INTER-SUBJECT VARIABILITY IN HYPERCAPNIC NORMALIZATION OF THE BOLD FMRI RESPONSE

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Introduction

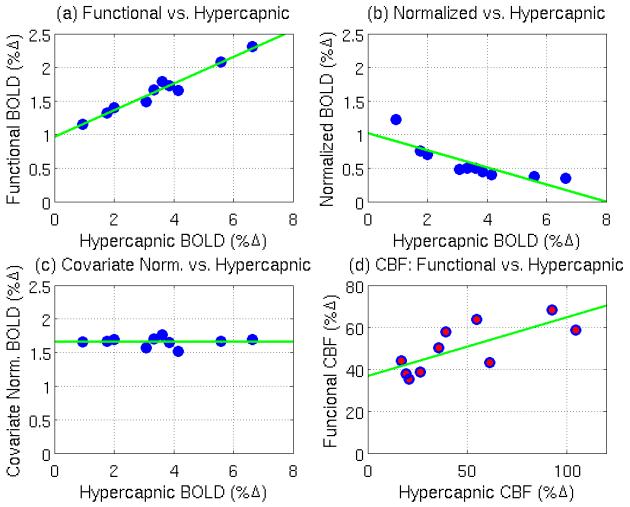
Although the blood oxygenation level dependent (BOLD) functional magnetic resonance imaging (fMRI) signal is widely used as a measure of neural activity, there is a growing appreciation that differences in the BOLD signal may reflect changes in other factors, such as inter-subject differences in baseline blood flow and volume. If these factors are not properly accounted for, differences in BOLD signal amplitude can be incorrectly interpreted as differences in neural activity. In addition, inter-subject differences in these factors can increase the variability of the BOLD signal across a group and thus decrease the statistical power of fMRI studies. Because the BOLD response to hypercapnia is thought to reflect primarily vascular factors, normalization by the hypercapnic response (i.e. division of the functional BOLD response by the hypercapnic BOLD response) has been proposed as a method to reduce BOLD signal variability due to non-neural factors [1]. With regards to inter-subject variability, some prior studies have shown that hypercapnic normalization can reduce inter-subject BOLD variability [2,3], while other studies have found an increase in inter-subject variability [4,5]. In this study, we used a combined theoretical and experimental approach to examine in detail the effect of hypercapnic normalization on inter-subject variability.

Theory

Prior studies [2,4] have noted a linear relation between the average functional BOLD responses B_i and the hypercapnic BOLD responses $B_{H,i}$ observed across a sample of healthy subjects of the form: $B_i = A \cdot B_{H,i} + G + E_i$, where A is the group slope, G is the group intercept, E_i is the residual to the linear fit, and the subscript i indicates the i^{th} subject. Normalizing by the subject average hypercapnic responses produces the normalized response for each subject of the form: $\hat{B}_i = B_i / B_{H,i} = A + G/B_{H,i} + E_i / B_{H,i}$, which is the sum of (a) the slope A between the functional and hypercapnic responses, (b) a systematic bias term $G/B_{H,i}$ that is inversely proportional to $B_{H,i}$, and (c) a residual term $E_i / B_{H,i}$. Note that the bias term $G/B_{H,i}$ represents systematic variability that is not eliminated by the hypercapnic normalization process. Using a mathematical model of the BOLD signal proposed by Davis et al. [6], it can be shown that the size of the intercept term G depends on the linear relation $F_i = c_1 \cdot F_{H,i} + c_2$ between the functional and hypercapnic CBF responses, denoted as F_i and $F_{H,i}$ respectively. Specifically, it can be shown that the BOLD intercept term G increases with the CBF intercept term c_2.

Experimental 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), and (c) two hypercapnia scans (2min room air, 3min 5% CO_2, 2min room air). Subjects wore a non-rebreathing mask that could be connected to a 5% CO_2 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 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/(100g-min)). Data from the two block design runs were concatenated, and voxels that showed both functional and hypercapnic cerebral blood flow (CBF) (1^{st} echo; $p<0.01$) and BOLD (2^{nd} echo; $p<0.01$) responses were used to form a region of interest (ROI) for each subject. 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. Hypercapnia normalized BOLD amplitudes were obtained by dividing each subject's average functional BOLD response amplitude by the corresponding hypercapnia BOLD response amplitude. As an alternative approach, we treated the hypercapnic BOLD amplitudes as a covariate and projected out the contribution of the hypercapnic functional response to obtain covariate normalized BOLD amplitudes. To facilitate comparison with prior studies, we also considered the effect of normalization under two additional conditions: (a) using an ROI based solely on the functional and hypercapnic BOLD responses and (b) normalizing on a per-voxel basis and then averaging to form a subject average response.



Results

As shown in panel (a), there was a strong linear relation (r =0.98) between the functional and hypercapnic BOLD responses with a significant ($p<0.001$) intercept term G = *0.97%*. The hypercapnia normalized BOLD response (panel (b)) showed an inverse dependence (r = -0.83) on the hypercapnic BOLD response, consistent with the presence of a systematic bias term $G/B_{H,i}$. In contrast, by construction the covariate normalized responses in panel (c) did not exhibit a linear dependence (r = 0.0) on the hypercapnic responses. As a measure of inter-subject variability, we computed the coefficient of variability (i.e., standard deviation over the mean) across the sample and obtained values of 0.21, 0.46, and 0.04 for the functional responses, the normalized responses, and the covariate normalized responses, respectively. Similar results (not shown) were found when using the BOLD-only ROI or when performing the normalization on a per-voxel basis. Panel (d) shows the linear relation (r =0.74) between the functional and hypercapnic CBF responses, with a significant ($p< 0.001$) intercept term c_2= *36.7%*. As discussed above, this CBF intercept term can be shown to give rise to the BOLD intercept term G.

Discussion

The presence of an intercept term G in the relation between the functional and hypercapnic BOLD responses resulted in a systematic bias term in the normalized responses and a 120% increase in inter-subject variability. Our finding of an increase in BOLD inter-subject variability with hypercapnic normalization is consistent with some prior studies [4,5], but not others [2,3]. Differences in the effect of hypercapnic normalization on inter-subject variability may reflect differences in the slope A and intercept G terms. The size of these terms are likely to depend on the experimental paradigm, specifically the type of hypercapnic task (e.g. breath-hold vs. 5% CO_2), the brain region, and the composition of the study group. Our findings indicate that the relative size of the positive intercept in the relation between the functional and hypercapnic BOLD responses needs to be considered in the analysis of hypercapnia normalized BOLD responses. Covariate-based hypercapnic normalization resulted in an 81% decrease in inter-subject variability and represents a promising approach for effectively dealing with the presence of the intercept term.

References: [1] Bandettini and Wong, NMR Biomed. 19:197, 2007; [2] Thomason et al, HBM 28:59, 2007; [3] Biswal et al, MRI 25:1359, 2007; [4] Handwerker et al , HBM 28:846, 2007, [5] Cohen et al, NIMG 23:613 2004 [6] Davis et al, PNAS 95:1834, 1998.