A novel approach to the quantitative estimation of the oxygen metabolism response to a neural stimulus that accounts for uncertainty due to unmeasured physiological parameters

Aaron Benjamin Simon[1], Valerie Griffeth[1], and Richard Buxton[2]

[1]Bioengineering, University of California San Diego, La Jolla, CA, United States, [2]Radiology, University of California San Diego, La Jolla, CA, United States

Target Audience: Researchers interested in using MRI to quantitatively measure changes in oxygen metabolism

Purpose: To measure the cerebral oxygen metabolism response to a stimulus requires simultaneous BOLD and CBF measurements and additional information about the quantity of deoxyhemoglobin in the baseline state. For example, in the classic calibrated BOLD approach, the baseline information is derived from hypercapnia responses analyzed with a simplified model of the BOLD response[1]. However, the uncertainty in such estimates due to physiological variability is difficult to assess because of the simplifications of the model. In addition, the hypercapnia calibration makes the practical implementation of the experiment more complex. Recent theoretical studies suggest that more complete BOLD models are useful for assessing uncertainty due to unmeasured physiological parameters and that measuring the baseline R_2' relaxation rate can account for variation in the baseline deoxyhemoglobin state[2]. In this study we examined whether we could measure the $CMRO_2$ response to a stimulus, as well as the uncertainty of that estimate, by measuring baseline R_2' and the CBF and BOLD responses. We related the three measurements to the $CMRO_2$ response through a detailed BOLD signal model with arterial, venous, capillary, and extravascular compartments and adopted a Bayesian approach to determine how uncertainty in the unmeasured physiological parameters of the model affected the precision with which we could estimate the $CMRO_2$ response. For this proof-of-principle demonstration, we used a simple 5% CO_2 breathing challenge as a stimulus, hypothesizing that we would measure a negligible $CMRO_2$ response using this technique.

Methods: *Imaging*: Three subjects were imaged for this work. Baseline R_2' was measured using a pair of GESSE imaging sequences[3]. First GESSE sequence produced 32 GRE samples at TEs from 63-83ms around a SE at 48ms. Second sequence produced 32 samples at TEs from 63-83ms around a SE at 98ms. Imaging parameters were FOV: 256mm, 64x64 matrix, 14slices, 2mm thick/4mm gap. BOLD/ASL imaging was accomplished with PICORE QUIPPSII[4] ASL with dual echo spiral readout (TI1: 700ms, TI2: 1800ms, TE1: 6ms, TE2: 30ms, TR: 3s). FOV: 256mm, 64x64 matrix, 14 slices 4mm thick/1mm gap aligned with GESSE stack. *Stimulus:* Stimulus was a CO_2 challenge consisting of 3.5 min baseline, 2 min 5% CO_2, 2min recovery. R_2' *Calculation:* Before calculation of R_2', GESSE images were corrected for macroscopic field inhomogeneties[5]. A region of interest containing grey matter voxels was chosen by thresholding baseline CBF measurements. R_2' was calculated by finding the slope of the ROI-averaged log decay curve for each GESSE sequence and using the formula $slope(-\ln(S_1(t))) = R_2 + R_2'$ for the first GESSE decay curve and $slope(-\ln(S_2(t))) = R_2 - R_2'$ for the second GESSE decay curve. *BOLD and CBF Calculation*. CBF time series were generated by taking the surround subtraction of the first echo ASL data. BOLD time series were generated by taking the surround average of the second echo data. Time series were averaged over the ROI. Baseline BOLD and CBF were averaged over the baseline period. The CO_2 response was measured during the second minute of CO_2 challenge. *CMRO$_2$ calculation*: $CMRO_2$ response to CO_2 was estimated from a detailed BOLD signal model based on those described by Griffeth et al[6] and He et al[7]. and modified to reflect the imaging parameters of this experiment. Because many of the underlying physiological parameters of the model are not precisely known, including tissue R_2, baseline fractional volumes of arterial, venous, and capillary compartments, the characteristic diffusion time for water around capillary vessels, and the constants that determine the exponential relationships between CBF and compartmental blood volume changes[6], 500 random combinations of these variables were drawn from uniform but finitely supported prior distributions. The oxygen extraction fraction (OEF) in the baseline and hypercapnic states were then fit for each set of variables to the baseline R_2' and the relative changes in BOLD and CBF, respectively, and Fick's principle was used to calculate relative the $CMRO_2$ change, $r = \frac{CMRO_2^{CO2}}{CMRO_2^0}$. The product of this analysis was a distribution of calculated $CMRO_2$ changes that reflect uncertainty in the metric due to uncertainty in the underlying physiological parameters. The approach we are using is similar to the Bayesian approach to estimating the marginal posterior probability of a parameter of interest by sampling the joint posterior distribution of all unfixed parameters. The simplification we have made here is that we are essentially ignoring the finite precision of our measurements in order to focus on the uncertainty attributable to the unmeasured physiological model parameters.

Results: Across subjects mean R_2' was 0.0043+/-0.001. Mean BOLD response was 1.0299+/-0.0061. Mean CBF response 1.34+/-0.08. Based on mean group measurements, $CMRO_2$ response to hypercapnia was calculated to be r=1.01 with a 95% credible interval [0.96, 1.09] (i.e., the values that cut off 2.5% of the samples from each side of the distribution) (Figure 1).

Discussion: The calculated $CMRO_2$ response was found to be in good agreement with previous studies[8,9], which typically demonstrate a small or negligible decrease in $CMRO_2$. In addition, the distribution of responses importantly demonstrates that uncertainty in the values of unmeasured physiological parameters contributes significantly to the uncertainty of the estimated $CMRO_2$ change.

Conclusion: We have demonstrated a novel method of combining BOLD, ASL, and GESSE imaging to quantitatively estimate the $CMRO_2$ response to a stimulus that takes into account estimation uncertainty attributable to the uncertain values of unmeasured physiological parameters. Using such a method will allow researchers interested in estimating $CMRO_2$ fluctuations to more completely account for uncertainty in their estimates.

References:
1. Davis TL et al.*Proc. Natl. Acad. Sci. U.S.A.* 1998; 95(4):1834–1839.
2. Blockley NP et al. *NeuroImage*. 2012;60(1):279–289.
3. Yablonskiy DA. *Magn. Reson. Med.* 1998;39(3):417–428.
4. Wong E, Buxton R. *Magn. Reson. Med.* 1998.
5. Dickson JD et al. *J. Magn. Reson. Imaging*. 2010;32(4):953–961.
6. Griffeth VEM et al. *NeuroImage*. 2011;58(1):198–212.
7. He X et al. *Magn. Reson. Med.* 2006;57(1):115–126.
8. Xu F et al. *JCBF&M*. 2010;31(1):58–67.
9. Chen JJ et al. *JCBF&M*. 2010;30(6):1094–1099.