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 Simon¹, Valerie Griffith¹, and Richard Buxton²

¹Bioengineering, University of California San Diego, La Jolla, CA, United States; ²Radiology, 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 deoxygenemoglobin 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 response¹. 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 R₂ relaxation rate can account for variation in the baseline deoxyhemoglobin state². In this study we examined whether we could measure the CMRO₂ response to a stimulus, as well as the uncertainty of that estimate, by measuring baseline R₂ and the CBF and BOLD responses. We related the three measurements to the CMRO₂ 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 CMRO₂ response. For this proof-of-principle demonstration, we used a simple 5% CO₂ breathing challenge as a stimulus, hypothesizing that we would measure a negligible CMRO₂ response using this technique.

Methods: Imaging: Three subjects were imaged for this work. Baseline R₂ was measured using a pair of GESSE imaging sequences³. 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 QUIPPSI⁴ 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 CO₂ challenge consisting of 3.5 min baseline, 2 min 5% CO₂, 2min recovery. R₂ Calculation: Before calculation of R₂, GESSE images were corrected for macroscopic field inhomogeneities⁵. A region of interest containing grey matter voxels was chosen by thresholding baseline CBF measurements. R₂ was calculated by finding the slope of the ROI-averaged log decay curve for each GESSE sequence and using the formula slope(−ln(S₁(t)))/slope(−ln(S₂(t))) = R₂. For the first GESSE decay curve and slope=-ln(S₁(t))/slope=-ln(S₂(t)) 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 CO₂ response was measured during the second minute of CO₂ challenge. CMRO₂ calculation: CMRO₂ response to CO₂ was estimated from a detailed BOLD signal model based on those described by Griffith et al⁶ and He et al⁷, 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 R₂, 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 changes⁸, 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 R₂ and the relative changes in BOLD and CBF, respectively, and Fick’s principle was used to calculate relative the CMRO₂ change, r = CMRO₂ Baseline CMRO₂ Hypercapnic. The product of this analysis was a distribution of calculated CMRO₂ 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 R₂ was 0.0043±0.001. Mean BOLD response was 1.0299±0.0061. Mean CBF response 1.34±0.08. Based on mean group statistics, CMRO₂ 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 CMRO₂ response was found to be in good agreement with previous studies⁹, which typically demonstrate a small or negligible decrease in CMRO₂. 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 CMRO₂ change.

Conclusion: We have demonstrated a novel method of combining BOLD, ASL, and GESSE imaging to quantitatively estimate the CMRO₂ 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 CMRO₂ fluctuations to more completely account for uncertainty in their estimates.

References: