Application of quantitative, multimodal fMRI to the estimation of the cerebral metabolic response to CO_2 and a visual stimulus in hypoxia

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Target Audience: Researchers interested in applying quantitative fMRI techniques to study cerebral physiology.

Purpose: The complex physiological origins of the Blood Oxygenation Level Dependent (BOLD) phenomenon make it challenging to quantitatively interpret BOLD signal changes in terms of neuronal activity. The Calibrated BOLD technique, in which the BOLD signal is combined with measurements of cerebral blood flow (CBF) within the Davis Model of the BOLD response, was designed to address this limitation by converting a BOLD signal change into a quantitative estimate of the change in cerebral oxygen metabolism ($CMRO_2$) associated with a cognitive task[1]. However, the Calibrated BOLD technique cannot be directly applied to the study of cerebral metabolic physiology under hypoxic conditions for two principal reasons: (1) this technique requires a calibration experiment in which the BOLD and CBF responses to hypercapnia are measured under the assumption that breathing CO_2 does not alter $CMRO_2$ – an assumption that has been challenged in recent studies[2], and (2) the Davis Model implicitly assumes that the arterial vasculature is fully saturated with oxygen. Here we attempted to measure the $CMRO_2$ response both to CO_2 and to a simple visual stimulus after six hours, two days, and seven days of exposure to hypoxic conditions at an altitude of 3800m. To make these measurements we made two fundamental alterations to the standard calibrated BOLD technique: (1) we directly measured arterial oxygen saturation (S_aO_2), hematocrit, and global oxygen extraction fraction (OEF) in normoxia and on each day of hypoxia so that the calibration experiment would only need to be completed under normoxic conditions, and (2) we combined these physiological measurements with CBF and BOLD (R2*) measurements within a detailed biophysical model that accounts for variability in S_aO_2 and uses a Bayesian framework to estimate the $CMRO_2$ response given the uncertainty in both the measured and unmeasured model parameters[3,4].

Methods: *Subjects.* Ten subjects (5 male) were included. *Hypoxic exposure.* Subjects spent two or seven nights at the White Mountain Research Station (3800m, atmospheric PO_2: 90 Torr) and then returned to San Diego for imaging. For each subject, the S_aO_2 achieved at altitude was maintained throughout the period of transportation and imaging. For the 6-hr study, subjects stayed at sea level but maintained an S_aO_2 of 80-85% using a venturi mask with variable $\%N_2$. In the MRI scanner subjects breathed a premixed normoxic (21% O_2, balance N_2) or hypoxic gas mixture (12.5% O_2, balance N_2) via a non-rebreathing mask. S_aO_2 was monitored throughout the experiment. *Physiological Measurements*. S_aO_2 was measured by pulse oximetry. Hematocrit was determined from direct measurements of packed cell height in a capillary tube. *MRI measurements.* CBF and BOLD (R2*) images were produced using a dual echo PICORE QUIPSS 2 arterial spin labeling (ASL) technique. T2 was measured in the superior sagittal sinus using a TRUST MRI technique with single shot spiral readout. T2 relaxation times were found by fitting TRUST measurements within the sagittal sinus, at 4 echo times to a mono-exponential decay. Cerebral venous saturation (S_vO_2) was derived from the T2 relaxation time constant in superior sagittal sinus blood. OEF was calculated using the equation $OEF=(S_aO_2-S_vO_2)/S_aO_2$. A high resolution FSPGR T1-weighted 3D anatomical MRI was acquired for tissue segmentation, and to facilitate rotating MRI data in standard anatomical space. *CO_2 Stimulus Paradigm.* Stimulus consisted of 3.5 minutes baseline followed by 2 minutes of 5% CO_2 (balance 12.5% or 21% O_2 and N_2). *Visual Stimulus Paradigm.* Subjects viewed a full field, 8Hz flickering checkerboard. Paradigm consisted of 60 seconds rest, followed by 4 epochs of 20 seconds stimulus and 60 seconds rest. This was repeated twice during each of the four sessions. *Analysis.* All images were transformed into Talairach space. An ROI within the visual cortex was defined for each subject based on their R2* and CBF responses to the first visual stimulus experiment in normoxia. CBF and R2* image series were then averaged over the ROI for each functional run. Baseline CBF and R2* were taken as the average of the first 60s of each functional run. Activation CBF and R2* were taken as the average of the last minute of CO_2 inhalation or the average of the last 10s of each visual stimulus. All measurements were then combined within the detailed biophysical model, the output of which was a posterior probability distribution of the estimated $CMRO_2$ response to a given stimulus as a percentage of the baseline $CMRO_2$ in normoxia.

Results: Figure 1a displays the estimated posterior probability distribution of $CMRO_2$ responses to CO_2 in hypoxia, with the assumption that the response was zero in normoxia (required for normoxic calibration). $CMRO_2$ was found to decrease significantly in response to CO_2 in hypoxia and not to recover with acclimatization ($CMRO_2$ response after 6 hrs of hypoxia: **-26.5%** [-50.2- -2.9%] (median [95% central interval]); after 2 days: **-19.9%** [- 50.1- 6.4%]; and after 7 days: **-26.9%** [-51.3- -8.4]). Figure 1b displays the estimated $CMRO_2$ responses to the visual stimulus, which in normoxia was 15.1% [9.6-21.5%]. The magnitude of the $CMRO_2$ response to the stimulus was found to be decreased by more than 50% after 6 hrs and 2 days of hypoxia, but then to recover after a week of acclimatization [expressed as the estimated difference in percent $CMRO_2$ responses, after 6 hrs of hypoxia: -9.4% [-19.7-1.3%]; after 2 days: -8.8% [-24.7-3.6%]; and after 7 days: 0.04% [-8.8-8.5%].

Conclusions: Our findings suggest that in sustained hypoxia, the acute response to a CO_2 challenge is a significant reduction in $CMRO_2$, and this does not change with up to a week of acclimatization. In contrast, the $CMRO_2$ response to an acute visual stimulus was significantly reduced for up to 2 days of sustained hypoxia, but recovered to the normoxic response by 7 days. This study demonstrates that a multimodal Bayesian approach can be used to estimate $CMRO_2$ responses in challenging physiological states.

References: 1. Davis, T. L., et al. (1998). PNAS. 95(4), 1834–1839. 2. Smith Z.M. et al. (2011). Proceedings of ISMRM 3. Simon A.B et al. (2013). Proceedings of ISMRM.4. Simon A.B. Beyond BOLD: Toward the application of quantitative functional magnetic resonance imaging to the study of brain function and physiology (Doctoral Dissertation). Retrieved from ProQuest Dissertations and Theses. (Dissertation number 3620025). 147-175.

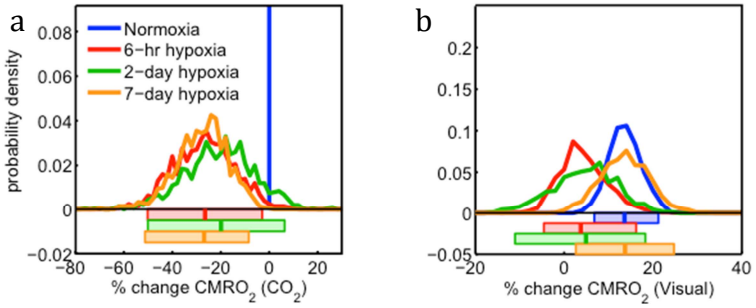

Figure 1: $CMRO_2$ responses to (a) CO_2 or (b) visual stimulus in normoxia and hypoxia. Estimated probability distributions are depicted above the abscissa. 95% central intervals are depicted below the abscissa. Thick central lines indicate estimated median.