DEPENDENCE OF BOLD SIGNAL AMPLITUDE ON BASELINE VENOUS OXYGENATION AND CEREBRAL BLOOD FLOW

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Introduction

The vast majority of functional magnetic resonance imaging (fMRI) studies use measures of the blood oxygenation level dependent (BOLD) signal as a reflection of neural activity. However, the BOLD signal is a complex function of a number of physiological variables, and there is growing evidence indicating that changes in the baseline vascular and metabolic state can significantly modulate the amplitude of the BOLD signal. In a recent set of studies, Lu et al [1,2] presented a non-invasive method for measuring the oxygenation of venous blood and demonstrated a strong dependence (R^2= 0.44) of the BOLD signal amplitude on venous oxygenation across a sample of healthy young subjects. They also found a strong correlation (R^2=0.64) between baseline venous oxygenation and baseline cerebral blood flow (CBF), but did not find a significant correlation (R^2=0.17) between BOLD signal amplitude and baseline CBF. In contrast, another recent study [3], reported a significant correlation (R^2= 0.60) between BOLD signal amplitude and baseline CBF. The goal of this study was to resolve these contradictory findings and to investigate in detail the dependence of BOLD signal amplitude on both baseline venous oxygenation and CBF.

Experimental Methods

Eleven subjects participated in the study after giving informed consent. Each experiment had: (a) two TRUST scans (4 min 16s each) to measure baseline venous oxygenation, (b) one scan to measure baseline CBF (4min 10s), (c) two block design scans (60s on, 4 cycles of 20s on/60s off, 30s off; 8-Hz flickering checkerboard visual stimulus), (d) two hypercapnia scans (2min room air, 3min 5% CO_2, 2min room air), and (e) a high-resolution anatomical scan. Images were acquired on a 3T GE whole body system with a body transmit coil and an 8 channel receive head coil. The TRUST scans utilized a single-shot echo planar readout (TR=8 s, TI=1200 ms, TE=26 ms, FOV=23cm, one 5-mm slice through the sagittal sinus, tag thickness=80 mm, tag gap =20 mm, 64x64 matrix, 90° flip angle, effective TEs=0, 40, 80, and 160 ms, τ_{CPMG}=10 ms, 4 reps for each effective TE). Scans (b-d) 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 ASL runs. The first and second echo data from the ASL runs were used to obtain the CBF and BOLD responses, respectively, and the CBF data were calibrated to physiological units of (ml/100g/min). To facilitate comparison with prior studies, we defined two separate regions of interest (ROI) for further analysis: (a) a BOLD ROI and (b) a BOLD+CBF ROI. For each subject, the BOLD ROI included all voxels that showed significant BOLD visual activation ($p< 0.01$) in the block design runs. The BOLD+CBF ROI included all voxels that showed both significant BOLD and CBF visual activation ($p< 0.01$) as well as positive BOLD and CBF hypercapnic responses. Data were averaged over the ROI of each subject, and the percent BOLD change (%ΔBOLD) and percent CBF change (%ΔCBF) were computed for both the block design and hypercapnia scans. The latter were used to estimate BOLD signal parameters [4], but are not further discussed here due to space limitations. Venous oxygenation values were computed using the method described in [1] and the values from the two runs were averaged.

Results

Figure 1 shows the results obtained with the BOLD+CBF ROI. Consistent with the findings in [2] and [3], the BOLD signal amplitudes across subjects showed significant correlations with baseline CBF (Fig 1a, R^2 =0.62) and venous oxygenation (Fig 1c, R^2 =0.56). The functional CBF amplitudes also showed a significant correlation across subjects with both baseline CBF and oxygenation (Fig 1b, R^2 =0.71 and Fig 1d, R^2 =0.69), in agreement with prior studies [2,5].

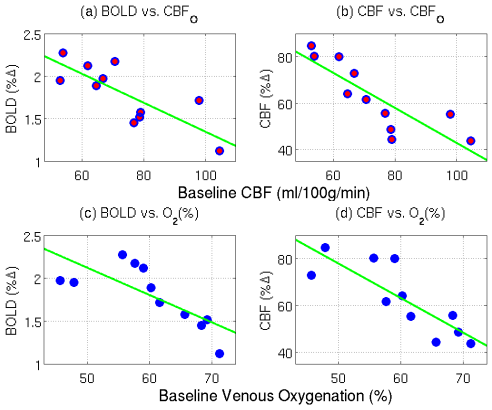

Figure 1. Results from BOLD+CBF ROI. BOLD and CBF functional amplitudes vs. CBF (top row) and baseline venous oxygenation (bottom row) .

Figure 2 shows results from the BOLD ROI, which was defined solely based on BOLD activation. Although the BOLD amplitude still shows a strong correlation (R^2=0.37, p=0.05) with baseline venous oxygenation (Fig. 2a), the correlation between BOLD and baseline CBF (Fig. 2b) is no longer significant (R^2=0.03, p=0.59). These results are consistent with those of [2] and suggest a potential issue with baseline CBF measures acquired within an ROI based on BOLD activation. Indeed, prior work [6] has pointed out that because arterial spin labeling primarily measures CBF in the gray matter, measures of CBF can be biased low in voxels that exhibit significant partial voluming with white matter and cerebrospinal fluid (CSF). To assess the effect of gray matter volume fraction on the results in the BOLD ROI, we used the high-resolution anatomical scan to estimate the gray matter volume fraction in each voxel and recomputed the baseline CBF values using only those voxels in the BOLD ROI that exceeded a specified gray matter volume fraction threshold. Figure 2c shows that the correlation between the baseline CBF and baseline oxygenation measures in the BOLD ROI increased monotonically as we increased the gray matter volume fraction threshold. Figure 2d shows a significant correlation (R^2=0.38, p=0.04) between BOLD amplitude and baseline CBF when a gray matter volume fraction threshold of 99% is used to compute baseline CBF for the BOLD ROI.

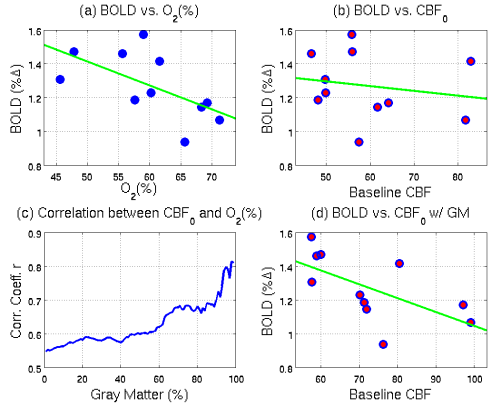

Figure 2. Results from the BOLD ROI. Baseline CBF measures in panel (d) were obtained with the application of a 99% gray matter volume fraction threshold.

Discussion

The results in Figure 1 show that both measures of baseline CBF and venous oxygenation are able to explain a large fraction of the inter-subject variability in the functional BOLD and CBF signals for a region of interest (BOLD+CBF) in which there is both significant BOLD and CBF activation. As functional CBF activation has been shown to be well localized to voxels with high gray matter volume fractions [7], the voxels within the BOLD+CBF ROI are more likely to have large gray matter volume fractions as compared to voxels within the BOLD ROI. For example, the BOLD ROI is likely to contain voxels with large draining veins that tend to have large BOLD activations and high CSF volume fractions. Application of a gray matter volume fraction threshold eliminates these voxels and restores the predictive power of the baseline CBF measures for the BOLD ROI (Fig 2d). In summary, both measures of baseline CBF and venous oxygenation are able to explain a significant portion of the inter-subject variability in the BOLD signal, but gray matter volume fraction needs to be considered when computing measures of baseline CBF with an ROI based solely on BOLD activation.

References: [1] Lu and Ge, MRM 60:357, 2008; [2] Lu et al, MRM 60:364, 2008; [3] Liau et al, ISMRM 2008, p. 854 ; [4] Davis et al, PNAS 95:1834, 1998; [5] Kastrup et al, Neuroreport, 10:1751, 1999. [6] Luh, W.M., ISMRM 2004, p. 1369. [7] Luh et al, MRM, 44:137, 2000.