**Specialty area** *fMRI: From Basic to Intermediate Brain Connectivity*
*Part 1 - Zero to Hero: Beginner's Crash Course*

**Speaker Name** Clarisse I. Mark (clarisse.mark@queensu.ca)

**Highlights (Take-home messages)**

1. The Blood-Oxygenation-Level Dependent (BOLD) effect does not measure neuronal activity directly.
2. The BOLD signal reflects changes in blood oxygenation resulting from the relative balance between cerebral blood flow (oxygen *supply*) and oxygen metabolism (oxygen *consumption*).
3. Cerebral blood flow and oxygen metabolism responses to brain activation can be accurately obtained through precisely calibrated fMRI studies.

**Title: The BOLD Effect & Its Use for Detecting Brain Activity**

**Target audience: (Who will benefit from this educational session)**
Researchers and clinicians interested in getting a fundamental understanding of the physiological sources underlying the most commonly used fMRI BOLD signal for detecting brain activity.

**OUTCOME/Objectives: (What you will be able to do differently because of this info)**
Develop an awareness of the importance of robust experimental conditions to move from BOLD being a simple *qualitative* localizer ('*blobology*') to being a reliable *quantifier* of cerebral activation.

**PURPOSE: (Why this research was performed / how it determined the problem)**
The BOLD signal detects a change in magnetic properties of haemoglobin in different oxygenation states. BOLD hence does not measure neuronal activity directly but reflects alterations in blood oxygenation resulting from the relative balance between oxygen ($O_2$) *delivery* and *consumption*. Accordingly, one cannot rely only on this complex signal; one must also quantify cerebral blood flow (CBF) and cerebral metabolic rate of oxygen consumption ($CMRO_2$). While the former can be measured using arterial spin labeling (ASL) to estimate the latter through an fMRI calibrated model involving changes in inspired levels of carbon dioxide ($CO_2$), conventional gas manipulation leads to estimation uncertainties. Recent advances in gas control produce more stable signals and reduce measurement variability to enlighten the intricate relationship between the haemodynamic and metabolic changes underlying the BOLD phenomenon.

**METHODS: (How this problem was studied)**
Careful and precise calibrated fMRI studies were performed with novel gas delivery methodologies in healthy adults at 3T during respiratory and neuronal tasks. We compared a robust computer-controlled gas system to 1) the traditional manual technique through randomized graded challenges of elevated $CO_2$ levels delivered via facemask, and 2) alternate calibration gas type of elevated $O_2$ challenges. Following each calibration, subjects performed simple visual and sensorimotor tasks, consisting of looking at an alternating radial checkerboard while performing voluntary bilateral finger-to-thumb apposition. The metabolic fMRI responses to neuronal activation were estimated based on acquired BOLD and CBF data under individual- and group-calibration in each activated brain region.

**RESULTS:** **(How this issue has been addressed)**

The precise automated gas control yielded signals of increased linearity and uniformity across the brain, with reduced intra-/inter-subject variations, compared to the manual traditional technique (Fig1)[1] and under high $O_2$ rather than $CO_2$ calibration (Fig2)[2]. While most fMRI studies to date have been limited to group-calibration due to excessively large errors, reduced variability allowed accurate calibration of localized neuronal activation in individual subjects (Fig3) and, therefore, proper quantification of their distinct blood flow and oxygen metabolism responses in each brain region (i.e., visual and sensorimotor cortices, Fig4).[3]

**DISCUSSION:** **(Interpretation of the data)**

Novel gas delivery methodology provided robust quantification of the haemodynamic and metabolic responses underlying brain activation. Accurate evaluation of relative changes in CBF and $CMRO_2$ is vital in assessing the validity of BOLD as an indicator of neuronal activation under various healthy and physiological conditions. The demonstrated linear flow-metabolic relationship (Fig4) ensures a monotonic relation of the BOLD signal with these surrogates, greatly simplifying its applicability in the human brain.

**CONCLUSION:** **(Relevance to future research and clinical practice)**

Despite the continuing debates surrounding which features of brain stimulation solicit higher $O_2$ metabolism and which mediate the flow response, one certainty remains in that the resulting BOLD phenomenon is critically sensitive to the exact coupling of these changes. Variations in the BOLD signal due to altered baseline states (e.g., neurovascular diseases, pharmacological manipulation, caffeine consumption and even attention) also play a crucial role in the interpretability of fMRI studies, hence necessitating precise calibration. Interpretation of BOLD results should be based on accurate measurements of underlying haemodynamic and metabolic responses, not only in basic neuroscience research but also in its countless clinical applications, where flow-metabolic coupling and baseline states may likely be impaired.

## References


1. **Mark C, Slessarev M, Shoji I, Han J, Fisher J, Pike B. Precise control of end-tidal carbon dioxide and oxygen improves BOLD and ASL cerebrovascular reactivity measures.** ***Magnetic Resonance in Medicine.*** **2010;64(3):749-756.**

2. **Mark C, Fisher J, Pike G. Improved fMRI calibration: Precisely controlled hyperoxic versus hypercapnic stimuli.** ***Neuroimage.*** **2011;54(2):1102-1111.**

3. **Mark C, Pike B. Indication of BOLD-specific venous flow-volume changes from precisely controlled hyperoxic versus hypercapnic calibration.** ***Journal of Cerebral Blood Flow and Metabolism.*** **2012;23(4):709-719.**

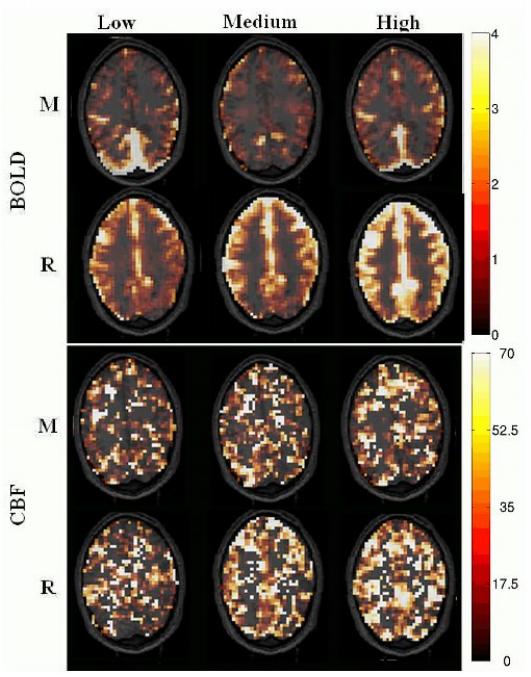


**Fig1.** Whole brain BOLD (top) and CBF (bottom) responses to graded levels (left to right: Low, Medium and High) of Manual (M) and computerized (R) high $CO_2$ calibration. Color scales indicate the % signal change from baseline.

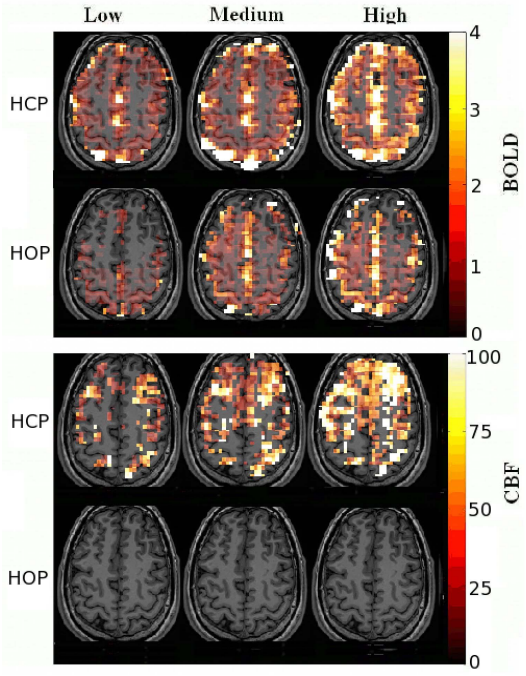


**Fig2.** Whole brain BOLD (top) and CBF (bottom) responses to graded levels (left to right: Low, Medium and High) of computerized high $CO_2$ (HCP) and $O_2$ (HOP) protocols. Color scales indicate the % signal change from baseline.

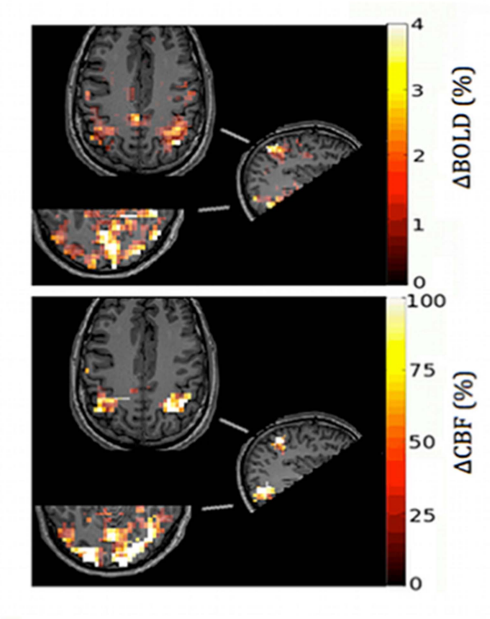


**Fig3.** Activity-localized BOLD (top) and CBF (bottom) responses induced by visual and sensorimotor tasks. Color scales indicate the % signal change from baseline.

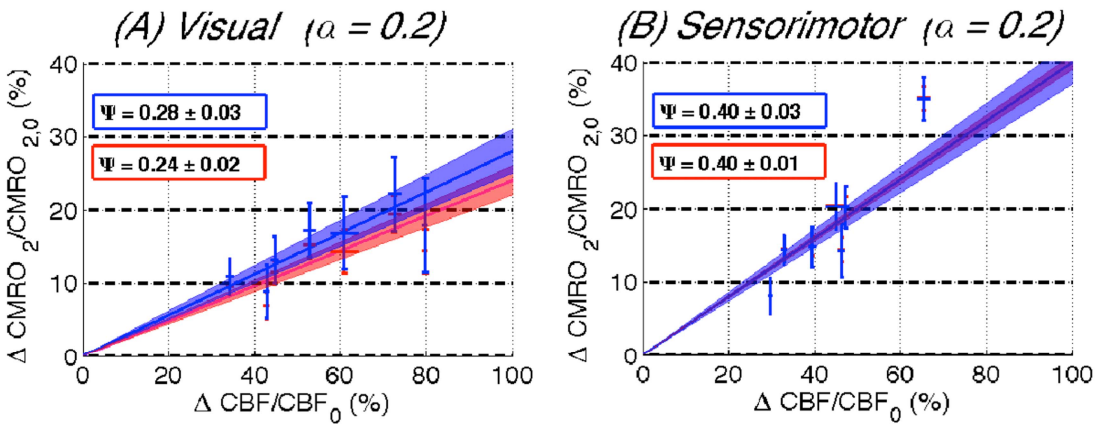


**Fig4.** Normalized $CMRO_2$ and CBF signal changes in the (A) visual and (B) sensorimotor cortices for each subject (N = 7). $CMRO_2$ estimates were obtained under high $CO_2$ (blue markers) and high $O_2$ (red markers) -calibration. Alpha represents an assumed model parameter for venous blood volume changes. Error bars indicate the standard error (SE). Across-subject averaged Ψ (=$CMRO_2$/CBF) -estimates are shown as shadowed regions (mean +/- SE).