A generalized procedure for calibrated MRI incorporating hyperoxia and hypercapnia

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Introduction: Calibrated MRI techniques for estimating changes in the cerebral metabolic rate of O_2 consumption ($CMRO_2$) have been the subject of increasing interest, given their potential for investigating the biological basis for changes occurring in aging and neurodegenerative disease [1,2]. Although different variants of calibrated MRI have been described, they generally involve estimation of a parameter *M*, equivalent to the maximum possible BOLD signal change that would occur upon complete removal of all deoxygenated hemoglobin [dHb] from the brain. Typically, *M* is extrapolated from smaller signal changes induced by hypercapnia (which achieves partial elimination of dHb through increased blood flow) [3] or hyperoxia (which reduces dHb through increased arterial PO_2) [4]. The quality of $CMRO_2$ estimations is critically dependent on the robustness of the *M* parameter estimation. Here, we present a generalization of previous BOLD signal models which can be applied to data acquired during hypercapnia (HC), hyperoxia (HO), or both of the latter conditions applied simultaneously (HO-HC). We demonstrate the application of this generalized model during all three of the above conditions, with HO-HC induced through inhalation of carbogen ($7\%CO_2/93\%O_2$). Simultaneous increases in inspired O_2 and CO_2 are known to produce larger BOLD signal changes than O_2 or CO_2 alone [5], allowing estimation of *M* based on a closer measured BOLD value.

Theory: Chiarelli et al. [4] adapted the original BOLD calibration model of Davis et al. [3] to estimate *M* during hyperoxia. The Chiarelli formulation makes a number of approximations which are likely to be valid under the small decreases in cerebral blood flow (CBF) expected during hyperoxia. We introduce here a modification which allows the model to be applied during arbitrary changes in both arterial PO_2 and CBF. Specifically, Equation 12 for Cv_{O2} in [4] can be modified to the form shown on the left, which takes into account changes in CBF during calibration. Here, Cv_{O2} is the venous oxygen content, Ca_{O2} is the arterial oxygen content (estimated using the arterial saturation obtained from the Severinghaus equation and assuming end-tidal O_2 values to be equivalent to arterial O_2 partial pressure), and OEF is the oxygen extraction fraction (assumed here to be 0.3). The subscript '0' is used to denote resting values. The venous O_2 saturation (Sv_{O2}) during global manipulations such as hypercapnia or hyperoxia can be estimated using Equation 14 from Chiarelli. With variable CBF incorporated explicitly in the revised expression for Cv_{O2}, we can drop the CBF correction term 'C' from Equation 8 in Chiarelli, yielding the expression shown on the right for fractional BOLD signal change. This equation can be solved for *M*, which can then be used to estimate $CMRO_2$ using the Davis et al. formula [3]. The extended model reduces to the Davis hypercapnia model [3] when arterial PO_2 does not change, and should be slightly more accurate in the case of a pure hyperoxia calibration.

$$Cv_{O2} = Ca_{O2} - \frac{\left(Ca_{O2}|_0 \cdot OEF_0\right)}{\left(\frac{CBF}{CBF_0}\right)}$$

$$\frac{\Delta BOLD}{BOLD_0} = M\left(1-\left(\frac{CBF}{CBF_0}\right)^{\alpha}\left(\frac{(1-Sv_{O2})}{(1-Sv_{O2}|_0)}\right)^{\beta}\right)$$

Methods: Acquisitions were conducted in seven subjects on a 3T MRI system. One subject was excluded from analysis because of technical problems during acquisition. Sessions included an anatomical, $1mm^3$ MPRAGE acquisition (TR/TE/alpha = 2300ms/3ms/90°, 256x240 matrix) and four pseudo-continuous arterial spin labeling (pCASL) runs, providing simultaneous BOLD contrast using dual-echo readouts (TR/TE1/TE2/alpha = 2000ms/10ms/30ms/90° with 4x4x7mm voxels, 64x64 matrix and 11 slices, post-label delay=900ms, tag duration=2s, with a 100mm gap). One run each of visual stimulation and three gas manipulation runs (100% O_2, 7% CO_2/93% air and 7% CO_2/93% O_2). During all functional runs, there was a single three-minute block of stimulus. The visual stimulus was a flashing black and white radial checkerboard, flashing at 8 Hz. The first 60 s after breathing-gas transitions were excluded from the analyses. Regions of interest (ROI's) were derived from thresholded ($p<0.05$ corrected) visual subjects activation maps and grey-matter automatic segmentation [6]. Percent changes were calculated by dividing effect sizes over the visual ROI by the constant term from the GLM fit over that region. *M* estimates were calculated using the model described above [5] and $CMRO_2$ using the formula in Davis et al. [3]. Standard error (SE) estimates on *M* values were obtained through Monte Carlo simulations of error propagation. *M* parameters for the hyperoxia method were calculated using a fixed flow decrease of 5% based on data from [7]. All CBF measurements acquired during hyperoxia were corrected for changes in the T1 of arterial blood as described in [4,5,7].

Results: Group average CBF changes measured during HO-HC and during HC alone were similar (65.0±9.1% and 65.6±6.2%, respectively). A group average flow response of -4.4±2.7% was measured during HO, but the assumed value of 5% was used in individual analyses since non-physical values (e.g. negative or imaginary numbers) resulted in a number of cases when the measured CBF was used. BOLD signal increases measured with the HO-HC calibration (4.3±0.3%) were larger than those measured during either HC (2.3±0.2%) or HO (2.0±0.2%). Group average M values over all grey matter (Fig. 1B) were 7.9±0.2% for HO-HC, 7.1±0.2% for HC, and 5.3±0.4% for HO. In visual cortex (Fig.1A), the average *M* value over all subjects was 6.7±0.7% with HO-HC, 5.1±0.7% with HC, and 6.6±0.9% with HO. Estimates of visually evoked $CMRO_2$ change in individual subjects using our extended model (Fig. 2) were comparable for all gas manipulations, with the exception of subject 2, for whom the HC calibration indicated an anomalously low $CMRO_2$ response.

Conclusions: The new model formulation was applied to the three different MRI calibration procedures: hypercapnia, hyperoxia, and a new hybrid calibration (HO-HC) made possible by the generalized model. While comparable group average results were achieved using the different calibration procedures, the HO-HC manipulation was the only method which yielded physiologically valid *M* and $CMRO_2$ estimates in all subjects based on individual measurements of BOLD and CBF changes during calibration. This latter finding is consistent with our prediction that estimation of *M* and $CMRO_2$ based on the higher BOLD and CBF changes yielded by the HO-HC manipulation will be more robust.

References: [1] Ances, BM et al., *HBM* 30, 1120-32 (2009); [2] Ances, BM et al., *Neuroimage*, Epub ahead of print (2010); [3] Davis, TL et al., *PNAS* 95, 1834-9 (1998); [4] Chiarelli, PA et al., *Neuroimage* 37(3), 808-20 (2007); [5] Gauthier, CJ et al., *Neuroimage*, Epub ahead of print (2010); [6] Ad-Dab'bagh et al., *OHBM* 2006; [7] Bulte DP et al., *JCBFM* 27,69-75 (2007)

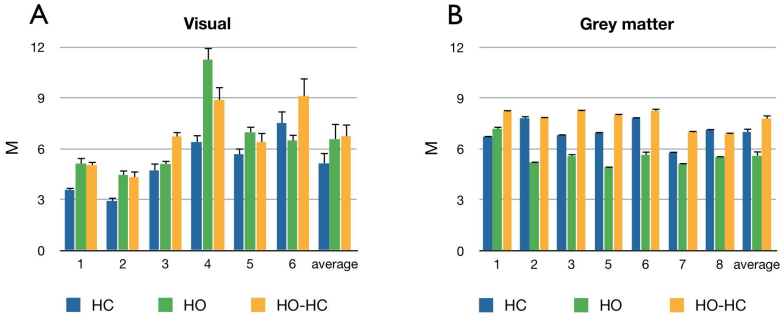

Fig. 1 Individual and average *M* values for each calibration technique
Individual and average *M* values in (A) visual cortex and (B) all grey matter are shown here for the hypercapnia (HC), hyperoxia (HO) and combined hypercapnia and hyperoxia (HO-HC) techniques.

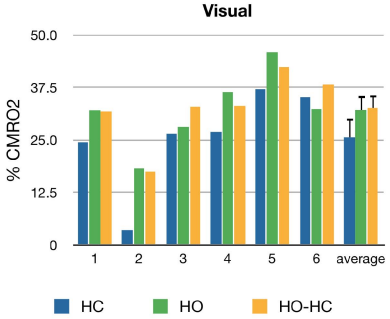

Fig. 2 Individual and average visual task $CMRO_2$ estimates for each calibration technique
Visually-evoked $CMRO_2$ responses were computed using *M* values estimated using the hypercapnia (HC), hyperoxia (HO) or combined hypercapnia and hyperoxia (HO-HC) calibration techniques.