A quantitative framework for interpreting relationships between GABA, BOLD fMRI, and hemodynamic reactivity in MRI voxels

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Target Audience: BOLD physiology and contrast mechanism researchers and clinicians with an interest in hemodynamic and neurochemical behavior.

Purpose: *The purpose of this work is to outline a quantitative framework for interpreting the primarily correlative relationships that have very recently been reported between blood oxygenation level-dependent (BOLD) contrast and ongoing inhibitory neuronal activity measured by baseline γ-aminobutyric acid (GABA) concentration.* BOLD signals are only indirect markers of neuronal activity that arise consequent to ongoing, and stimulus-evoked modulations in, hemodynamics (cerebral blood flow: CBF; and volume: CBV), neurotransmission (involving the major excitatory and/or inhibitory agents glutamate (GLU) and γ-aminobutyric acid (GABA), respectively) and metabolism (cerebral metabolic rate of oxygen: CMR_{O2}). While much progress has been made in understanding the hemodynamic and metabolic contributions to BOLD contrast, important gaps remain in even our very basic understanding of how BOLD signals are related to underlying neurochemistry. Recent correlative findings between neurotransmission, behavior, and BOLD responses are being presented more frequently[1], yet no efforts have been made to our knowledge to describe these relationships as more than qualitative correlations. It is the purpose of this work to incorporate recent observations on GABA, and BOLD, CBF, CBV and $CMRO_2$ reactivity to propose a quantitative framework that can be used to interrogate neurochemical and hemodynamic reactivity relationships.

Methods: Data from recently published human and animal literature were pooled to propose a quantitative model relating the BOLD fMRI response to CBF, CBV, and CMR_{O2}, separately in GLUergic and GABAergic neurons. The two-phase model is a synthesis of proposed models for how (i) excitatory and inhibitory neuronal activity elicit changes in CBF, CBV and $CMRO_2$ (Phase I[2]) and (ii) CBF, CBV and $CMRO_2$ changes contribute to BOLD (Phase II[3]).

Results and Discussion: For brevity, only the most salient terms are summarized here, however more extensive descriptions can be found in Sotero et al. for Phase I[2] and Donahue et al. for Phase II[3]. *Phase I.* Normalized glucose consumption (g_k) as a function of time (t) can be written in terms of the cerebral metabolic rate of glucose (CMR_{Glc}) and the instantaneous level of synaptic activity (u_k),

$$g_k(t) = \frac{CMR_{Glc}|_k}{CMR_{Glc}|_k^0} = g_k^0 + (h_k(t-\delta_k)) * (u_k(t) - u_k^0)$$

where u_k^0 and g_k^0 are the resting (hereon denoted by ^{0}) neuronal activities and cerebral glucose consumptions at baseline, h_k is a impulse response function for neuronal activity, and $\delta_k \approx 0.1$s is the delay after stimulation before CMR_{Glc} response begins, for *k=(e)xcitatory or (i)nhibitory neurons*. Total glucose consumption can be written,

$$g(t) = \frac{CMR_{Glc}|_e + CMR_{Glc}|_i}{CMR_{Glc}|_e^0 + CMR_{Glc}|_i^0} = \frac{\left[2\gamma/(2-x_0)\right] g_e(t) + g_i(t)}{2\gamma/(2-x_0)+1}$$

for

$$\gamma = \frac{\eta_e^0}{\eta_i^0}$$

where x_0 is the fraction of glucose following the glycogenolytic pathway at rest, h_k^0 is the level of synaptic activity at rest, and $\gamma \approx 5$ is the baseline ratio of excitatory to inhibitory synaptic activity in a voxel. Existing data suggest that glycolysis is the only metabolic process accounting for glucose consumption during inhibition, whereas for excitatory activity, the glial glucose flux depends on glycolysis and glycogenolysis. To account for this, the oxygen consumptions, $m(t)$, can be expanded:

$$m_i(t) = \frac{CMRO_2|_i}{CMRO_2|_i^0} g_i(t) \qquad m_e(t) = \frac{CMRO_2|_e}{CMRO_2|_e^0} \frac{2-x}{2-x_0} g_e(t) \qquad m(t) = \frac{CMRO_2|_e + CMRO_2|_i}{CMRO_2|_e^0 + CMRO_2|_i^0} = \frac{\gamma m_e(t) + m_i(t)}{\gamma+1}$$

where x is the fraction of glucose following the glycogenolytic pathway and sigmoidally depends on $g_e(t)$, reflecting higher glycogenolytic activity and a fast production of ATP during increased neuronal activity. *The above equations outline how excitatory and inhibitory neuronal activity elicit changes in $CMRO_2$* in a voxel. *Phase II.* Recent evidence has suggested that CBF depends almost exclusively on excitatory activity and is uncoupled from glucose and oxygen consumption. Thus, the CBF response can separately be approximated from the balloon model of Buxton et al., or CBF and CBV or can be measured using CBF- and CBV-weighted MRI and ΔR2* quantified according to multi-modal fitting[3]. The relationship between ΔR_2^* and CBF, CBV and venous oxygenation changes has been outlined in the literature[3].

Fig. 1 graphically depicts the influence of BOLD responses for different levels of inhibitory and excitatory activity using the above model, which reflects the recently published trends between BOLD and GABA that have recently been reported in the literature[1]. Importantly, the basal level of excitation/inhibition balance influences both the amplitude and shape of the measured BOLD response (Fig. 1e). We anticipate that this quantitative framework should provide a useful resource for interpreting the primarily correlative relationships that have recently been presented between multi-modal fMRI and GABA measurements.

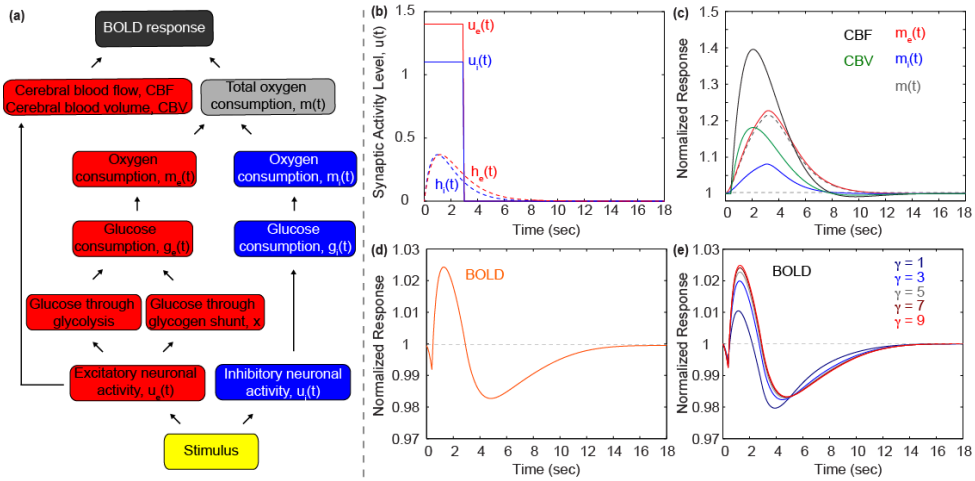

Fig. 1. *Model describing the relationship between excitatory/inhibitory neuronal activity and the BOLD response. (a) Events leading to BOLD signal, (b) relative levels of excitatory/inhibitory neuronal activity, with example impulse response functions (dashed). (c) Simulated CBF, CBV and CMR_{O2} responses, and (d) evoked BOLD response. (e) Predicted BOLD signal variation with differing baseline inhibitory level ($\gamma = h_e^0/h_i^0$). Multi-modal imaging will allow for acquisition of many observables and model evaluation.*

Conclusion: This work provides a theoretical framework whereby the large amount of correlative neurotransmitter studies that are being proposed can begin to be evaluated in the context of quantitative physiology. Adjustments to the model are intended to be required as more multi-modal imaging data becomes available.

References: [1]Muthu SD, et al. HBM. 2012;33(2):455-65. [2]Sotero RC, et al. Neuroimage. 2007;35(1):149-65. [3]Donahue MJ, et al. JCBFM. 2009;29(11):1856-66.