Modeling of BOLD Components in the Statistical Analysis of Perfusion-Based fMRI Experiments

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Introduction: As compared to blood oxygenation level dependent (BOLD) based imaging, perfusion-based functional magnetic resonance imaging (fMRI) with arterial spin labeling (ASL) has the potential to provide a more accurate reflection of neural activity because it measures functional changes in cerebral blood flow (CBF), a fundamental physiological quantity. However, due to the low inherent sensitivity of ASL acquisition methods, optimization of ASL analysis methods is necessary to make perfusion-based fMRI a robust and widely applicable tool for the study of brain function. A general linear model (GLM) has been previously proposed as a mechanism for the analysis of ASL data [1]. This model was later generalized to allow for arbitrary filtering schemes (i.e. pairwise subtraction, running subtraction, sinc subtraction), including an optimal unfiltered model [2]. Here we extend the unfiltered model in [2] to include an additional regressor to model a BOLD-weighted static tissue component. Since physiological noise correction has been shown to improve the sensitivity of ASL [3], we also incorporated physiological noise regressors. The impact of the additional BOLD regressor on statistical performance was assessed with ASL experiments measuring functional activation in visual cortex.

Theory: The extended general linear model is as follows:

$$\mathbf{y} = \mathbf{X}\mathbf{h}_{BOLD} + \mathbf{M}\mathbf{X}\mathbf{h}_{perf} + \mathbf{S}\mathbf{a} + \mathbf{P}\mathbf{c} + \mathbf{e} \qquad \text{(Eqn 1)}$$

where $\mathbf{y}$ is the acquired data representing tag and control images, $\mathbf{X}$ is the design matrix describing the stimulus pattern, $\mathbf{S}$ is a matrix of nuisance regressors consisting of a DC component and a linear trend, $\mathbf{P}$ is a matrix of cardiac and respiratory regressors, and $\mathbf{e}$ is an additive noise term. In this model, the term modeling perfusion $\mathbf{X}\mathbf{h}_{perf}$ is modulated by a diagonal matrix, $\mathbf{M}$, consisting of alternating -1's and 1's representing the tag and control images. The term $\mathbf{X}\mathbf{h}_{BOLD}$ models a BOLD weighted static tissue component. Equation 1 may be considered a matrix formulation of the signal processing model described in [4].

Methods: Data were collected on three healthy subjects. Images were acquired on a General Electric 3.0 Tesla EXCITE system with an 8-channel array coil. Three 8 mm slices were acquired through the primary visual cortex. A pulsed ASL sequence (PICORE QUIPSS II) with dual echo spiral readout was used (TR 2.0 sec, TI1 600ms, TI2 1500ms, tag width 100mm, FOV 24cm, θ=90°, data matrix size 64x64, 150 repetitions, TE1=9.1ms, TE2=30ms). Four functional runs were acquired on each subject using a block design paradigm with an 8Hz flashing checkerboard as stimulus (4 cycles 20/40sec on/off). Cardiac pulse and respiratory data were continuously recorded using a pulse oximeter and respiratory effort transducer, and the corresponding regressors were incorporated in the GLM. To achieve optimal parameter estimation, prewhitening using an autoregressive plus white noise model was implemented on a per-voxel basis as described in [5]. The F-statistic was used as the test statistic for the GLM, and was converted to a z-score for further analysis. For each echo, we compared the z-scores obtained when the BOLD component $\mathbf{X}\mathbf{h}_{BOLD}$ was present to z-scores obtained when the BOLD component was not included. Voxels were chosen for comparison based on the z-scores ($z>1.645$ corresponding to $p < 0.05$) obtained with the BOLD component in the GLM. All voxels across subjects and across functional runs that satisfied these criteria were used in a paired t-test to determine differences in sensitivity between the two models (with and without the BOLD component).

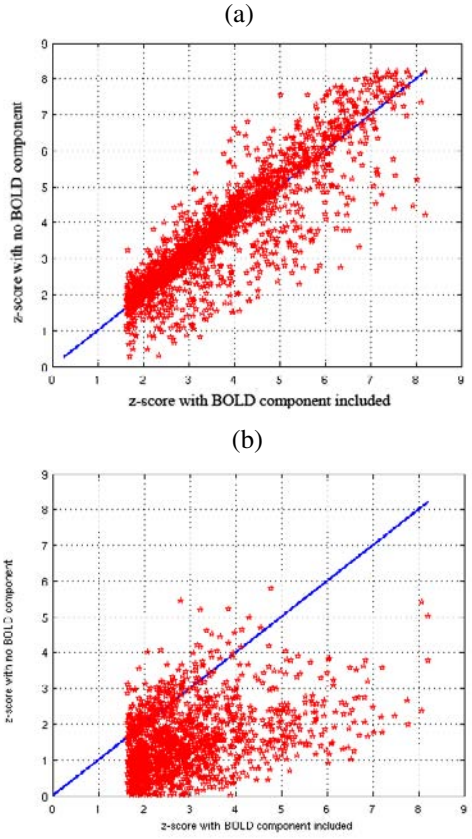

Figure 1
Comparison of Z-scores for voxels with significant perfusion activation in the (a) 1st and (b) 2nd echos

Results: The presence of the BOLD component in the GLM for the first echo data did not result in a significant difference in z-scores (p=0.37) and had a very small effect size (0.019) as seen in Figure 1a. For the second echo data, however, the presence of the BOLD component in the GLM resulted in a significant increase in z-scores (p<1e-278), with a large effect size (1.151) as shown in Figure 1b.

Discussion: For relatively short echo times (TE~9.1ms) the BOLD weighted static tissue term can be neglected without any loss in statistical power. However, for longer echo times (TE~30ms) the BOLD weighted static tissue term should be included in the analysis of ASL data in order to optimize sensitivity.

References: [1] Liu et al, Neuroimage 16, 269-282, 2002 [2] Hernandez et al, Proc. ISMRM 13, 1579, 2005 [3] Restom et al, Proc. ISMRM 12, 2525, 2004 [4] Liu et al, Neuroimage 24, 207-215, 2005 [5] Burock and Dale, Hum. Brain Mapp. 11, 249-260, 2000.