The Ratio of CBF to CMRO2 Change with Brain Activation Increases with Increasing Stimulus Amplitude in Human Visual Cortex

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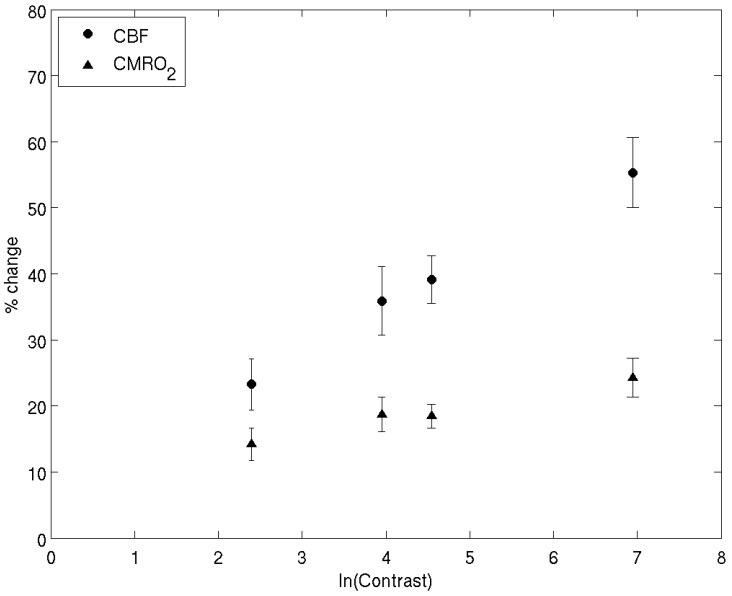
Purpose: Although functional magnetic resonance imaging (fMRI) based on blood oxygenation level dependent (BOLD) signal changes provides a useful tool for mapping brain activation, a quantitative interpretation of the magnitude of the BOLD response remains problematic. The BOLD response is primarily driven by cerebral blood flow (CBF) changes, but is strongly modulated by *n*, the ratio of the fractional change in CBF to the change in cerebral metabolic rate of oxygen consumption ($CMRO_2$). A number of studies have found significant regional variation of *n* across the brain [1,2], but variability within the same brain region for different stimuli has been relatively unexplored (with the exception of [3]). We used a calibrated BOLD method to test whether *n* varies with the contrast of a visual stimulus within a single brain region.

Methods: Nine healthy adult subjects were studied using a dual-echo spiral arterial spin labeling (ASL) method (single-shot PICORE-QUIPSS II [4]) that provides simultaneous measurements of CBF and BOLD responses. For each subject, responses were measured to four levels of contrast between the gray levels of a radial checkerboard flickering at 8 Hz. Contrast was calibrated with a photometer, and the background gray level was adjusted to avoid any change in overall luminance between task and control conditions. Stimuli were presented in a 20s block, with 60s of neutral gray between blocks. Four runs were collected for each subject, each consisting of one block each of the four different contrast levels, with the order of presentation randomized across runs. To select a region of interest (ROI) for averaging in each subject, the CBF responses for all stimuli were pooled and significant activations were found with a general linear model approach. ROI-averaged BOLD and CBF response curves to the four stimulus levels were constructed, and the corresponding change in $CMRO_2$ for each stimulus level was calculated using the Davis model [5]. For these calculations, we used an assumed value of the scaling parameter *M* (7%), and tested the significance of this assumption by repeating the calculations for different values of *M* over a range (5-9%) we have found with hypercapnia calibration under similar experimental conditions.



Results: The CBF response was approximately linear with the log of the absolute contrast expressed in candelas/m^2 (see Figure). For a fixed coupling ratio *n*, the ratio of the CBF change to the BOLD change is expected to increase with a larger CBF response due to the ceiling effect on the BOLD signal. In this data, however, that ratio *decreased* by a factor of 2 from lowest to highest contrast, implying that the $CMRO_2$ change rolled off with increasing stimulus contrast (calculated $\Delta CMRO_2$'s shown in the Figure are for *M*=7%), leading to an increase of *n* from 1.72 ± 0.26 to 2.3 ± 0.30 (mean ± SD). The increase of *n* was significant for all of the assumed values of *M* tested.

Discussion and Conclusions: Recently we showed that relatively modest differences in the CBF/$CMRO_2$ coupling ratio *n* from ~1.6 to about ~2.2 observed in basal ganglia and visual cortex have a strong effect on the magnitude of the BOLD response relative to the change in CBF [1]. While these were interpreted as regional differences in *n*, we could not exclude the possibility that *n* varies with the magnitude of the evoked response. The current study demonstrates a similar range of variation within the visual cortex as the stimulus amplitude, and the associated evoked CBF response, increases. The important implication for BOLD-fMRI studies is that CBF/$CMRO_2$ coupling is not fixed, even within the same brain region. A possible hypothesis for the observed variation is that the CBF change is driven directly by excitatory synaptic activity in a feed-forward manner, while $CMRO_2$ responds as needed to meet the total energy demands of the neural activity. The observed change in *n* would then reflect a tapering off of the full evoked response as the driving stimulus continues to increase.

[1] Ances, Neuroimage 39:1510, 2008; [2] Chiarelli, MRM 57:538, 2007; [3] Hoge PNAS 96:9403, 1999; [4] Wong MRM 39:702, 1998; [5] Davis, PNAS 95:1834,1998