Baseline Cerebral Blood Flow Modulates Functional Perfusion Activation Maps but not BOLD Activation Maps

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Introduction

Measures of the spatial extent of functional activation are important for a number of functional MRI (fMRI) applications, such as longitudinal tracking of changes in brain activation with disease, cross-sectional studies of medical treatment, and pre-surgical planning. The interpretation of activation maps based on the blood oxygenation level dependent (BOLD) signal can be complicated by the BOLD signal's dependence on a number of physiological variables. As an alternative, functional perfusion or cerebral blood flow (CBF) activation maps obtained with arterial spin labeling (ASL) reflect the response of a single physiological variable. Functional CBF maps have been suggested to provide better localization to sites of neural activity as compared to BOLD [1] and more robust behavior in the presence of baseline signal drifts [2]. Prior studies have shown that the BOLD signal amplitude may be inversely related to baseline CBF [3], while the functional absolute CBF change may be either directly proportional to [4] or independent of [5] baseline CBF. These prior findings suggest that modulation of baseline CBF may alter the spatial extents of functional activation maps. In this study, we directly assess the dependence of both functional CBF and BOLD activation maps on baseline CBF.

Methods

Ten subjects participated in the study after giving informed consent and refraining from caffeine usage for at least 12 hours. Experiments included two 1-hour long imaging sessions (pre-dose and post-dose). Between sessions, subjects ingested a 200 mg caffeine pill and waited outside the magnet room for 30 minutes. Images were acquired on a 3T GE whole body system with a body transmit coil and an 8 channel receive head coil. Two block design (60s on, 4 cycles of 20s on/60s off, 30s off; radial 8-Hz flickering checkerboard visual stimulus) functional scans were acquired with a PICORE QUIPSSII ASL sequence with dual echo spiral readout (TE1/TE2=2.9/24ms; TI1/TI2=600/1500ms; TR=2.5s). Six oblique 5-mm slices were prescribed about the calcarine sulcus. High-resolution anatomical scans were used to align the post-dose to the pre-dose data. Data from the two functional runs were concatenated, and active voxels ($p<0.05$, corrected for multiple comparisons) in the pre-dose and post-dose (first echo) data were used to define the pre-dose and post-dose CBF regions of interest (ROIs), respectively. For each subject, a joint CBF ROI was formed from the intersection of the pre-dose and post-dose CBF ROIs. This process was repeated with the second echo data ($p<0.05$) to form the pre-dose, post-dose, and joint BOLD ROIs. Contrast-to-noise ratio (CNR) values were defined as (functional signal change)/(noise standard deviation), and CNR estimates were averaged over all voxels within the joint ROI (CBF or BOLD) to form average pre-dose and post-dose CNR values for each subject. ASL data were calibrated to physiological units of (mL/(100mg-min)), and values of baseline CBF, the absolute CBF change (ΔCBF), and CBF noise standard deviation ($\sigma_{n,CBF}$) were obtained in physiological units using a general linear model fit to the functional CBF responses; per-subject pre-dose and post-dose values for these measures were obtained by averaging over the joint CBF ROI. Paired t-tests were used to compare pre-dose versus post-dose values of the various measures. Finally, correlation analyses were performed between baseline CBF values and both the number of active CBF voxels and CBF CNR values.

Results

The top row of Figure 1 shows representative data from Subject 1, where pre-dose and post-dose (a) CBF and (b) BOLD activation maps are overlaid on baseline CBF maps (CNR indicated by colorbar). The number of active CBF voxels was visibly decreased from the pre-dose (1a, left) to post-dose (1a, right) conditions. In contrast, there was no clear caffeine-related effect on the number of active BOLD voxels (1b). Figure 1 also shows scatter plots of the post-dose vs. the pre-dose (c) number of active CBF voxels and (d) CBF CNR, where the black diagonal lines indicate lines of equality. Consistent with the activation maps, the caffeine dose significantly reduced the number of active CBF voxels ($p=0.003$) but not the number of active BOLD voxels ($p=0.69$, plot not shown). In agreement with the caffeine-induced decrease in the number of active CBF voxels, caffeine significantly decreased the CBF CNR ($p=0.024$). The caffeine dose did not significantly change the BOLD CNR ($p=0.39$, plot not shown), consistent with caffeine's lack of effect on the number of active BOLD voxels. The decrease in CBF CNR is consistent with a significant caffeine-induced decrease in ΔCBF (-18.9%, $p<0.001$) accompanied by no significant change in $\sigma_{n,CBF}$ ($p=0.25$). As expected, caffeine also led to a significant decrease in baseline CBF across subjects (-36.8%, $p<0.001$). The bottom right portion of Figure 1 shows scatter plots of the (e) number of active CBF voxels and (f) CBF CNR vs. baseline CBF for data from the pre-dose (blue +'s) and post-dose (red +'s) sessions. Green lines indicate linear fits. There was a significant correlation between baseline CBF and the number of active CBF voxels for the pre-dose data ($r=0.76$, $p=0.011$), the post-dose data ($r=0.65$, $p=0.042$), and the union of the pre and post-dose data ($r=0.72$, $p<0.001$). Significant correlations were also observed between baseline CBF and CBF CNR (pre-dose: $r=0.65$, $p=0.043$; post-dose: $r=0.71$, $p=0.022$; pre and post-dose $r=0.66$, $p=0.001$).

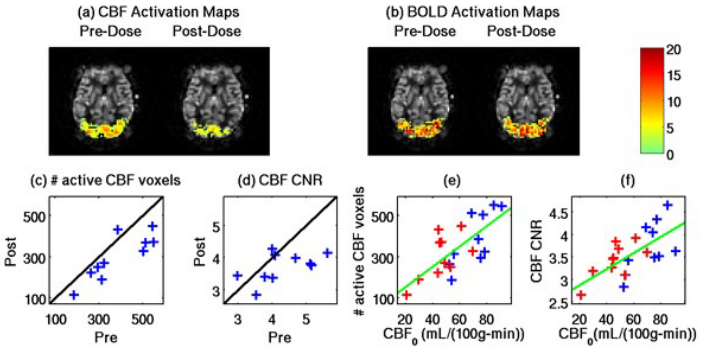

Figure 1 (a,b) CBF and BOLD Activation maps; (c,d) Post-dose vs. pre-dose plots for number of active voxels and CNR; (e, f) Number of voxels and CNR versus baseline CBF.

Discussion

The caffeine-induced reduction in baseline CBF was accompanied by a decrease in the activation map area and CNR of the CBF but not the BOLD response. The reductions in CBF activation map area and CBF CNR are consistent with a decrease in ΔCBF without a significant change in $\sigma_{n,CBF}$. Measures of baseline CBF also accounted for a significant portion of the inter-subject variability in CBF activation map area and CNR. Factors that can modulate baseline CBF, such as age, medication, and disease, should therefore be carefully considered in the interpretation of studies that use functional CBF activation maps.

References: [1] Luh et al., MRM 44:137;2000. [2] Wang et al., MRM 49:796;2003. [3] Cohen et al., JCBFM 22(9):1042;2002. [4] Shimosegawa et al., JCBFM 15(1):111;1995. [5] Kastrup et al., Neuroreport 10(8):1751;1999.