The model specific log-evidences were then used for family-wise BMS under fixed-effect (FFX) assumptions. This provided posterior probabilities of specific model components within each model family; i.e., the likelihood that a certain model component is supported by the data. The relative model log-evidences and posterior probabilities were calculated for both BOLD-data-alone and ASL-data.

Results

How does the connectivity depend on the model and the data?

In the following, we describe group connectivity estimates (obtained by BMA and BPA) using S-, 2S- and P-DCM, first for the BOLD-data-alone and later for the ASL-data. In Figure 4 and 5 we show: (i) the average connectivity that is associated with signal changes observed during the ipsilateral conditions (i.e. connectivity matrix A , left column in Figure 4 and 5); (ii) the average connectivity during contralateral conditions (i.e. connectivity matrix $A + \sum_{m=1}^2 B^{(m)}$),

middle column in Figure 4 and 5); and (iii) the effective (condition-dependent) changes in connectivity due to experimental manipulation (i.e. the difference between ipsilateral and contralateral conditions, connectivity matrix $\sum_{m=1}^2 B^{(m)}$, right column in Figure 4 and 5). We encode positive connection weights between nodes with red color arrows and negative weights with blue color arrows (PVEs values color-code the central part of the nodes for the BOLD signal and outside ring for CBF, see details below). The direction and strength of the connection is depicted using an arrow and line thickness, respectively. We display only absolute connection weights larger than 0.05. For a complete set of connection weights see Table A1.

BOLD-data-alone

S-DCM connectivity results (see Figure 4 top row) during the ipsilateral conditions show positive feedforward connections from left and right V1 to left and right M1, respectively, but also to SMA. In return, SMA influences both left and right V1 via strong negative feedback connections. Moreover, there are positive reciprocal connections between left and right V1. During contralateral conditions, the feedforward connections from left and right V1 to left and right M1, respectively, are mostly suppressed and additionally, stronger positive connections between SMA and left and right M1 emerged. The remaining connections are very similar to the ipsilateral conditions (see right column of Figure 4).

In 2S-DCM connectivity results (see Figure 4 middle row) during the ipsilateral conditions, we can see a fully connected network. As in S-DCM, the network is dominated by feedforward connections from left and right V1 to left and right M1, respectively, and to SMA. In contrast to S-DCM, all connections are positive and reciprocal. During contralateral conditions, feedforward connection strengths from left and right V1 to SMA are slightly increased and to left and right M1 are decreased, but still strong. We can also notice a large increase in some of the feedback connections, such as from left and right M1 to left and right V1, respectively, and from SMA to left V1 and left M1.

P-DCM connectivity results represent a sparse network (see Figure 4 bottom row). As in S-DCM, during ipsilateral conditions, we see positive feedforward connections from V1 to M1 and to SMA, but with stronger weights. In contrast to S-DCM, there are no negative feedback connections from SMA to left and right V1 and the reciprocal connections between left and right

V1 are negligible. During contralateral conditions, the connections from V1s to M1s are completely suppressed and the activity propagates to contralateral M1s via connections from V1s to SMA and then via strongly enriched connections from SMA. Although the connectivity patterns seen with ipsilateral and contralateral conditions are different compared to S-DCM, the difference between these two conditions is similar to S-DCM (see right column of Figure 4).

Figure 4

ASL-data (CBF&BOLD signal)

S-DCM results obtained from ASL-data (both ipsilateral and contralateral conditions) show similar connectivity patterns as obtained from BOLD-data-alone (see Figure 5 and 4, top row), albeit with some qualitative and quantitative differences. The Pearson correlation coefficient between connectivity patterns estimated using BOLD-data-alone and ASL-data (only extrinsic connections included) is 0.8967 (see Table 2). The main differences are in the strength of significant connections. Some connections exhibit much higher strengths in the case of ASL data. For example using ASL data, positive connections between left, right V1 and left, right M1 are ~1.6 times stronger during ipsilateral conditions and ~2.7 times stronger during contralateral conditions as compared to BOLD data. Additionally, negative connections from SMA to left and right M1 during ipsilateral conditions, which are negligible in BOLD data, are ~4.3 times stronger if ASL data are used. The difference between conditions is generally comparable to BOLD-data-alone (see right column of Figure 5).

2S-DCM connectivity results based on ASL-data are again not too different from those based on BOLD-data-alone (Figure 5 and 4, middle row). The Pearson correlation coefficient between connectivity patterns based on BOLD and ASL-data is 0.8532, which is slightly lower than for S-DCM. In general, most connection strengths estimated from ASL-data are slightly weaker compared to estimates based on BOLD-data-alone. This is an opposite effect compared to the results based on S-DCM. The largest discrepancy between estimated connectivity by BOLD-data-alone and ASL-data can be seen in between condition differences. There is slightly

more similarity to S-DCM results in the condition differences provided by ASL-data than when BOLD-data-alone is used (see Figure 4 and 5).

P-DCM results obtained from ASL-data (both ipsilateral and contralateral conditions) strongly resemble the sparse connectivity patterns as obtained from the BOLD-data-alone (Figure 5 and 4, bottom row). The Pearson correlation coefficient between connectivity patterns that is 0.9576; i.e. higher than both S-DCM and 2S-DCM. The main noticeable difference to BOLD results is in the overall higher strength of significant connections for ASL-data. For example, connections from V1s to M1s are ~1.7 times stronger; connections from V1s to SMA are ~1.2 times stronger; and connections from SMA to M1s are ~1.9 times stronger.

Figure 5

How does the model explain hemodynamic responses in multiple areas?

PVE values are encoded in the color of network nodes for the BOLD signal and outer rings for CBF (Figures 4 and 5). Individual subjects and group average PVE values for both BOLD-data-alone and ASL-data can be found in Table 3. Average responses of the observed data and fitted responses (from a single subject) are displayed in Figures 6 and 7.

BOLD-data-alone

For S-DCM, the region-specific PVE values range between 61% and 90%. This wide range of PVE values can be explained by the predicted single subject BOLD responses (red lines in Figure 6). The positive peaks of hemodynamic responses, including their delays, are well explained during ipsilateral conditions. However, during contralateral conditions, the positive response in left M1 is significantly delayed with respect to the measured BOLD data. Furthermore, S-DCM was mostly able to explain negative responses in M1 regions during both ipsilateral and contralateral conditions. Although S-DCM fits the undershoot in left M1 during ipsilateral conditions, it only provides a partial explanation in left and right V1s and right M1 areas during contralateral conditions (see Figure 6); i.e. explained variance reduces during the

contralateral conditions. We note that when S-DCM fits the post-stimulus BOLD undershoot well in a certain brain area (e.g. left M1 during ipsilateral condition), then there are stronger negative feedback connections targeting the area in question (see Supplementary Material S2).

PVE range for 2S-DCM is between 68% and 89%. 2S-DCM fits the positive peaks of hemodynamic responses with similar accuracy as S-DCM (cyan lines in Figure 6). In contrast to S-DCM, the two-state model cannot explain contralateral negative responses in M1 areas. Furthermore, the majority of post-stimulus BOLD undershoots are under-fitted, resulting in lower PVE values than S-DCM (see Table 3).

P-DCM generally scores higher PVE values in all regions, ranging between 83% and 96%, but the majority is above 90%. P-DCM was able to fit the positive peak of BOLD responses more accurately than S-DCM and 2S-DCM, especially during rising and falling phases of the hemodynamic response. As with S-DCM, P-DCM explains negative responses in contralateral M1 areas (blue lines in Figure 6). Finally, P-DCM explains post-stimulus BOLD undershoot with high accuracy in all five brain regions during both ipsilateral and contralateral conditions. Importantly, compared to S-DCM, P-DCM fits post-stimulus BOLD undershoots without relying on extrinsic negative feedback connections (see Figure 4 and Supplementary Material 2); i.e., using local neuronal and hemodynamic mechanisms.

Table 3. Average PVE values for individual subjects and entire group.

	S-DCM	2S-DCM	P-DCM
BOLD (alone):			
Subject 1	80.27±4.12	81.14±3.47	92.55±2.16
Subject 2	78.34±3.83	74.98±3.64	92.14±2.36
Subject 3	77.14±4.66	78.22±2.51	94.85±1.49
Subject 4	72.43±3.66	73.70±4.84	88.03±2.66
Subject 5	76.23±4.42	77.67±3.71	90.35±2.30
Group average	76.89±4.20	77.13±3.75	91.58±2.28
BOLD (ASL):			
Subject 1	75.50±4.55	75.94±4.39	93.72±1.93
Subject 2	80.91±2.59	80.84±3.04	95.19±0.97
Subject 3	82.80±2.08	87.07±1.85	95.22±1.49
Subject 4	73.36±3.48	76.63±3.45	90.80±2.21
Subject 5	78.07±3.79	77.86±4.36	91.48±2.11
Group average	78.89±3.50	79.69±3.66	93.27±1.85
CBF (ASL):			

Subject 1	85.02±3.36	82.65±2.28	88.65±3.44
Subject 2	90.22±2.43	86.48±3.88	92.53±2.45
Subject 3	91.43±1.29	90.75±1.73	94.54±1.29
Subject 4	82.79±3.66	81.10±3.54	90.36±2.51
Subject 5	80.05±4.83	73.11±5.18	86.36±3.54
Group average	85.92±3.47	82.81±3.78	90.49±2.84

Figure 6

ASL-data (CBF&BOLD)

In Figure 5, the PVE values are color-coded separately for CBF (purple-blue in the outer ring) and the BOLD signal (yellow-red in the inner circle) responses in each of network node. The average PVE values of CBF and BOLD signal predictions are displayed within nodes.

For S-DCM, PVE values for the BOLD responses are between 65% and 89%, which is slightly higher than in the case of BOLD-data-alone. However, the majority of post-stimulus undershoots in BOLD responses are not well explained. On the other hand, PVE values for the CBF responses are between 81% and 91%. Thus, in majority of cases, CBF responses have surprisingly higher PVE values than BOLD predictions in ASL data given that CBF data typically are noisier than BOLD signals. In terms of single subject predictions of CBF responses (orange lines in Figure 7), the post-stimulus deactivations are fitted with high accuracy.

In 2S-DCM results, the PVE values for BOLD predictions are between 72% and 92%. BOLD response predictions are comparable to predictions based on BOLD-data-alone – here 2S-DCM does not explain post-stimulus undershoots (see Figure 6 and 7). For CBF predictions, PVE values are between 73% and 89%. CBF predictions provide moderately accurate fit to measured CBF responses, including post-stimulus deactivations; with lower PVE values compared to S-DCM (see Figure 4 and 5). It can be seen that the CBF predictions of 2S-DCM are more ‘wrinkled’ compared to S-DCM (purple lines in Figure 7). Negative contralateral responses in M1 are not explained at the CBF or BOLD signal level.

In P-DCM results, the PVE values for BOLD predictions range between 88% and 97%, which is somewhat higher than PVE values scored with BOLD-data-alone (see Table 3). More accurate fits of BOLD responses using ASL-data compared to BOLD-data-alone reflect more precise fitting of post-stimulus BOLD undershoots. CBF predictions have also higher PVE values compared to S-DCM and 2S-DCM, ranging between 85% and 95%. In contrast to S-DCM and 2S-DCM, these are – in the majority of cases – slightly lower than for BOLD predictions. In short, P-DCM provides the most accurate fits of CBF and BOLD responses compared to 2S-DCM and 2S-DCM (green lines in Figure 7).

Figure 7

Does model inversion benefit from ASL-data?

From the model inversion perspective, all three models (S-, 2S- and P-DCM) benefit from additional information in ASL-data, as the KL divergence between prior and posterior distributions of extrinsic connections is always larger for ASL-data (see Table 4). This means that the posterior distribution departs more significantly from the prior distribution using ASL-data than using BOLD-data-alone. NEP and KL divergence scored by P-DCM is very close to S-DCM, which has the highest NEP and KL divergence scores. The same information gain is reflected in the number of effectively estimated parameters, which is always higher for ASL-data and generally higher than the actual number of free parameters. Note that the ASL generative model has in general two additional free parameters in the output signal model (plus one more in the feedforward NVC) per ROI compared to the DCM for BOLD signals. Moreover, the adaptive neuronal model embedded in P-DCM has one more free parameter compared to S-DCM and 2S-DCM per ROI. The higher number of free parameters in the model can, in principle, result in the lower confidence about the estimates of connectivity weights, hence in a smaller departure from the prior distributions. This suggests that observed increase in KL divergence (by ~ 7) or in NEP (by ~ 2) in the case of ASL-data (i.e. higher confidence about the estimates) represents a significant improvement.

Table 4 KL divergence and number of effectively estimated connectivity parameters (NEP).

	S-DCM		2S-DCM		P-DCM	
	BOLD	ASL	BOLD	ASL	BOLD	ASL
KL divergence	250.69	258.89	163.77	171.27	248.76	253.38
NEP (N = 44)	84.74	86.94	55.00	57.51	84.20	85.29

Which is the best model and how does it depend on data?

Fixed effect Bayesian model selection performed on posterior parameter estimates, obtained by fitting models to BOLD-data-alone, over all individuals revealed that P-DCM (Model 12) had the highest relative log-evidence, outperforming the S-DCM (Model 1) and 2S-DCM (Model 5) by very strong⁴ log-evidence differences $\Delta F = 1705$ and $\Delta F = 1411$, respectively (see Figure 8A). Log-evidence differences are consistently very large also at the level of individual subjects (see Table 5). Overall, this results in posterior probability >99% for BOLD-data-alone being compatible more with data predicted by P-DCM rather than by S- or 2S-DCM. Furthermore, comparing S-DCM and 2S-DCM using BOLD-data-alone showed strong log-evidence difference ($\Delta F = 294$) in favor of 2S-DCM, which confirms previous results (Marreiros et al., 2008).

Table 5. Log-evidence difference between competing models.

	P-DCM vs. S-DCM		P-DCM vs. 2S-DCM		S-DCM vs. 2S-DCM	
	BOLD	ASL	BOLD	ASL	BOLD	ASL
Subject 1	408	795	333	754	-75	-41
Subject 2	220	568	342	792	122	224
Subject 3	594	719	297	649	-297	-70
Subject 4	49	324	31	427	-18	103
Subject 5	434	449	408	621	-26	172
Total	1705	2855	1411	3243	-294	388

Results obtained by comparing the same models using ASL-data revealed even more striking differences (see Figure 8B). Here, the differences in log-evidence are more than 1.5

⁴ Usually, a difference in log-evidence above three is considered as strong evidence (Kass and Raftery, 1995).

times larger than in the case of BOLD-data-alone. In particular, P-DCM is chosen over S-DCM and 2S-DCM with very strong log-evidence differences $\Delta F = 2855$ and $\Delta F = 3243$, respectively. In contrast to BMS results obtained using BOLD-data-alone, ASL-data favors S-DCM over 2S-DCM ($\Delta F = 388$).

Figure 8

At the level of model families, all three new model components of P-DCM; i.e., the adaptive two-state neuronal model, the feedforward NVC, and the CBF-CBV uncoupling, are very strongly supported by the family comparison with posterior probability >99%. This was the case for both BOLD-data-alone and ASL-data (see Figure 8A and B, bottom panels). In general, models that include the adaptive two-state neuronal model brought the largest model improvement (Models 9-12), scoring a larger log-evidence than models without this component (Models 1-8). Models that include CBF-CBV uncoupling (Models 2, 4, 6, 8, 10, 12) were also always supported over competing models where CBF-CBV is coupled (Models 1, 3, 5, 7, 9, 11). Considering the feedforward NVC instead of the feedback based NVC results in moderate differences in log-evidence. Note that not all models benefit from modeling this physiological mechanism. While for P-DCM the feedforward NVC increases log-evidence for both coupled and uncoupled CBF-CBV scenarios (see Models 11-12 vs. Models 9-10 for both BOLD-data-alone and ASL-data), removing feedback in S-DCM and 2S-DCM can result in decrease of log-evidence (see Models 3 vs. Models 1 and Models 7-8 vs. Model 5-6, respectively, for BOLD-data-alone). However, in the case of ASL-data, S- and 2S-DCM both benefit from the feedforward NVC if used together with the CBF-CBV uncoupling.

Discussion

In this paper, we compared connectivity estimates obtained by fitting generative models to BOLD-data-alone and, for the first time, jointly to CBF and BOLD data with a novel DCM for

ASL. ASL-DCM differs from BOLD-DCM by including neuronally induced CBF and baseline CBF signals in the output equation of the physical model. Crucially, we implemented the full model of ASL signal, rather than fitting derived CBF and BOLD time-courses from ASL data. In addition, we have statistically evaluated the impact of several key physiological mechanisms as implemented in S-, 2-S and P-DCM (Havlicek et al., 2015) on the estimated connectivity weights among multiple ROIs.

P-DCM differs from S-DCM and 2S-DCM in the following physiological model features: adaptation of neuronal response by local inhibitory population; feedforward NVC; and possibility of CBF-CBV uncoupling (see Figure 1). In a previous paper (Havlicek et al., 2015), we have evaluated the impact of these mechanisms on fitting single ROI time-courses and established their physiological relevance. However, all these features may also influence connectivity estimates when they are applied jointly with the bi-linear DCM neuronal connectivity model. This is because, in model inversion, any model component lying between the neuronal level and the output fMRI signal (i.e. the biophysical model) can have an effect on estimated neuronal signals (Roebroeck et al., 2009; Valdes-Sosa et al., 2011).

BOLD-data-alone

DCM is most often applied to BOLD fMRI data using S-DCM (Friston et al., 2003; Seghier, 2010). Based on a standard FFX Bayesian procedure for model selection (Penny et al., 2010), our results provided clear evidence that for the given BOLD data, P-DCM is statistically by far the superior model in comparison to S-DCM and 2S-DCM; not only for single regions, as shown in the previous paper (Havlicek et al., 2015)), but also for estimating connectivity in a network. This was demonstrated through very large log-evidence differences between P-DCM and the other two models ($\Delta F = 1705$ and $\Delta F = 1411$ with respect to S-DCM and 2S-DCM, respectively). These results also showed that for BOLD-data-alone, 2S-DCM is a better model than S-DCM, confirming previous BMS results (Marreiros et al., 2008). Note that, in general, difference in log-evidence $\Delta F > 3$ is considered as strong evidence (Kass and Raftery, 1995).

These large differences in log-evidence are mainly due to substantial fitting errors with S-DCM and 2S-DCM, which are unable to accurately explain the form of hemodynamic responses (see below). As we have shown previously (Havlicek et al., 2015), P-DCM includes basic

physiological mechanisms that are necessary to account for the repertoire of measured BOLD responses, that are insufficiently modeled by S-DCM and 2S-DCM. This is further supported by the fact that the log-evidence is accumulated (summed up) over five subjects (each with 4 runs and 382 data points per run), thus allowing for very powerful inference. The log-evidence differences for a single functional run ranged from 30 to 120. Differences of this magnitude between log-model evidences have been reported before (Marreiros et al., 2008; Rosa et al., 2011; Stephan et al., 2007), even in cases where the compared models had rather subtle differences in physiological mechanisms (or their impact on the shape of hemodynamic response function was small).

Next, by performing model comparison at the level of model families (Penny et al., 2010), we were able to show that all three new components of the generative model as implemented in P-DCM (i.e. adaptive two-state neuronal model; feedforward NVC; and CBF-CBV uncoupling) are statistically superior to their previous counterparts (see Figure 8 for family comparison of posterior probabilities). This means that all the physiological mechanisms as proposed in (Havlicek et al., 2015) are well supported by experimental BOLD data and they are suitable for modeling both single and multiple ROI fMRI data.

Examining the connectivity pattern obtained by the different DCMs, the endogenous connectivity estimates (see ipsilateral conditions in Figure 4) were different for all three models applied to the same data. While 2S-DCM yielded a fully connected network, connectivity estimated by P-DCM is sparse, including only positive connections. S-DCM provided a less sparse network with additional negative feedback connections. Nevertheless, the actual changes in connectivity weights due to experimental manipulation (i.e. difference between ipsilateral and contralateral conditions) are similar between S-DCM and P-DCM, yet differ remarkably from 2S-DCM. Note that a larger agreement between S-DCM and P-DCM in connectivity modulation is well expected, because they share the same neuronal model for long-range connections. On the other hand, larger differences in endogenous connectivity are related to different physiological mechanisms embedded in S-DCM and P-DCM, because this connectivity generates neuronal responses also outside stimulation periods (Friston et al., 2003; Stephan et al., 2008). Therefore, it can reflect local temporal variation often seen in both neuronal and hemodynamic responses, such as post-stimulus deactivation and undershoot (Gonzalez-Castillo et al., 2012; Hoge et al.,

1999). The reason why connectivity estimates provided by 2S-DCM differ dramatically from S-DCM and P-DCM is due to different assumptions about extrinsic connections, which are forced to be positive (excitatory) by log-normal transformation⁵ (Marreiros et al., 2008; Stephan et al., 2008). In contrast to our results, Stephan et al. (2007) showed that the neuronal connectivity parameters are fairly robust to changes in the output form of BOLD signal equation. Mechanisms compared in our paper (i.e. neuronal models, NVCs, CBF-CBV couplings) have a much greater impact on the shape of BOLD response function and thus can result in larger differences.

To further examine the observed differences in connectivity estimates provided by different models, we have carefully evaluated how well each model fits region-specific BOLD responses (see Figure 6). Although comparing the accuracies of model fit is not a sufficient measure to determine which model is better or more useful (Friston et al., 2013), examining the accuracy (that is part of the log-evidence) next to the BMS can help us draw a more detailed (quantitative) picture about the model performance and its physiological relevance. The majority of BOLD responses associated with the five nodes of the network exhibit strong hemodynamic transients in the form of post-stimulus undershoot (see Figure 6). These transients in observed hemodynamic responses – possibly caused by neuronal and/or vascular physiological mechanisms – are repeatedly reported (e.g. see (Chen and Pike, 2009; Hoge et al., 1999; Logothetis and Wandell, 2004; Mandeville et al., 1999; Sadaghiani et al., 2009; Shmuel et al., 2002)). Our results showed that P-DCM explains a larger variance of the hemodynamic response in all regions, compared to the other models, with average PVE values of ~91% (see Table 3). Both S-DCM and 2S-DCM achieved considerably lower PVE values (~77%), resulting mostly from under-fitted post-stimulus BOLD undershoot. Note that the post-stimulus undershoot can be in some extreme cases almost as large as the main positive BOLD response (see Figure 6). S-DCM was able to explain post-stimulus undershoot in some regions, but 2S-DCM was more accurate in fitting the rising phase of the positive BOLD response.

In P-DCM, the presence of post-stimulus undershoot may be explained by a local adaptation mechanism of inhibitory populations and by uncoupling between CBF and CBV,

⁵ Note that while S-DCM and P-DCM have the prior means on connections equal zero, 2S-DCM due to the log-transform has the prior mean equal to 1/8. In general, this can result in more non-zero connections if the evidence from the data does not give enough support that these connections should be actually zeros (i.e. scaling parameters involved in log-transforms have to be strongly negative).

resulting in sparser endogenous connectivity. Since S-DCM does not include these local physiological mechanisms, it naturally attempts to model variation in neuronal/hemodynamic response, not explainable by local physiological processes, by long-range excitatory connections. Therefore, we see stronger negative feedback connections that cause more pronounced post-stimulus response deactivation (at the neuronal level) and undershoot (at the BOLD signal level). Note that the general mechanism of negative feedback based NVC used by both S-DCM and 2S-DCM may in principle modulate post-stimulus BOLD signal time-course as well. However, as we have shown earlier (Havlicek et al., 2015), for longer stimulus durations (as in our paradigm), this modulation is minimal – even with large variation of the decay parameter κ controlling the flow inducing signal. Furthermore, even though 2S-DCM possesses a mechanism to locally control excitatory activity by the inhibitory population within the two-state model, its parameterization is ineffective in explaining a wide range of neuronal/hemodynamic response transients (see Figure 6, and see also (Havlicek et al., 2015)). Put simply, fitting errors due to physiologically less plausible mechanisms implemented in S-DCM and 2S-DCM can be partially compensated by endogenous connectivity estimates. Moreover, it is important to remember that the log-evidence accounts for both model fit accuracy and model complexity (Penny, 2012). That is, a good model has to be accurate and still reasonably simple (in terms of the number of free parameters) in order to win the Bayesian model comparison. In this respect, P-DCM can accurately fit the entire shape of hemodynamic response with only a low or negligible increase in complexity (measured with KL divergence and NEP, see Table 4) compared to S-DCM.

The finding that the endogenous connectivity in S- and 2S-DCM is possibly more susceptible to hemodynamic variations, while the additive (or multiplicative (Stephan et al., 2008)) changes in connectivity due to experimental manipulation are not, agrees with the original characterization of connectivity S-DCM (Friston et al., 2003). Indeed, one of the main recommendations for DCM analysis is to design experimental modulations of endogenous connectivity couplings (Roebroeck et al., 2009; Stephan et al., 2010). However, there are situations, especially in clinical studies, which call for comparing endogenous connectivity between two different groups (e.g. controls vs. patients) (Agosta et al., 2010; Crossley et al., 2009; Miyake et al., 2010; Rocca et al., 2007). In addition, DCM analysis has been recently developed for resting-state data (Friston et al., 2014), which inherently assumes only endogenous

connectivity. Therefore, in these cases, connectivity estimates provided by S-DCM and 2S-DCM may be more susceptible to variations of vascular (in addition to neuronal) signals than P-DCM.

In summary, results based on BOLD-data-alone suggest that models in S-DCM and 2S-DCM may be too restrictive for certain hemodynamic changes (e.g. adaptation and post-stimulus undershoot) observed in many fMRI experiments. P-DCM, in comparison, provides a more sparse connectivity accompanied with a locally-rich repertoire of neuronal and hemodynamic processes, which is statistically supported by the experimental data used in this study. Additionally, compared to S-DCM, P-DCM provides significantly more stable connectivity estimate across subjects and functional runs (see Supplementary Material 2 for more details).

ASL-data

The DCM framework is not limited to BOLD-data-alone but can also be extended to ASL fMRI data (and other hemodynamic measures, such as CBV), which simultaneously measures CBF and BOLD signal. In this study, we have developed such an extension, which enabled us to estimate effective connectivity and perform model comparisons with ASL data.

BMS on ASL-data revealed even stronger log-evidence differences in favor of P-DCM. In contrast to BMS results obtained using BOLD-data-alone, ASL-data favors S-DCM over 2S-DCM. Therefore, one can speculate that 2S-DCM might be a better model for BOLD data than S-DCM from a statistical point of view (as summarized by BMS) but not from physiological point of view, when constrained with CBF. The model comparison at the family level confirmed the results from BOLD-data-alone, but ASL-data further showed that both S- and 2S-DCM can benefit from the feedforward NVC and the CBF-CBV uncoupling, if used together. The KL divergence between prior and posterior distributions of extrinsic connections (and NEP) showed that parameter estimation in all models benefit from ASL data (i.e. from additional CBF component) compared to BOLD-data-alone, even though the generative model for ASL-DCM has higher number of free parameters (see Method section and Table 4).

We showed that connectivity estimates for DCM variants using ASL-data are similar (albeit stronger) to their counterparts obtained using BOLD-data-alone. The correlation between connectivity estimates based on BOLD-data-alone and ASL data was the lowest for 2S-DCM ($r \sim 0.85$), slightly higher for S-DCM ($r \sim 0.90$) and highest for P-DCM ($r \sim 0.96$). As CBF is more

closely related to neuronal activity, it is reasonable to assume that ASL data – with sufficient SNR – provides a more accurate connectivity estimate than BOLD-data-alone. Nevertheless, the high correlation of the connectivity patterns using both data sets suggests that BOLD-data-alone provides reasonably accurate estimates of connectivity, even without additional information in CBF data (but see below). The stability of the connectivity estimates is the highest for P-DCM, arguing for the physiologically informed assumptions embedded with P-DCM. Moreover, there is not only a good agreement between estimated connectivity from these two modalities, but also between local (within-subject) parameter estimates of the generative model such as: inhibitory-excitatory connections μ ; inhibitory gain factors λ ; global self-inhibition σ ; mean transit times t_{MTT} ; and viscoelastic constants τ (results not shown). In addition, the decay parameter χ controlling the NVC in ASL data diverged negligibly from its prior mean (see the Supplementary Material 1 for parameter description).

We showed that in comparison to BOLD-data-alone, all models fitted to ASL-data scored higher PVE values. For BOLD responses, the PVE values were on average ~2% higher (see Table 3 and Figure 7). Interestingly, in case of S-DCM and 2S-DCM, the PVE values for CBF responses were even higher than for BOLD responses. One explanation of this result could be that the size of post-stimulus CBF deactivation is smaller than the post-stimulus BOLD undershoot (as generally observed). This means that neuronal and NVC mechanisms as implemented in S-DCM and 2S-DCM can explain this size of post-stimulus CBF deactivation; however, they are insufficient to explain the even larger post-stimulus BOLD undershoot. This is because S-DCM and 2S-DCM assume coupled dynamics between CBF and CBV, which can only result in a post-stimulus BOLD undershoot that is smaller or comparable to the post-stimulus deactivation in the CBF response (Havlicek et al., 2015). Unlike S-DCM and 2S-DCM, P-DCM explains the discrepancy between post-stimulus deactivation in the CBF and post-stimulus undershoot in the BOLD response by CBF and CBV being uncoupled; i.e. BOLD response can have more pronounced post-stimulus undershoot than CBF (Havlicek et al., 2015). This result points to the importance of CBF-CBV uncoupling as a component of the generative model, and that the generative models of S-DCM and 2S-DCM are not well suited for modeling of ASL data, where it is necessary to account for differences in dynamic behavior of CBF and BOLD responses.

Finally, it is worth mentioning that there are some interesting differences in connectivity estimates as provided by P-DCM compared to other models (see Figure 4). In particular, in P-DCM connectivity results based on ASL-data, we see negative contralateral connections between left and right M1s. These small negative weights are in good agreement with our observations that most of the subjects showed small ipsilateral deactivation in M1 during finger tapping. Moreover, these ipsilateral deactivations in M1 and in sensory areas are regularly observed (e.g. see (Hlushchuk and Hari, 2006; Klingner et al., 2011a; Klingner et al., 2011b; Mullinger et al., 2014; Stefanovic et al., 2004)). Furthermore, P-DCM does not show any significant connections between right and left V1s (in both ASL-data and BOLD-data-alone), but there are stronger cross-hemispheric connections estimated by S-DCM and 2S-DCM. Given the fact that we tried to minimize possibility of contralateral activation of V1 by experimentally controlling background iso-luminance with respect to checkerboard stimuli, and we did not observe any significant activations and deactivations in hemodynamic responses on ipsilateral sides of the visual cortex, we can quite safely assume that these connections detected by S-DCM and 2S-DCM are spurious. Therefore, by considering this specific experimental manipulation, P-DCM (especially with ASL-data) provides more sensible connectivity estimate with better reflection of the underlying physiological processes. In short, the construct validity of P-DCM, with respect to known functional anatomy and our assumptions about connectivity architecture is reasonable.

Generalizability and limitations

We used experimental data of visio-motion task with five significantly involved brain regions. Theoretically, this task and number of regions allow for testing many competing hypothesis about different connectivity structures and their induced changes. Although our experimental task naturally resembles a fully factorial design, where we could investigate the main effect of switch (ipsilateral vs. contralateral conditions) and interaction between switch and response side (right vs. left), we focused our analysis only on average connectivity changes between ipsilateral and contralateral conditions. This specific choice of connectivity structure (see Figure 3) was motivated by an initial BMS analysis, which showed that the fully factorial design is statistically inferior to the design reported in this paper (results not shown).

Moreover, weights modulating callosal connections between left and right V1 were excluded from the analysis, even though one may think that these pathways can play an

important role in explaining propagation of neuronal activity during contralateral conditions (e.g. transferring activity from left V1 to right M1 via right V1). However, also this hypothesis was not supported by our data and was rejected during initial BMS analysis as well (mainly because there no significant increase in the BOLD response in opposite V1 was observed, see Figure 6). Therefore, design of connectivity structure applied in this paper was selected based on prior results of BMS, where it was compared with other plausible connectivity designs (two of them mentioned above). Importantly, the selected model was strongly preferred by all DCM variants (S-DCM, 2S-DCM, and P-DCM). Note, however, it is highly unlikely that alternative (but also plausible) connectivity architectures (also if less ROIs are considered) would result in fundamentally different conclusions with respect to the necessity of the physiological components in P-DCM to model fMRI time courses. This is due to the fact that fMRI transients, as observed in this study, cannot be fully accounted for by S-DCM and 2S-DCM neither locally (see Havlicek et al., 2015) nor remotely via interaction of other brain regions. As a consequence, large differences in log-evidences for the different DCM variants are obtained (but see also below).

Importantly, it should be emphasized that the primary goal of this paper was not to identify the best structural connectivity model for the task, but rather to evaluate relevant parts of neuronal and hemodynamic models and their impact on connectivity estimates. That is, the experimental data is a show-example of transients observed in fMRI data and how these transients affect connectivity estimates derived by the different DCM variants. Therefore, the statistical superiority of P-DCM as compared to S- and 2S-DCM may not be generalizable to all experimental designs and functional activation patterns. For example, we used a block design with resting duration long enough to allow for full evolution of the post-stimulus BOLD undershoot. It might be that if other experimental designs are used (e.g. fast event-related design, where the post-stimulus undershoot cannot be easily detected) or if none of selected ROI responses contains a post-stimulus undershoot and/or exhibit adaptation profile during stimulation, the Bayesian model comparisons may lead to different conclusions. However, as undershoot and adaptation are commonly observed features of the fMRI signal and the ability of P-DCM to effectively model those in contrast S- and 2S-DCM, the results of the comparison of the DCM variants are, in our minds, generalizable to the majority of fMRI studies. Note that

even in those cases for which S- and 2S-DCM are statistically superior, it is expected that the connectivity patterns obtained with P-DCM are similar to those with S- and 2S-DCM.

We compared DCM models using BOLD-data-alone and ASL-data, and showed that the CBF part of ASL-data can improve the model inversion (see above). However, since the estimated neuronal signal can be contaminated by vascular dynamics that were not sufficiently explained by the hemodynamic model (as shown for S- and 2S-DCM), one may wonder if inverting the model directly from CBF time-courses (derived from ASL data using surround subtraction) would be a better choice. This means that one would connect the neuronal model only with NVC to generate CBF responses and fit these to the data. We have also tested this model in the early phase of our DCM analysis, and found it to resemble results observed using BOLD-data-alone and ASL-data. However, due to low SNR of CBF, the variability in estimated parameters was significantly higher (results not shown). Moreover, since there is a chance that CBF derived from ASL data is partly contaminated by the BOLD signal (due to signal interpolation involved within surround subtraction), it makes it less suitable for estimation of effective connectivity using DCM (Mumford et al., 2006).

Summary

Using experimental fMRI data, we found that P-DCM is statistically superior to S-DCM and 2S-DCM for evaluating effective connectivity among distributed ROIs. This was demonstrated by fitting these models to both BOLD-data-alone and combined BOLD/CBF-data via an extended DCM for ASL data. Our results indicate that P-DCM is the most consistent among all three models, in terms of the agreement between connectivity estimates, and had the lowest inter-subject variability. Nevertheless, connectivity differences between conditions are also well characterized by S-DCM. These results speak in favor of using P-DCM in the standard DCM for fMRI effective connectivity analysis performed on BOLD data. Overall, the statistical superiority of P-DCM over S-DCM and 2S-DCM suggests the importance of accurately modeling physiological mechanisms to deduce the neuronal connectivity from indirect fMRI data. These results, thus, confirm our earlier premise that P-DCM is a physiologically plausible model of fMRI data.

In addition, we argue that P-DCM has the potential to provide better estimates of effective connectivity and is less dependent on vascular sources of hemodynamic response variability, compared to S- and 2S-DCM. The validity of P-DCM is further strengthened if ASL data is used, since it provides direct access to CBF, a crucial variable that helps identifying vascular transients in hemodynamic responses. Finally, we could speculate that the ability of P-DCM to model neuronal transients due to neuronal inhibition/adaptation that are reflected in observed hemodynamic responses (in addition to the vascular transients) could provide a unique opportunity to study changes in effective connectivity driven by neuronal inhibition.

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Appendix A

Table A1. The mean connectivity parameter estimates across subjects (\pm standard error) for the ipsilateral and contralateral conditions as provided by S-, 2S-, and P-DCM for both BOLD-data-alone and ASL-data.

Connection	S-DCM		2S-DCM		P-DCM	
	BOLD	ASL	BOLD	ASL	BOLD	ASL
<i>Ipsilateral conditions</i>						
leftV1 \rightarrow rightV1	0.13\pm0.02	0.15\pm0.02	0.10\pm0.01	-0.10\pm0.10	0.05 \pm 0.02	0.03 \pm 0.01
leftV1 \rightarrow leftM1	0.16\pm0.02	0.25\pm0.03	0.41\pm0.04	1.29\pm0.13	0.21\pm0.02	0.34 \pm 0.03
leftV1 \rightarrow SMA	0.09\pm0.01	0.12\pm0.01	0.29\pm0.03	0.91\pm0.11	0.25\pm0.03	0.36 \pm 0.03
rightV1 \rightarrow leftV1	0.06\pm0.02	0.12\pm0.02	0.07\pm0.02	-0.49\pm0.14	0.01 \pm 0.01	0 \pm 0.01
rightV1 \rightarrow rightM1	0.19\pm0.02	0.23\pm0.02	0.39\pm0.04	1.26\pm0.11	0.20\pm0.02	0.32 \pm 0.02
rightV1 \rightarrow SMA	0.10\pm0.02	0.13\pm0.02	0.30\pm0.04	0.81\pm0.14	0.30\pm0.03	0.36 \pm 0.04
leftM1 \rightarrow leftV1	0.04 \pm 0.03	0.08\pm0.05	0.12\pm0.01	-0.26\pm0.05	0.01 \pm 0.00	0.02 \pm 0.01
leftM1 \rightarrow rightM1	0.04 \pm 0.02	0.03 \pm 0.02	0.06\pm0.01	-0.80\pm0.07	-0.04 \pm 0.02	-0.09 \pm 0.03
leftM1 \rightarrow SMA	0.02 \pm 0.01	-0.01 \pm 0.02	0.12\pm0.01	-0.11\pm0.03	0.00 \pm 0.00	0 \pm 0.00
rightM1 \rightarrow rightV1	-0.03 \pm 0.02	-0.08\pm0.03	0.12\pm0.01	-0.15\pm0.08	0.02 \pm 0.01	0.02 \pm 0.01
rightM1 \rightarrow leftM1	0.05 \pm 0.02	0.06\pm0.03	0.07\pm0.01	-0.76\pm0.14	-0.02 \pm 0.01	-0.04 \pm 0.01
rightM1 \rightarrow SMA	0.02 \pm 0.01	0.00 \pm 0.02	0.12\pm0.01	-0.14\pm0.07	0.01 \pm 0.00	0.00 \pm 0.00
SMA \rightarrow leftV1	-0.21\pm0.05	-0.3\pm0.05	0.10\pm0.01	-0.42\pm0.07	0.03 \pm 0.02	0.01 \pm 0.01
SMA \rightarrow rightV1	-0.21\pm0.04	-0.10\pm0.04	0.10\pm0.01	-0.36\pm0.07	0.04 \pm 0.02	0.05 \pm 0.01
SMA \rightarrow leftM1	-0.11\pm0.04	-0.11\pm0.03	0.15\pm0.01	-0.04 \pm 0.13	0.09\pm0.02	0.14 \pm 0.03
SMA \rightarrow rightM1	-0.04 \pm 0.02	-0.05 \pm 0.03	0.12\pm0.01	-0.37\pm0.08	0.09\pm0.03	0.11 \pm 0.02
<i>Contralateral conditions</i>						
leftV1 \rightarrow rightV1	0.13\pm0.02	0.15\pm0.02	0.10\pm0.01	-0.10\pm0.10	0.05 \pm 0.02	0.03 \pm 0.01

leftV1 → leftM1	0.02±0.06	0.06±0.07	0.15±0.04	0.29±0.18	-0.01±0.02	-0.03±0.02
leftV1 → SMA	0.13±0.02	0.19±0.02	0.31±0.07	0.80±0.16	0.26±0.03	0.37±0.03
rightV1 → leftV1	0.06±0.02	0.12±0.02	0.07±0.02	-0.49±0.14	0.01±0.01	-0.00±0.01
rightV1 → rightM1	0.09±0.05	0.13±0.04	0.18±0.03	0.69±0.15	0.02±0.02	0.02±0.02
rightV1 → SMA	0.15±0.02	0.20±0.02	0.33±0.06	0.84±0.11	0.34±0.03	0.42±0.03
leftM1 → leftV1	0.07±0.04	0.12±0.04	0.14±0.04	-0.56±0.13	0.01±0.00	0.01±0.01
leftM1 → rightM1	0.00±0.03	0.04±0.04	0.04±0.01	-1.26±0.10	-0.06±0.02	-0.10±0.02
leftM1 → SMA	-0.01±0.01	-0.05±0.02	0.09±0.01	-0.67±0.10	-0.01±0.00	-0.02±0.01
rightM1 → rightV1	0.00±0.02	-0.04±0.03	0.23±0.05	-0.07±0.20	0.02±0.01	0.03±0.01
rightM1 → leftM1	0.03±0.03	0.04±0.03	0.04±0.01	-1.28±0.15	-0.04±0.01	-0.05±0.02
rightM1 → SMA	-0.01±0.02	-0.05±0.02	0.09±0.01	-0.70±0.11	-0.01±0.00	-0.02±0.01
SMA → leftV1	-0.24±0.05	-0.31±0.06	0.15±0.04	-0.59±0.21	0.02±0.02	0.03±0.02
SMA → rightV1	-0.23±0.04	-0.08±0.04	0.13±0.03	-0.39±0.19	0.04±0.02	0.06±0.02
SMA → leftM1	0.22±0.04	0.22±0.05	0.31±0.04	0.59±0.23	0.44±0.05	0.70±0.06
SMA → rightM1	0.16±0.04	0.17±0.06	0.17±0.03	-0.18±0.16	0.39±0.05	0.58±0.03

Connections weights above 0.05 are highlighted in bold.

Figures

Figure 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.

Figure 2. (A) Illustration of the ASL data acquisition. The ASL pulse sequence involves labeling of the inflowing arterial blood proximal to the imaging slices by magnetic inversion (during inversion time, TI_1). Once the labeled blood, having its spins inverted, is delivered to the rest of the brain (after a certain inversion time, TI_2), it reduces the total signal magnitude in the subsequently acquired ‘tagged’ images. After collecting labeled images, the procedure is repeated without applying the magnetic inversion, and so called ‘control’ images are acquired while the inflowing blood is fully relaxed. Then dynamic alternation between acquiring labeled and control images gives the typical ASL measurement where the difference between control and labeled images is proportional to the local CBF and where the envelope represents the BOLD signal. (B) Schematic illustration of the ASL generative model for DCM that is common to all S-, 2S- and P-DCM. The output from NVC (i.e. CBF signal) and the BOLD signal are combined together with the CBF baseline to form the output ASL signal.

Figure 3. Illustration of connectivity structure (A) and experimental design of visuo-motor task (B) assumed for DCM model inversions. This illustrates driving inputs entering the network of

brain regions during left and right visual stimulation (red and blue colors) and modulatory inputs introducing changes to ipsilateral connectivity, while contralateral motor responses are enforced (green and orange colors).

Figure 4. Group connectivity results based on BOLD-data-alone estimated using S-DCM (top row), 2S-DCM (middle row) and P-DCM (bottom row). The left column depicts the endogenous connectivity during the ipsilateral conditions. The middle column shows modulation of the endogenous connectivity during the contralateral conditions. The right column displays the difference between ipsilateral and contralateral conditions; i.e. the effective change in connectivity due to the experimental manipulation. The causal direction and strength of the connection are depicted using an arrow and the line thickness, respectively. The positive connection weights between nodes are encoded with red color arrows and negative weights with blue color arrows (only absolute connection weights larger than 0.05 are shown). The region-specific PVE values are displayed within each node that is further color-coded based on the scale depicted in the color bar.

Figure 5. Group connectivity results based on the ASL-data estimates. This figure adheres to the same description as Figure 3 with the following exceptions: The PVE values are color-coded separately for CBF (purple-blue in the ring) and BOLD (yellow-red in the inner circle) responses in each of network node. The average PVE values of CBF and BOLD signal predictions are displayed within the nodes.

Figure 6. Single-subject average region-specific hemodynamic responses fitted by S-DCM, 2S-DCM and P-DCM to BOLD-data-alone. The observed BOLD responses for both ipsilateral and contralateral conditions are displayed with solid black lines, including error bars that represent the 95% confidence interval. Side of visual stimulation is marked in the upper right corner of each plot with colored wedge (blue color represents ipsilateral hand response and red color contralateral hand response). The fitted BOLD responses fitted by S-DCM, 2S-DCM and P-DCM are displayed using solid red, cyan and blue lines, respectively. Region-specific responses are normalized with respect to the maximum amplitude of the observed responses across all conditions, i.e. the proportional differences in amplitudes between conditions are preserved.

Figure 7. Single-subject average region-specific hemodynamic responses fitted by S-DCM, 2S-DCM and P-DCM to ASL-data. Organization of this figure is the same as in Figure 6 except that only responses to contralateral conditions are displayed. Observed CBF responses are displayed left to the BOLD responses. These are underlaid with CBF response predicted by S-DCM, 2S-DCM and P-DCM, depicted with solid orange, purple and green colors, respectively.

Figure 8. Summary of the Bayesian model comparison results for BOLD-data-alone (A) and ASL-data (B). The figure compares twelve DCMs resulting from the factorial structure of

family-wise comparison between the generative model components (i.e. single-state vs. two-state vs. adaptive two-state neuronal model, feedback vs. feedforward NVC, coupled vs. uncoupled CBF-CBV relationship) as described in Table 1. The first row shows the relative model log-evidence summed across all subjects (i.e. the model log-evidence minus the log-evidence of the reference model). The second row displays posterior probability of each model component within a specific model family (i.e. neuronal model, NVC, CBF-CBV relationship). The same description applies to the results from the ASL-data.

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