# Changes in CBF/CMRO$_2$ coupling with graded visual stimuli are modulated by baseline perfusion

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*Target audience:* Researchers interested in BOLD physiology

*Introduction:* The BOLD response to a stimulus is acutely sensitive to the coupling *n* between CBF and CMRO$_2$. There is emerging evidence that *n* may be modulated by mental state (e.g. attention) or stimulus [1]; as shown by Liang et al who found that *n* varied with luminance contrast in the visual cortex [2]. This demonstrated that the magnitude of the BOLD response does not accurately reflect the magnitude of underlying physiological and metabolic processes. We investigated whether this divergence between CBF and CMRO$_2$ responses is also dependent on baseline CBF, which we modulated with CO$_2$ inhalation.

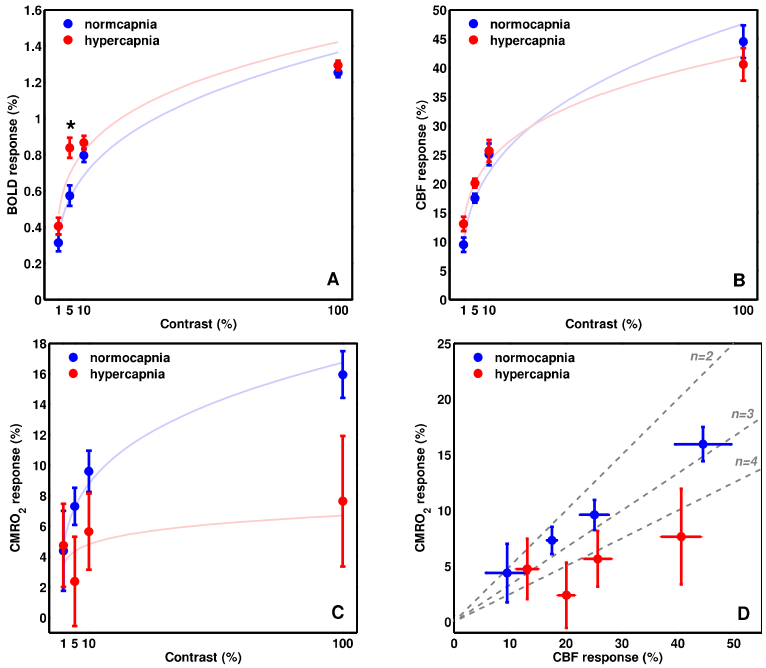


Figure 1: A) Mean **BOLD** (±SEM) response to each contrast level with * indicating significant differences ($p < 0.5$). B) Mean **CBF** (±SEM) response to each contrast level. C) **CBF/BOLD** coupling based on mean values (±SEM) at each contrast level. All lines of best fit based on a power law, i.e. $\%BOLD=a(\%contrast)^b$ D) **CBF/CMRO$_2$** coupling based on mean values (±SEM) at each contrast level. Dotted grey lines show different *n* trajectories in the **CBF/CMRO$_2$** coupling space.

*Methods:* Two separate runs of a graded visual stimuli were acquired for 9 subjects on a 3T GE HDx scanner using a PASL sequence (PICORE QUIPS II) with a dual-echo gradient echo spiral readout (TR/TE$_1$/TE$_2$=2200/3/29ms; 64x64x8 matrix; 655 volumes). A visual stimulus consisted of a grey scale radial checkerboard reversing at 8Hz at 4 different contrast levels (1,5,10, and 100%). Runs contained six 30 s blocks of each contrast in a pseudorandom order, and interleaved 4 min blocks of normocapnia (NC) and hypercapnia (HC) (target +8 mmHg from baseline $P_{ET}CO_2$), reversed for each run, and balanced across subjects.

Following pre-processing (AFNI), BOLD and CBF weighted time series were extracted, via surround averaging /subtraction of the first and second echo data respectively. A GLM analysis formed an ROI within an occipital lobe grey matter mask from the union of CBF responses to each contrast using a threshold of p=0.01 and a minimum cluster size (α=0.05). Mean ROI time series for BOLD and CBF were separately scaled to NC and HC baselines and entered into a GLM to obtain percentage changes. The calibrated BOLD framework was used to calculate ΔCMRO$_2$ [3], with scaling parameter *M* calculated from BOLD and CBF responses to HC. Additionally, by examining response ratios (relative to 100% contrast), we estimated ΔCMRO$_2$ using a range of assumed values of *n*, without the need to calculate *M*.

*Results:* A one-way repeated measures ANOVA showed that only %ΔBOLD was found to be significantly different between conditions ($p < 0.05$) as seen in Fig. 1A. Post-hoc paired t-tests showed a significant difference in the 5% contrast only (p=0.037). The average %ΔCMRO$_2$ (mean±SD) at 100% contrast during NC and HC was 15.9±4.3 and 7.6±12.1 respectively. Average %ΔCBF and %ΔCMRO$_2$ return *n* values of {2.2, 2.4, 2.6, 2.8} and {2.8, 8.4, 4.5, 5.3} at each contrast level for NC and HC respectively. Fig. 1C suggests different %ΔCMRO$_2$ between conditions at 100% contrast, but no significant difference was found, reflecting the high degree of noise in estimated values.

*Discussion:* We found larger HC BOLD responses primarily driven by the 5% contrast, suggesting that BOLD saturates more quickly during HC, due to altered underlying CBF/CMRO$_2$ coupling dynamics. No significant differences in absolute *n* values or changes in *n* within or between conditions were found. However, by examining response ratios, we have demonstrated an increase in *n* with contrast that is in agreement with Liang et al [2] (Fig. 2A). These ratios do not rely on estimations of *M*, but show that the magnitude of the change in *n* depends only on the absolute values of *n*, and that there is a divergence in the relationship between %ΔCBF and %ΔCMRO$_2$ across NC and HC conditions (Fig. 2B). These data highlight the complex physiological dependencies of the BOLD response, and reinforce the desire for accurate measurement of underlying physiology in order to fully understand BOLD signal changes. More data will improve statistical power and provide a more definitive picture of how baseline physiology alters CBF/CMRO$_2$ coupling.

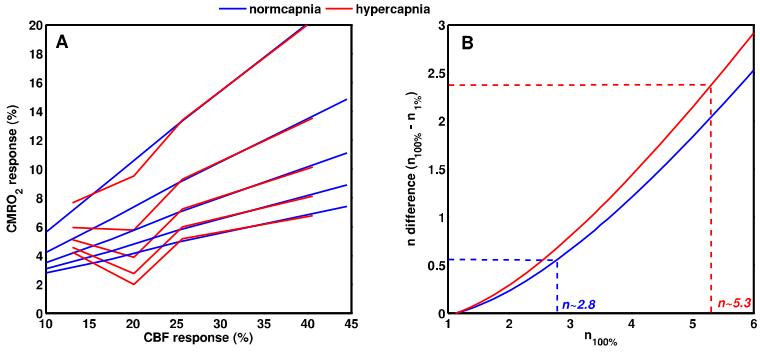


Figure 2: A) **CBF** vs. **CMRO$_2$** for different assumed values of n (top to bottom n=2,3,4,5,6) at 100% contrast. B) The change in n (100% - 1%) for different assumed values of n at 100% contrast. Dotted lines indicate the values of *n* calculated with the Davis model.

*Conclusion:* Our study confirms that BOLD signal changes to different stimuli are not a true quantitative reflection of the relative changes in CBF and CMRO$_2$. Furthermore, differences in *n* between stimuli are dependent on baseline conditions, influencing BOLD signal changes. This may be of serious concern for BOLD studies comparing healthy and clinical populations where changes in baseline CBF and CMRO$_2$ are expected.

*References:* 1. Buxton, R.B., et al., Front Neurosci, 2014. **8**: p. 139. 2. Liang, C.L., et al., Neuroimage, 2013. **64**: p. 104-11. 3. Davis, T.L., et al., Proc Natl Acad Sci U S A, 1998. **95**(4): p. 1834-9. *Acknowledgements*: The Wellcome Trust funded this work [WT090199]