

The Hemo-Neural Hypothesis: A Proposed Role for Blood Flow in Neuromodulation and Information Processing

Christopher I. Moore^{1,2}, Ulf Knoblich^{1,2}, Rosa Cao^{1,2}, Jessica Cardin^{1,2}, Bryan Higashikubo, and Joshua C. Brumberg³

¹McGovern Institute for Brain Research, Cambridge, MA, ²MIT, Cambridge, MA, ³Queens College, CUNY, Flushing, NY

Hemodynamics are typically considered to serve as a metabolic support system, or to play another physiologic role that has no direct impact on neural excitability. In contrast to this canonical view, we recently proposed the Hemo-Neural hypothesis (Moore and Cao, 2007). This hypothesis predicts that functional hyperemia, enhanced blood flow to a discrete brain region evoked by neural activity (the effect measured in the BOLD fMRI response), impacts neural information processing. We predict that hyperemia modulates the excitability of sensory cortical neurons, altering their gain and spatio-temporal receptive field structure.

Hemodynamics may impact neural activity through *direct* and *indirect* mechanisms. Direct mechanisms include delivery of diffusible blood-borne messengers, and mechanical and thermal modulation of neural activity. Indirect mechanisms are proposed to act through hemodynamic modulation of astrocytes, which can in turn regulate neural activity.

To test this hypothesis, we induce hyperemia with a pharmacological agent (Pinacidil) that causes vasodilation by relaxation of smooth muscles on the neocortical surface. We simultaneously conduct neurophysiological recordings. Our preliminary data indicate that Pinacidil is selective, as predicted by the absence of its receptor in neurons and astrocytes and as confirmed by intracellular *in vitro* slice data showing an absence of effects on membrane and firing properties (N=26 neurons). Intracellular *in vivo* recordings in Barrel cortex indicate that hyperemia is correlated with neuron (N=6/9) and glia (N=4/5) depolarization, enhancing sensory transmission (see Knoblich et al., this meeting). Ongoing studies include 2-photon imaging during hyperemia induction.

This hypothesis has implications for understanding computation in the brain, as it proposes an entirely novel form of neuromodulation and 'state'-dependent regulation of sensory representation. If hemodynamics modulate neurons, this finding is also important for interpretation of widely-used functional imaging signals (e.g., the BOLD response), as functional imaging is probing a part of the process of computation, and not just a derivative marker of activity. This hypothesis also has potential clinical implications. If functional hyperemia is a neuromodulator, then this discovery may inform the understanding, diagnosis and treatment of neurological and psychiatric diseases with vascular involvement.