Deoxyhemoglobin and hypercapnia based fMRI calibration methods

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Introduction: Stimulus-induced BOLD signal change is dependent on changes of the brain cerebral blood flow (CBF), venous cerebral blood volume (vCBV) and cerebral metabolic rate of oxygen ($CMRO_2$), as well as baseline physiological parameters (e.g. hematocrit level, baseline CBV and oxygen extraction fraction, OEF)[1]. There are generally two methods of fMRI calibration for determining the maximal BOLD signal change from baseline: deoxyhemoglobin(dHb)-based R2' and CBF/CBV based hypercapnia or hyperoxia methods. The individual baseline physiological parameters needed for hypercapnia calibration involve baseline $CMRO_2$, reported by Jain et al to vary by ~8%, together with other unknown physiological parameters such as vascular geometries and OEF.[2] The advantage of using R2', in comparison to hypercapnia/hyperoxia, includes simple experimental setup, and no need for baseline physiological parameter estimation or assumptions about the metabolic response of the stimulus. However, R2' calibration might be complicated by non-dHb related field inhomogeneity sources such as brain iron. The purpose of this study was to compare the calibration parameter, M, using the two methods, and to establish a possible scaling factor between them.

Methods: For dHB based calibration, an asymmetric spin echo (ASE) pulse sequence[3] using a segmented EPI with 33 lines of phase space were obtained for each excitation (i.e., EPI factor=33) at 3T field strength, with TE=40 ms, and 180° (sinc) echo offsets (t_s) equal to 0, −4ms, and −16 ms (negative signs indicating a reduction in the interval between the refocusing pulse and the initial 90° excitation pulse). Scan parameters include: FOV: 220×220 mm^2, matrix size: 128x128 mm^2, slice thickness: 1.7 mm, yielding an isotropic resolution of 1.7 mm, and TR: 3420 ms to obtain a total of 48 axial slices. The acquisition was repeated four times to facilitate error estimation. R2' maps were obtained with a quadratic exponential fitting[4], given the short echo offset at 3T. The macroscopic (i.e. large scale, greater than voxel size) magnetic field inhomogeneity (yielding $R2'_{macro}$) was obtained from the phase difference between two successive echo offsets. Maps of R2' and corrected R2' (termed $R2'_{meso}$ to express that the relaxation rate due to mesoscopic inhomogeneities caused by venous blood in the microvasculature) were scaled by TE to derive the calibration factor $M_{R2'}$ based on the equation $M_{R2'} = TE \cdot k \cdot V_0 \cdot [dHb]_0^{\beta} = TE \cdot R2'$ [1]. Hypercapnia based calibration involved the subject breathing both room air and 5% CO_2 in 95% room air. CBF and BOLD images were used for calibration assuming that mild hypercapnia does not change $CMRO_2$. BOLD data were acquired with a gradient-echo EPI sequence (TR/TE: 2 sec/25 msec, FA: 70°, FOV: 220 x 220 mm^2, matrix size: 74 x 74), and pseudo-continuous ASL (pCASL)[5] based on 2D EPI (TR/TE: 3.9 sec/17 msec, FA: 90°, 1.5 sec labeling duration and 1.23 sec of post label delay) was implemented for CBF quantification. $M_{hypercapnia}$ was calculated based on Davis' biophysical model[6]. As of this publication, sixteen healthy subjects have performed the hypercapnia study (mean age: 37.8 ± 14.3 years) and three subjects for the dHB study.

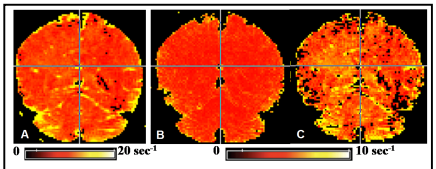

Figure 1. A: R2' map based on ASE sequence using quadratic exponential fitting, B: macroscopic magnetic field inhomogeneity map derived from phase images with larger variations around tissue boundaries and vessels. C: Corrected $R2'_{meso}$ map obtained by subtraction of B from original R2' data.

Results: R2' and corrected R2' are shown in **Figure 1A-C** for a representative subject. The whole-brain calibration M-value based on R2' were 5.4%, 7.8%, and 8.6% respectively for three subjects. As expected, the M-values based on $R2'_{meso}$ ($M_{R2'}$) after magnetic field inhomogeneity correction were lower (4.3±1.3%, 5.9±1.7% and 7.8±2.0% respectively).

BOLD and CBF based cerebral vascular reactivity (CVR) under hypercapnia as well as calibrated M of a representative subject is shown in **Figure 2**. The mean group $M_{hypercapnia}$ calculated based on whole-brain CBF and BOLD signal change was 6.0±0.6%. A negative trend between the calibration parameter $M_{hypercapnia}$ and subject age was observed (r=-0.45, P=0.08). Comparison of R2' and hypercapnia-based methods with simulation shows a possible under-estimation of the M factor derived by the R2' method to achieve the same BOLD signal changes, given the normal variation of 8% in baseline $CMRO_2$ (**Figure 3A**). Voxel-wise scatter plot of two M-values are shown in **Figure 3B**, with an estimated up-scaling factor of 1.242 (=1/0.805) for the $M_{R2'}$.

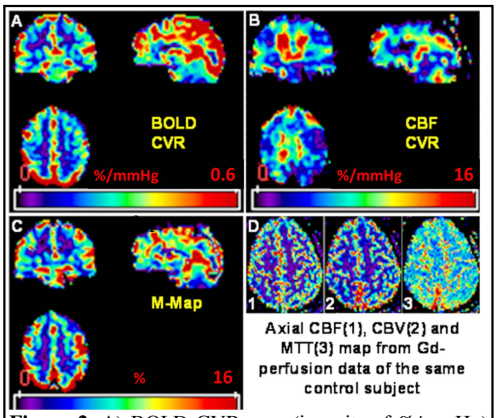

Figure 2. A) BOLD CVR map (in units of %/mmHg) of a representative subject; B) pCASL CVR map from CBF (%/mmHg) in the same subject. C) Relative deoxyhemoglobin concentration in % (i.e. calibration factor M)-map obtained by combining and fractional BOLD and CBF signal change based on Davis model with constant α-β = -1.12. D) Dynamic gadolinium (Gd)-contrast perfusion based CBF and CBV, mean transit time (MTT) maps with slightly greater MTT in white matter and similar CBF values to pCASL.

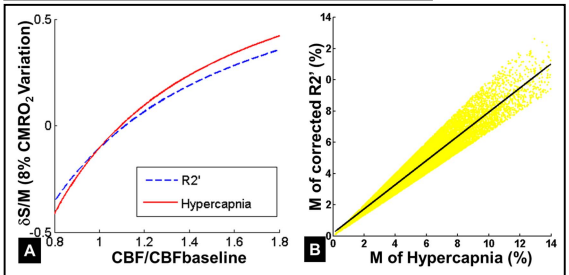

Figure 3. A: Simulation of $CMRO_2$ variation (normal ~8%) on the calibration methods (blue: R2', red: hypercapnia). B: Scaling factor derived by linear fitting of $M_{hypercapnia}$ to $M_{R2'}$ with a slope of 0.775, and intercept of 0.192 (black line). The slope was 0.805 for a constrained zero intercept.

Discussion and Conclusions: Our preliminary results show comparable calibration M values using R2' and hypercapnia methods, with slight underestimation of $M_{R2'}$ relative to $M_{hypercapnia}$. One potential limitation of the R2' method is that it assumes deoxyhemoglobin as the dominant source of paramagnetism, which needs further inhomogeneity correction. Simulations suggest a quantitative scaling factor might be useful for applying the RF reversible faster R2' calibration method alone at the same magnetic field strength.

References: [1] Blockley et al NMR Biomed 2013; 26:987-1003. [2] Jain et al. JCBFM 2011;31(7):1504-12. [3] Jensen et al. Magn Reson Med 2009; 61:481-5. [4] Yablonskiy and Haacke. MRM 1994; 32:749-63. [5] Wang et al. MR Imag 2008;26(2):261-69. [6] Davis et al. PNAS 1998;95(4):1834-1839.

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