Hyperoxic versus hypercapnic BOLD calibration under precise end-tidal control to improve the estimation of oxygen consumption

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Introduction: While primarily driven by changes in cerebral blood flow (CBF), the BOLD phenomenon is also modulated by brain tissue levels of deoxyhaemoglobin (dHb) generated by oxidative metabolism. Hence, crucial to the quantification of the BOLD contrast are baseline dHb levels (M-values) and coupling ratios (n) of relative changes in CBF and cerebral metabolic rate of oxygen consumption ($CMRO_2$). However, the validity of $CMRO_2$-estimates derived from the widely used dHb dilution model (1) depends on the accuracy of M-values which, under the traditional hypercapnic (HC) calibration, are prone to large intra- and inter-subject as well as inter-session variations (2). We hypothesized that an improved calibration procedure in individual subjects and brain regions (3,4) would, aside from allowing the essential and appropriate characterization of inherent disparities, translate to reduced variability in $CMRO_2$- and n-estimates. We thus applied alternate well-controlled graded HC and hyperoxic (HO) challenges as well as visual and sensorimotor stimulation in the same set of subjects during the same scanning session.

Methods: Nine healthy adults (4 males; mean age 26 years) were studied on a 3T TIM Trio (Siemens, Erlangen, Germany) using a 32-channel head coil and QUIPSS II echo planar imaging (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 due to head motion. A 3D T1-weighted data set (1x1x1 mm^3) and a BOLD functional localizer were collected for anatomical placement of nine oblique axial slices through the visual (VC) and sensorimotor (SMC) cortices. *Neuronal:* Maximal contrast black/white checkerboard (alternating at 8 contrast-reversal per sec, in four OFF/ON/OFF blocks of 24-s/48-s/24-s) coincident with voluntary bilateral sequential finger-to-thumb apposition. *Respiratory:* A computerized system [RespirAct™, Thornhill Research Inc, Toronto] (5) delivered precisely graded HO and HC levels for M-estimates (6). For each subject, $CMRO_2$ and n were calculated in VC and SMC t-maps ($p < 0.05$, corrected for multiple comparisons) (index i), using per-subject and group M-values (index j) (6) obtained under HC and HO (index k), with $\alpha = 0.38$ or 0.2 and $\beta = 1.3$:

$$\frac{CMR_{O_2}}{CMR_{O_{2a}}}\bigg|_{i,j,k} = \left(1 - \frac{\Delta BOLD / BOLD_0\big|_i}{M_{i,j,k}}\right)^{1/\beta} \left(CBF / CBF_0\big|_i\right)^{1-\alpha/\beta} \quad (Eq.\,1) \qquad \& \qquad \frac{1}{n}\bigg|_{i,j,k} = \frac{\Delta CMR_{O_2} / CMR_{O_{2a}}\big|_{i,j,k}}{\Delta CBF / CBF_0\big|_i} \quad (Eq.\,2)$$

Variability was quantitatively assessed based on the coefficient of variation (CoV) under error propagation consideration.

Results and Discussion: *Group-Calibration:* Our $CMRO_2$- and $1/n$-estimates display reduced variabilities (CoV_{HC} ~ 6-11 % & CoV_{HO} ~ 6 %, Fig.1A-B) compared to those commonly reported in HC-calibrated-fMRI studies (CoV up to ~ 16 % (3,7,8)), most likely arising from increased M-accuracy under precise gas manipulation (CoV_{HC} ~ 13-14 % & CoV_{HO} ~ 6 % vs CoV_{HC} ~ 20-75 % in quoted studies). This improvement is despite the facts that (1) we include error propagation throughout the calibrated model whereas most studies report instead the confidence interval of linear fits and (2) our M-values are lower than habitually reported, resulting in smaller $CMRO_2$ with larger CoV for equivalent absolute error. Interestingly, the ubiquitous α-value of 0.38 has been shown under HC-calibration to yield an overestimation of M and an underestimation of $CMRO_2$ (9). Under a reduced value of 0.2, reflecting venous rather than total blood volume as appropriate for BOLD signals (9), our M-, $CMRO_2$- and n-estimates come into closer agreement between HC and HO (not shown). Moreover, a reduced α leads to further reduction of variabilities under HO compared to HC (VC: CoV_{HO} / CoV_{HC} = 0.6-0.8 & SMC: CoV_{HO} / CoV_{HC} = 0.3-0.5). *Per-Subject-Calibration:* While most fMRI-calibrated studies to date have only applied group-calibration due to excessively large errors on individual M-values, our lower variability in either cortex (CoV_{HC} ~ 20-40 % & CoV_{HO} ~ 20 %) allowed a per-subject-calibration for proper quantification of individual responses (Fig.1C-D). The few previously attempted per-subject-calibrations led to large errors in $CMRO_2$ and $1/n$ (CoV_{HC} up to ~ 60 % (3,10)), which our methodology reduced by up to 95 % (VC: CoV_{HC} as low as ~ 6 %, CoV_{HO} ~ 3 % & SMC: CoV_{HC} ~ 24 %, CoV_{HO} ~ 13 %). Also, our group- versus per-subject-calibration results are in better agreement under HO than HC due to the elimination of variability in individual vascular reactivity and increased SNR of measurements. *Brain-region:* Given the non-vasoactive nature of HO compared to vasoactive-HC, the extended vascularization of the visual cortex might (1) be causing the HO and HC coupling-estimates to significantly differ in this region under $\alpha = 0.38$ (VC: n_{HO} ~ 8.3 vs n_{HC} ~ 4.3, Fig.1A-C) while they are similar in the less vascularized region (SMC: n_{HO} ~ 3.7 vs n_{HC} ~ 3.1, Fig.1B-D) and (2) explain that the largest impact of a reduced α occurs in the VC under HO-calculations (VC: n_{HO} ~ 4.2 vs n_{HC} ~ 3.6 & SMC: n_{HO} ~ n_{HC} ~ 2.5).

Conclusion: We document for the first time simultaneous BOLD and CBF measurements under neuronal and precisely controlled HC- and HO-challenges in the same set of healthy humans. In the context of BOLD-calibration, our reduced variability in M-values provided improved $CMRO_2$- and coupling-estimates to enable proper calibration of individual subject data and brain regions, with greater confidence in the correctness of our findings. Moreover, our study indicates the appropriateness of employing HO-calibration in the pursuit of evaluating oxidative metabolism in fMRI studies.

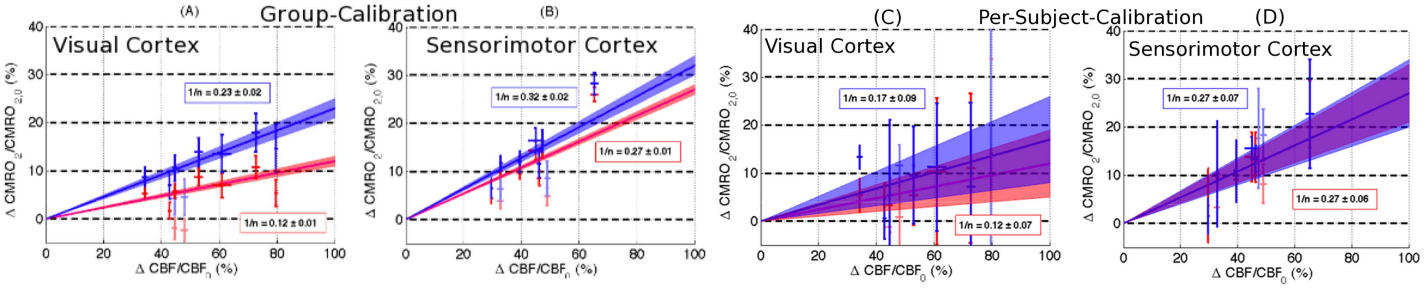

Fig1. $CMRO_2$ and CBF signal changes for each subject, obtained from HC (blue) and HO (red) group- (A & B) and per-subject- (C & D) calibrations under α = 0.38. Error bars = SE. Cases of negative $CMRO_2$ (shadowed) were excluded (N=7) from $1/n$-averages (shaded region: mean ± SE).

References: (1) Hoge RD,et al. Magn Reson Med (1999). (2) Chiarelli PA,et al. Neuroimage (2007). (3) Chiarelli PA, et al. Magn Reson Med (2007). (4) Ances B, et al. NeuroImage (2008). (5) Slessarev M, et al. J Physiol (2007). (6) Mark CI, et al. Magn Reson Med (2010). (7) Stefanovic B, et al. Neuroimage (2006). (8) Hoge RD, et al. Proc Natl Acad Sci U S A (1999). (9) Chen JJ, et al. NMR Biomed (2009). (10) Kastrup A, et al. Neuroimage (2002).

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