CBF/CMRO2 coupling measurements with calibrated BOLD-fMRI: Bias due to voxel selection

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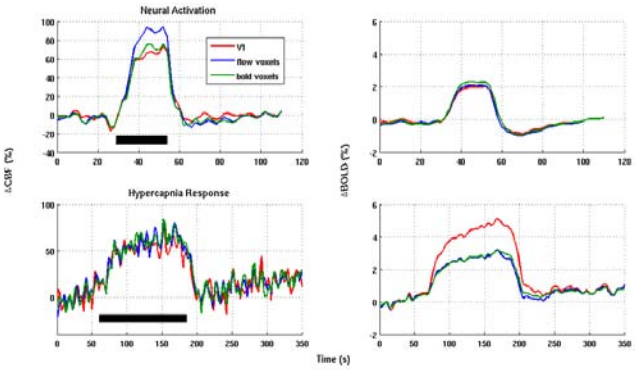
Introduction

The coupling of cerebral blood flow (CBF) and the cerebral metabolic rate of oxygen ($CMRO_2$) during brain activation can be characterized by the ratio *n* of the fractional CBF change to the fractional $CMRO_2$ change. The consistent observation of the BOLD effect supports the conclusion that $n>1$, but measurements of *n* with MRI and PET techniques have yielded a wide range of values from 2-5 [1-5]. It is not known whether this variability is due to the measurement techniques or to the physiological quantity itself. Calibrated BOLD techniques [3,4] provide a way to measure *n* based on combined detection of both BOLD and CBF changes, measured with arterial spin labeling (ASL) techniques, and comparison of the responses to neural activation with the responses to CO_2 inhalation. By averaging over a defined region of interest (ROI), this approach provides a potentially powerful tool for quantitatively assessing local brain function in both health and disease, and in a test/retest study we found a reproducibility of about 7% in visual cortex [6]. However, relatively little attention has been paid to the degree to which the method of voxel selection for averaging biases the estimate of *n* with this approach. In this study we measured perfusion and oxygen metabolism in the visual cortex using an ASL/BOLD technique and compared the results obtained with three different approaches for defining an ROI for averaging: 1) visual area V1, defined by retinotopic mapping; 2) a functional localizer choosing flow-weighted voxels; and 3) a functional localizer choosing BOLD-weighted voxels.

Methods

Seven healthy subjects were recruited and scanned according to guidelines of the UCSD IRB. All subjects underwent a preliminary scan session in which standard stimuli for retinotopic mapping [7] were shown and visual area V1 was mapped. For functional studies, subjects viewed a stereotyped block design 8 Hz flashing checkerboard stimulus (20 s on, 40s off, 4 cycles) during 4 separate runs while simultaneous acquisition of BOLD and CBF images were acquired using a dual echo spiral acquisition of *k*-space. During an additional 2 runs, subjects breathed a gas mixture consisting of 5% CO_2 for two periods of two minutes each separated by 4 minutes breathing air. The first activation run was acquired with PICORE [8] and data from this scan was used to construct two binary masks, each consisting of either CBF or BOLD activated voxels, defined by a correlation threshold of 0.6 with 12 neighbor clusters. For all remaining functional runs a QUIPSSII/PICORE [8] pulse sequence was used with: TR=2000ms, TI1=700ms, TI2=1400ms, TE1=9.4ms, TE2 = 30ms,tag thickness=20cm, 4 oblique slices centered on the calcarine sulcus, in-plane resolution 2.68x2.68 mm and a slice thickness of 7mm. Additionally, pulse waveforms and respiratory motions were recorded and algorithms for physiological noise reduction were applied [9]. For each subject the average CBF and BOLD curves in the activation and CO_2 experiments were constructed for each of the three ROI selection methods, and analyzed with a model of the BOLD signal [3] to first calculate *M*, the maximum possible BOLD signal increase based on the CO_2 experiment with the assumption that $CMRO_2$ remained constant, and then using that value of *M* to calculate the $CMRO_2$ change in the activation experiment and compute *n*.



Results

As shown in the figure and table, the average values of *n* varied from 2.2-5.1 for the different ROI selection methods, although the values for each method were reasonably tightly clustered. Compared with values calculated using a flow localizer, the BOLD localizer ROI produced a similar value of *M* but a much higher value of *n*, while a V1-averaged ROI produced a much higher estimate of *M* and a lower value of *n*.

ROI	*M*	*n*
V1	.12±.02	2.23 ± .15
BOLD	.07±.03	5.10 ± .16
FLOW	.07±.03	3.44 ± .14

Conclusion: The $CBF/CMRO_2$ coupling ratio *n* estimated from a calibrated-BOLD experiment varies substantially depending on how an ROI is constructed for averaging. A possible explanation for these results is that the flow-localizer is the most accurate, and the other two approaches are biased because: 1) the BOLD-localizer approach includes some gray matter voxels that are not directly activated but contain veins draining an active area, resulting in an artifactually high BOLD response in the activation study but a similar response in the CO_2 study; and 2) the V1-localizer approach includes voxels containing larger veins that only respond to the global CO_2 challenge, biasing the calculation of *M* to higher values and thus underestimating *n*.

References: [1] Fox and Raichle, PNAS USA 83:1140,1986 [2] Marrett et al., Adv.Exp.Med.Biol. 413:205,1997; [3] Davis et al., PNAS USA 95:1834, 1998; [4] RD Hoge et al., MRM. 42:849, 1999; [5] Kastrup et al, Neuroimage 15:74, 2002; [6] Leontiev, et al., Proc. SFN, 2005; [7] Engel et al., Nature 369:370, 1994; [8] Wong et al., MRM 39:702,1998; [9] Restom et al., Proc. ISMRM,2004.