NEUROVASCULAR METABOLISM COUPLING IN THE HUMAN VISUAL CORTEX: A BIOPHYSICAL BOLD FMRI MODEL COMPARISON

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Introduction: Based on the steady state calibrated deoxyhemoglobin dilution model of the blood level dependent (BOLD) signal [1-2], fMRI has been used to show a linear coupling between changes in human cerebral metabolic rate of oxygen ($\Delta CMRO_2$) and blood flow (ΔCBF) under neuronal activation [3]. Based on an alternate model [4], recent data by Lin *et al* [5] suggest a significant variation of this neurovascular coupling as a function of stimulus frequency in the primary visual cortex. The alternate model eliminates three approximations on which the calibrated model is based: (1) the relationship between steady state CBF and blood volume (CBV) is measured directly using VASO [6] rather than estimated using the Grubb relationship [7], (2) the intra- and extra-vascular BOLD components are evaluated separately rather than together and (3) no global hypercapnic calibration is involved. Since stimulus dependent variations in coupling would seriously limit the interpretability of BOLD results, we evaluated $\Delta CMRO_2$ and associated coupling ratio by both models in an fMRI study measuring measuring BOLD and CBF under five visual stimulus frequencies. The results were further compared to those from Lin *et al* [5].

Methods: Eleven healthy subjects were presented with a maximal contrast radial yellow/blue checkerboard (30 spokes and 3 rings) reversing contrast at 1,4, 8, 16, and 32 Hz. At each frequency, the visual stimulus alternated with a baseline (uniform grey field) in two sessions of 20 s / 80 s / 80 s OFF/ON/OFF blocks preceded by an 80 s baseline. An hypercapnic condition was induced with 7.5 % inhaled CO_2 (21 % O_2 and balance N_2) based on the same paradigm. A 3D T1-weighted data set was collected for anatomical reference to guide placement of six 5 mm oblique axial functional slices in the primary visual cortex. An interleaved QUIPSS II ASL-BOLD echo planar imaging (EPI) sequence was used with a TR of 2 s and a TE of 23 and 30 ms for ASL and BOLD images, respectively. The inversion slab thickness was 100 mm, the delay (TI_1), 700 ms and the post-label delay (TI_2), 1300 ms. The pixel size was 4.0 x 4.0 mm^2. A 3T Siemens Trio scanner was used.

Data Analysis: After separating the interleaved fMRI data into perfusion and BOLD frames, the perfusion data was formed by subtracting adjacent non-selective and selective images. Motion correction, spatial smoothing and drift removal were carried out before applying student's t-tests to identify areas of statistically significant task correlated activation. Regions of interest (ROI) in the visual cortex were defined separately for BOLD and CBF by thresholding the respective t-maps at t=4.5 ($p<0.05$, corrected for multiple comparisons). Overlapping ROIs were obtained to ensure the calculated signal changes occurred over the subset of voxels common to both BOLD and CBF. Two subjects were rejected from further analysis as their t-maps did not show significant activation. Average time courses were calculated at each stimulus condition for each remaining subject by averaging across the two sessions. The mean amplitude of the functional response was then obtained by averaging the signal intensity across all steady state activation frames, excluding the first 16 s. CBV was estimated from CBF measurements through Grubb's relationship ($\alpha = 0.38$).

Results and Discussion: The range of per-subject calibration values ($M_{subject}$ = 3.20 ± 0.25 % to 7.45 ± 0.22 %) and the group calibration value (M_{group} = 6.34 ± 0.16 %) agree with results from others [8-9]. Based on CBV estimates from Grubb and a per-subject calibration, the calibrated model yields a similar frequency trend in $\Delta CMRO_2$ as the non-calibrated model, although displaying smaller mean amplitudes (Figure 1). On the contrary, Lin *et al* results from the calibrated model showed larger $\Delta CMRO_2$ values with a peak at a higher frequency.

This discrepancy in $\Delta CMRO_2$ mean amplitudes arises from their use of a large group calibration value (M_{group} = 24 %) extrapolated from the value of M = 22 % of another study at 1.5 T [1]. We reproduced this effect in our results by recalculating $\Delta CMRO_2$ with the calibrated model but this time, performing a group calibration based on the M_{group} they used. It has been shown here and elsewhere [8] that larger M values generate greater linearity in coupling ($n = \Delta CBF/\Delta CMRO_2$) independently of the experimental data (Figure 2). A subject-specific calibration may be more appropriate to characterize the inherent variability in flow-metabolism coupling between individuals.

The large dependency of n on frequency reported by Lin *et al* based on the non-calibrated model diminishes if we recalculate $\Delta CMRO_2$ using their experimental data but replacing VASO measurements with estimates from Grubb's relationship. The recalculated coupling ratios (n = 2.1-3.0) display the same slight frequency trend as our results from the calibrated model (n = 3.1-4.1), which agree with previous results from our group at 4 Hz (n ~ 4) [9]. The main source of coupling non-linearity reported by Lin *et al* hence appears to arise not from the model employed but rather from VASO measurements showing a dependence of the CBF-CBV relationship upon stimulus frequency. This requires further investigation.

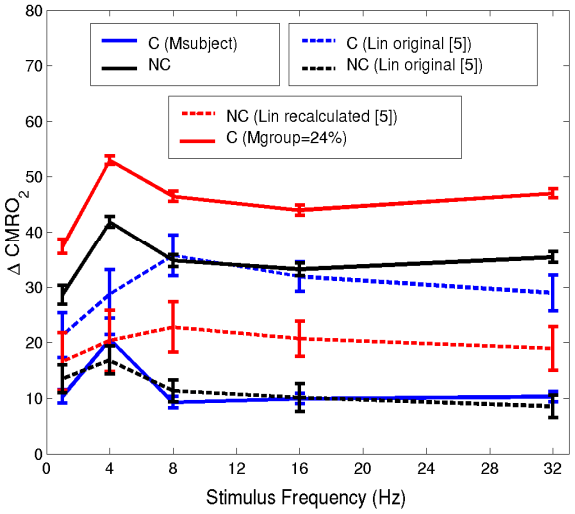

Fig.2 Changes in $CMRO_2$ calculated in our study (solid lines) based on the calibrated (C) and non-calibrated (NC) models and their comparison to Lin *et al* [5] (dash lines) original and recalculated values.

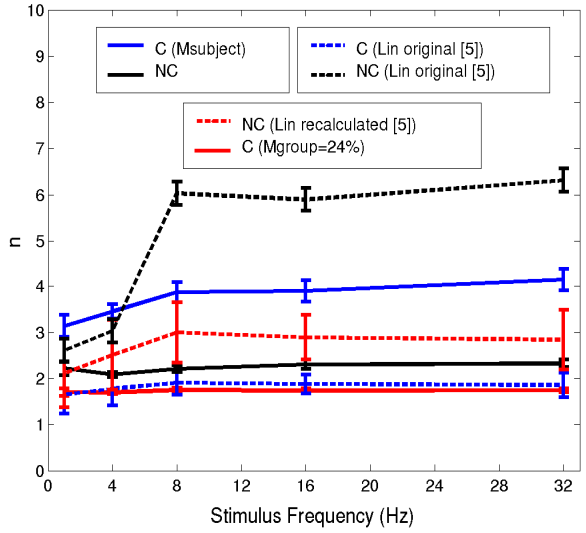

Fig.2 Changes in coupling ratio (n) calculated in our study (solid lines) based on the calibrated (C) and non-calibrated (NC) models and their comparison to Lin *et al* [5] (dash lines) original and recalculated values.

References: [1] Hoge et al., Mag Reson Med 1999; 42:849-863. [2] Davis et al., Proc Natl Acad Sci USA 1998; 95:1834-1839. [3] Hoge et al., Proc Natl Acad Sci USA 1999; 96:9403-9408. [4] Lu et al., J Cereb Blood Flow Metab 2004; 24:764-770. [5] Lin et al., Proc ISMRM 2006; 14:539. [6] Lu et al., Mag Reson Med 2006; 54:1403-1411. [7] Grubb et al., Stroke 1974; 5:630-639. [8] Chiarelli et al., Neuroimage 2006; doi:10.1016/j.neuroimage.2006.08.033. [9] Stefanovic et al., Neuroimage 2006; 30:726-734.