The Relation between BOLD amplitude and Baseline Cerebral Blood Flow Depends on the Analysis Scale

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Introduction
Previous functional magnetic resonance imaging (fMRI) studies have revealed substantial variation in the amplitude of the blood oxygenation level dependent (BOLD) response both across subjects and across brain regions and voxels within a subject. Although the source of this variability is not clear, growing evidence suggests the presence of significant vascular contributions, particularly through differences in baseline cerebral blood flow (CBF). For example, prior findings suggest that the BOLD response is inversely proportional to the baseline CBF [1] and venous oxygenation [2] across subjects (where venous oxygenation was found to be directly related to baseline CBF). Another study found the BOLD response is directly proportional to the baseline CBF across voxels [3]. These prior studies suggest that the relationship between the BOLD response and baseline CBF depends on the scale (per subject vs. per voxel) at which the signals are measured. In this study, we evaluate the mechanism by which the BOLD response depends on baseline CBF across subjects and voxels.

Theory
We use the deoxyhemoglobin dilution model [4] to examine the relationship between the BOLD response and baseline CBF. In this model, the BOLD signal change is given by:

$$\Delta BOLD_a/BOLD_0 = M\left(1 - (CMRO2_a/CMRO2_0)^{\beta}(CBF_a/CBF_0)^{\alpha-\beta}\right)$$

where $M \cong A \cdot (CBF_0)^{\alpha}(OEF)^{\beta}$ is the maximum BOLD response, CMRO2 is the cerebral metabolic rate of oxygen metabolism, β is a deoxyhemoglobin exponent, α is Grubb's exponent, A is a proportionality term representing scan and sample parameters, OEF is the oxygen extraction fraction, and the subscripts a and 0 indicate the active and baseline states, respectively. Within the framework of the model, here are two main mechanisms through which baseline CBF (CBF_0) may influence the BOLD response. In the first mechanism, CBF_0 may modulate the percent change in CBF ($\%\Delta CBF=100(CBF_a/CBF_0-1)$) as shown in a previous study [5]. In the second mechanism, changes in CBF_0 modulate M through their effect on OEF, which is defined as $OEF=(C_A CMRO2_0/CBF_0)$ where C_A is the arterial concentration of oxygen.

Methods
Ten subjects participated in the study after giving informed consent. Each experiment had: (a) a resting-state scan (8min 20s off), (b) two block design scans (60s on, 4 cycles of 20s on/60s off, 30s off; 8-Hz flickering checkerboard visual stimulus), (c) two hypercapnia scans (2min room air, 3min 5% CO2, 2min room air), and (d) CBF calibration scans. Subjects wore a non-rebreathing mask that could be connected to a 5% CO2 gas mixture. Images were acquired on a 3T GE whole body system with a body transmit coil and an 8 channel receive head coil. Scans (a)-(c) were acquired with a PICORE QUIPSSII arterial spin labeling (ASL) sequence with dual echo spiral readout (TE1/TE2=2.9/24ms; TI1/TI2=600/1500ms; TR=2.5s). Six oblique axial 5-mm slices were prescribed about the calcarine sulcus for all runs. ASL data were calibrated to physiological units (mL/(100mg-min)). Data from the two block design runs were concatenated, and voxels that showed both CBF (1^{st} echo; $p<0.05$) and BOLD (2^{nd} echo; $p<0.05$) activation were used to form a region of interest (ROI) for each subject. Data were then analyzed by subject and by voxel:

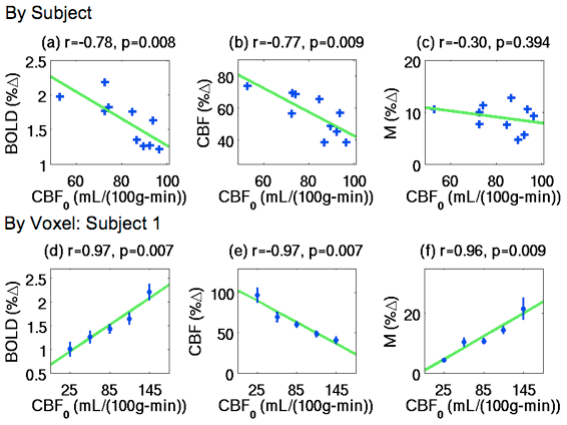
By Subject: Data were averaged over the ROI of each subject, and the percent BOLD change (%ΔBOLD) and %ΔCBF were computed for both the block design and hypercapnia scans. The maximum BOLD response (M) for each subject was calculated from per subject %ΔBOLD and %ΔCBF hypercapnia values using the Davis model [4]. The per subject CBF_0 values were calculated from the resting-state scan.

By Voxel: The per voxel %ΔBOLD and %ΔCBF were calculated for the block design and hypercapnia scans. M values were calculated from the hypercapnia values for each voxel. Per voxel CBF_0 were computed from the resting-state scan. To overcome the low signal-to-noise of voxel-wise measurements, it was necessary to average data over bins based on voxel-wise CBF_0 values. For voxels in the ROIs of each subject, %ΔBOLD, %ΔCBF, and M values were sorted into five bins by their corresponding per voxel CBF_0 values (bin thresholds (mL/(100g-min)): (1) >10 to ≤40, (2) >40 to ≤70, (3) >70 to ≤100, (4) >100 to ≤130, (5) >130 to ≤160). The per voxel %ΔBOLD, %ΔCBF, and M values were averaged within each CBF_0 bin for each subject. In addition, we also averaged bin values across subjects.

Results
By Subject: The figures in the top row show scatter plots of the per subject (a) %ΔBOLD, (b) %ΔCBF, and (c) M versus CBF_0, where all green lines in the figures denote linear fits. The CBF_0 was significantly correlated to both %ΔBOLD ($r=-0.78$, $p=0.008$) and %ΔCBF ($r=-0.77$, $p=0.009$). However, M was not significantly correlated to CBF_0 ($p=0.394$). Furthermore, %ΔBOLD was significantly correlated to %ΔCBF ($r=0.91$, $p<0.001$) but not M ($p=0.30$), suggesting that %ΔCBF is the main contributor to CBF_0 related BOLD variability across subjects.

By Voxel: The figures in the bottom row show scatter plots of the per voxel (d) %ΔBOLD, (e) %ΔCBF, and (f) M values versus the five CBF_0 bins for Subject 1, where the CBF_0 bins are labeled by their midpoint CBF_0 values, and vertical bars indicate standard error. Similar to the per subject data, per voxel %ΔCBF showed a significant negative correlation with CBF_0 ($r=-0.97$, $p=0.007$). In contrast to the per subject data, the per voxel CBF_0 exhibited a significant positive correlation with both %ΔBOLD ($r=0.97$, $p=0.007$) and M ($r=0.96$, $p=0.009$). In addition, per voxel %ΔBOLD showed a positive correlation with per voxel M ($r=0.99$, $p=0.002$) and a negative correlation with per voxel %ΔCBF ($r=-0.91$, $p=0.034$), indicating that either M or %ΔCBF may contribute to CBF_0 related BOLD variability across voxels. When the voxel-wise data was averaged in bins across subjects, CBF_0 was significantly correlated to the %ΔBOLD ($r=0.99$, $p=0.002$), %ΔCBF ($r=-0.93$, $p=0.02$), and M ($r=0.98$, $p=0.002$) values, indicating that voxel-wise trends found in Subject 1 are also representative of the remaining subjects.

Discussion
Our results suggest that variations in CBF_0 across subjects affect the BOLD response mainly through the dependence of %ΔCBF on CBF_0. In contrast, variations in CBF_0 across voxels appear to modulate the BOLD response through the dependence of M on CBF_0. Although %ΔCBF also showed a dependence on CBF_0 across voxels, the decrease in %ΔCBF with increased CBF_0 is unlikely to have given rise to the observed increase in %ΔBOLD with increases in CBF_0. The inverse correlation between M and CBF_0 across voxels indicates that the OEF may be relatively independent of CBF_0 across voxels, reflecting a tight coupling between $CMRO2_0$ and CBF_0 that is consistent with the conclusions of a previous study [6]. In contrast, the lack of significant correlation between M and CBF_0 across subjects suggests that the OEF may be inversely related to CBF_0 across subjects. These findings shed light on the basic mechanisms of the BOLD signal and suggest that different factors should be considered in the interpretation of the BOLD response when analyzing data across subjects versus across voxels.



References: [1] Cohen et al., JCBFM 22(9):1042;2002. [2] Lu et al., *Proc. ISMRM*:#613;2007. [3] Behzadi et al., *Proc. ISMRM*:#373;2006. [4] Davis et al., PNAS 95:1834;1998. [5] Kastrup et al., NeuroReport 10:1751;1999. [6] Fox et al., PNAS 83(4):1140;1986.