Per-subject and per-brain-region Hyperoxic (HO) and Hypercapnic (HC) BOLD calibration to investigate neurovascular metabolism coupling linearity

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Introduction: The linearity of the coupling relationship (n) between changes in cerebral metabolic rate of oxygen ($\Delta CMRO_2$) and blood flow (ΔCBF) under neuronal activation in the human cortex, established based on the deoxyhaemoglobin dilution model (1) under graded HC and functional stimuli (2), has recently been challenged (3,4), questioning the interpretability of BOLD results. Given the large dependence of estimates in $\Delta CMRO_2$ and n on variability in BOLD calibration (M)-values (5) and brain regions (6), we sought to acquire precise calibration-values in individual subjects ($M_{subject}$) and specific brain regions (M_{VC}, M_{MC}) from alternate well-controlled respiratory challenges. Computer-controlled graded HC and HO levels, together with visual stimulation of varying frequency and voluntary motor tasks, were acquired during the same scanning session, to appropriately characterize the inherent variability in flow-metabolism coupling between individuals.

Methods: Nine nonsmoking healthy adults (7 females; mean age 27 years) were studied on a 3T TIM Trio system (Siemens, Erlangen, Germany) using a 32-channel head coil and a QUIPSS II echo planar imaging sequence (4x4x6 mm^3, labeling slab/gap of 150 mm/5 mm, $TI_1/TI_2/TE/TR$ of 700 ms/1400 ms/25 ms/3 s). Two subjects were excluded from the study due to large stimulus-correlated-head-motion during the respiratory challenges. A 3D T1-weighted data set (1x1x1 mm^3) and functional localizer were collected for anatomical placement of nine oblique axial functional slices through the VC and MC. Sequence and imaging parameters were identical under neuronal and respiratory tasks. *Neuronal:* Subjects were presented with five randomized frequencies of a maximal contrast black/white checkerboard (1,4,8,16 and 32 contrast-reversal per second, each in four ON/OFF/ON blocks of 24 s/48 s/24 s) and instructed to perform voluntary bilateral cyclic finger tapping coincident with the visual stimulus. *Respiratory:* An automated feed-forward system [RespirAct™, Thornhill research Inc, Toronto] (7) delivered precisely graded HO and HC levels for M-estimates [ref: other abstract]. BOLD and CBF images were separately statistically thresholded in each subject (cluster-p < 0.05, corrected for multiple comparisons) and the signal changes calculated in the region-of-interest (ROI) formed by the overlap of all visual frequencies (VC) and motor trials (MC). Flow-metabolism coupling was evaluated for VC, MC (index i) with $M_{subject}$ from HC, HO (index j), with $\alpha = 0.38$ and $\beta = 1.5$ (1):

$$\frac{CMR_{O_2}}{CMR_{O_{2,0}}}\bigg|_{i,j} = \left(1 - \frac{\Delta BOLD/BOLD_0\big|_i}{M_{subject,i,j}}\right)^{1/\beta} \left(CBF/CBF_0\big|_i\right)^{1-\alpha/\beta} \quad (Eq1),$$

$$\Phi_i = \frac{\Delta CBF/CBF_0\big|_i}{\Delta BOLD/BOLD_0\big|_i} \quad (Eq2),$$

$$n_{i,j} = \frac{\Delta CBF/CBF_0\big|_i}{\Delta CMR_{O_2}/CMR_{O_{2,0}}\big|_{i,j}} \quad (Eq3)$$

Results and discussion: BOLD and CBF signal changes across subjects peaked at visual frequency 8 Hz whereas they were constant across motor trials (Fig1a), with approximately linear fit on their ratios (Fig1b) of $\Phi_{VC} = 35.90 \pm 1.31$ and $\Phi_{MC} = 41.66 \pm 1.99$. The slight upward trend in Φ_{VC} with visual frequency might indicate a ceiling effect on BOLD with high frequency. Both HC and HO calibrations yielded an adequate number of activated voxels in either ROI-defined VC and MC (> 100 voxels) to enable low-variability per-subject ($M_{subject}$) and per-brain-region (M_{VC} and M_{MC}) estimates (Fig2, $M_{subject,VC} = 5.02 \pm 1.16$ %, $M_{subject,MC} = 5.43 \pm 0.72$ %). The estimated $CMRO_2$ changes in both brain-regions followed very similar trends to BOLD and CBF changes across subjects (Fig3a), with linear coupling relationships (Fig3b) of $n_{VC} = 1.43 \pm 0.01$ and $n_{MC} = 1.42 \pm 0.01$, when employing M-values from either calibration method (HC visually indistinguishable from HO data shown).

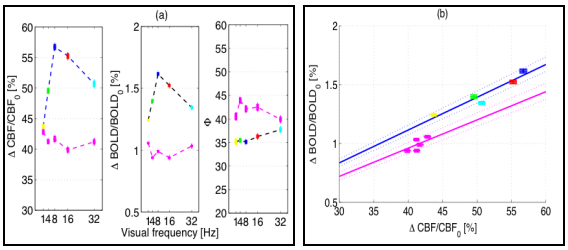

Fig1. (a) Changes in CBF, BOLD and their ratio (Φ) over visual frequency (blue) and corresponding motor trial (magenta) across subjects (N=7). (b) BOLD versus CBF changes showing linearity of fit on Φ in both cortices, dotted lines for 95 % confidence interval. Error bars represent the standard deviation over the stimulation period, propagated across subjects.

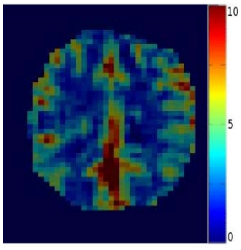

Fig2. Spatial map of M-values (color range in percentage) in a single slice obtained by averaging three HO levels for one subject.

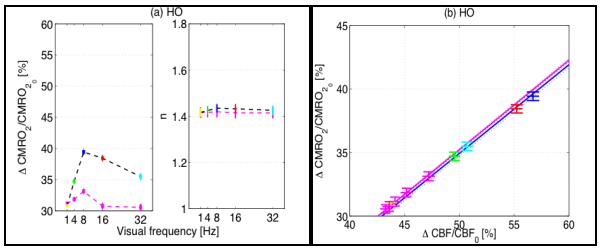

Fig3. (a) Changes in $CMRO_2$ and coupling ratio (n) over visual frequency (VC) and corresponding motor trial (MC) across subjects (N=7). (b) $CMRO_2$ versus CBF changes showing linearity of fit in coupling in both cortices (same color code and error bars definition as Fig1).

Conclusion: The current study demonstrates a tightly coupled and linear flow-metabolism relationship in the human visual cortex, an indication that oxygen demand from activated neurons across visual-frequencies is met by oxidative metabolism. It is the first thorough comparison of well-defined HO challenges as a suitable alternative technique to HC in the context of BOLD calibration for estimates of $CMRO_2$ and coupling ratio in specific brain regions of individual subjects. By consistently yielding low-variability M-values of small magnitudes, controlled HC and specially HO, enabled us to gain confidence in the correctness of our findings, since large M-values have proven to yield linear $\Delta CBF/\Delta CMRO_2$ relationships independently of experimental data (5). Our findings and methodology open the door to robust investigations of alternate biophysical BOLD models.

References: (1) Davis TL, et al. Proc Natl Acad Sci U S A (1998). (2) Hoge R, et al. Magn Reson Med (1999). (3) Liang C, et al. Proc Int Soc Magn Reson Med (2009). (4) Lin A-L, et al. Magn Reson Med (2008). (5) Chiarelli P, et al. Neuroimage (2007). (6) Ances B, et al. NeuroImage (2008). (7) Slessarev M, et al. J Physiol (2007).

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