Cortical specificity in neurovascular coupling

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Scott NA. Cortical specificity in neurovascular coupling. J Neurophysiol 114: 3031–3032, 2015. First published June 10, 2015; doi:10.1152/jn.00915.2014.—Despite mounting contrary evidence, the metabolic hypothesis is viewed as the predominant theory underlying neurovascular coupling, or the link between neural activity and cerebral blood flow. In a recent study, Huo et al. (Huo BX, Smith JB, Drew PJ. J Neurosci 34: 10975–10981, 2014) combined multimodal imaging and electrophysiology in experiments using awake, voluntarily moving mice to explore whether neurovascular coupling is uniform throughout the cortex. Whereas their results can be viewed as demonstrating that neural activity and blood flow are uncoupled in the frontal cortex during movement, the importance of this study is the elucidation that the metabolic hypothesis may not be the principle facilitator of neurovascular coupling in some regions of the cortex.

The link between neural activity and cerebral blood flow is thought by many to be a unidirectional phenomenon: increased neural activity is successively followed by increased blood flow. Certainly, any psychology undergraduate student would be quick to recite the textbook paradigm, “initial neuronal energy demand produces rapid, localized changes in glucose and oxygen concentrations that in turn elicit a compensatory increase in the flow of oxygenated blood.” Known as the metabolic hypothesis, this phenomenon is controlled by a negative feedback system. The metabolic hypothesis has remained well accepted in the field of neurovascular coupling, forming the basis of our current understanding of the blood oxygen level-dependent signal in functional magnetic resonance imaging, which measures the interrelated hemodynamic parameters of cerebral blood flow (or perfusion) and cerebral blood volume in response to neural activity.

Notwithstanding its ubiquity, the metabolic hypothesis does not clearly explain how blood flow is matched to neural activity in both time and space. Considering this flaw, the last decade has seen an insurgence of clever studies that challenge the basis of the metabolic hypothesis. A recent study found increased blood flow in the presence of experimentally induced high levels of oxygen (Lindauer et al. 2010). Another study by Devor et al. (2008) found decreased blood flow in regions with high neural activity and correspondingly high glucose uptake. These two studies provide evidence against the metabolic hypothesis, which would have suggested a decrease in blood flow in the presence of high oxygen levels and an increase in blood flow in regions with high neural activity. Sirotin and Das (2009) showed that vascular changes could precede neuronal events, implying a bilateral interaction between blood flow and neural activity that is more anticipatory than reactive. Taken together, these recent studies highlight the implausibility of a metabolically driven, negative feedback mechanism linking neural activity to cerebral blood flow.

In a recently published article, Huo et al. (2014) combined modern surgical methods and experimental conditions to further question the reliability of using functional hyperemia to infer regional neural activity. Rather than surgically removing the skull to allow imaging of hemodynamic signals, Huo et al. (2014) employed thinned-skull preparations that involve gently thinning the cortical bone that overlies frontal and parietal cortices using a high-speed burr. When polished and reinforced using a glass coverslip, this bone/glass optical window allows for clear, stable multimodal imaging, which is essential during lengthy experiments on moving animals. Because the bone is not removed during the surgical procedure, there is a decreased risk of damaging the underlying cortical tissue and superficial blood vessels, which is advantageous in bilateral preparations.

To avoid the complicated effects of anesthesia on both neural activity and hemodynamic signals, Huo et al. (2014) performed all imaging and electrophysiological recordings on awake mice that had been habituated to the voluntary use of a treadmill.

Linking intrinsic optical imaging of cerebral blood volume of the topmost cortical layer to electrophysiological recordings at deeper infragranular levels (800-1,000 μm below the pia), Huo et al. (2014) compared signals between the frontal and somatosensory cortices during both spontaneous activity and voluntary locomotion. As expected, locomotor activity evoked a characteristically rapid decrease in fractional reflectance, corresponding to an increase in cerebral blood volume, in the somatosensory cortex. Accompanying this increase in cerebral blood volume, electrodes in the somatosensory cortex revealed an expected increase in gamma-band power in local field potential and an increase in multunit activity. Thus, in the somatosensory cortex, increased neural activity is tied to increased blood volume. Yet, simultaneous measurements of reflectance changes in the bilateral frontal cortex revealed no equivalent decreases in reflectance, despite neural activity in the frontal cortex co-occurring with that of the somatosensory cortex. According to Huo et al. (2014), these results indicate that frontal cortex neural activity occurred in the absence of an increase in blood volume, which suggests an uncoupling of functional hyperemia from neural activity.

Although simultaneous imaging of intrinsic signals and electrode recordings in the same animal would have strengthened the study of Huo et al. (2014), methodologically this is difficult to implement when using chronic thinned-skull preparations, because it would require the drilling of several electrode-sized holes through the imaging window. This procedure would risk inadvertent shifting of the electrodes over time, which would affect both the integrity of the cortical tissue and
the stability of repeat recordings. If we accept the results from imaging and electrophysiological recordings in separate animals, we can begin to question why such a discrepancy in neurovascular coupling exists, such that neural activity and blood volume changes are strongly linked in the somatosensory cortex but not in the frontal cortex. While Huo et al. (2014) submit many possibilities underlying the supposed uncoupling in the frontal cortex, one possible explanation merits greater weight: that neurovascular coupling is not cortically invariant but likely differs in degree and kind in accordance with local structural variation and inherent differences in the functional linking of neural activity to blood flow.

To resolve whether an observed uncoupling reflects differences in the kind of neurovascular coupling, further examination of the degree of the response may be required. In support of this, the results of Huo et al. (2014) showed that broadband power in local field potential was significantly higher in the somatosensory cortex than in the frontal cortex, both at rest and during voluntary locomotion. Thus, because neural activity was relatively lower in the frontal cortex, the lack of an observable increase in cerebral blood volume may be a consequence of the “safety factor,” which is the theory that small evoked changes in blood flow, such as those often masked by noise, are sufficient to compensate for a certain level of neuronal activity (Sirotin et al. 2009). The absence of a change in frontal cortical blood volume, despite evoked neural activity, may be a consequence of cortex-specific safety factor thresholds. Because safety factors are consistent with activity-driven feedforward changes in blood flow rather than a feedback mechanism, the results of Huo et al. (2014) might suggest that neurovascular coupling in the frontal cortex is neurogenic rather than metabolic (Attwell et al. 2010). Indeed, neurogenic, astrocyte-dependent coupling has already been suggested to underlie sensory-evoked changes in intrinsic optical signals (Gurden et al. 2006) and blood flow (Petzold et al. 2008) in the olfactory bulb. As with the olfactory bulb, neurovascular coupling in the frontal cortex may be mediated in part by a similar mechanism (Attwell et al. 2010).

Astrocytes, which relay synaptic activity to the vasculature via end-feet, are sensitive regulators of neurovascular coupling, bridging the synaptic release of glutamate to blood vessel diameter changes in accordance with a delimited set point (Blanco et al. 2008). Because this set point determines whether a given oxygen level leads to either vasodilation or vasoconstriction, region- or cortex-specific set points would produce differences in both the degree and kind of neurovascular coupling. Moreover, because laminar variation in astrocytic density corresponds to the upward propagation of functional hyperemia, from parenchymal neurons to the surface vasculature (McCaslin et al. 2010), determining if the frontal cortex differs in astrocytic density from the somatosensory cortex would clarify whether localized anatomical variation drives cortex-specific hemodynamic responses.

Although much research has focused on excitatory neurons, evoked neural activity does not preclude involvement from inhibitory interneurons. Indeed, it is possible that both excitatory and inhibitory neurons function in tandem, in accordance with the type of neural activity and the relative proportions of neuronal subtypes. Thus regional variation in neuronal populations might produce differences in the degree or even direction of hemodynamic response. The findings of Huo et al. (2014) should prompt research into the functional and anatomical differences underlying regional differences in neurovascular coupling. Doing so may reveal that no individual hypothesis is sufficient alone to describe neurovascular coupling across the brain and that the link between neural activity and functional hyperemia should be accordingly interpreted during functional imaging. With further investigation into the precise nature of the link between neural activity and blood flow, the question might shift from whether regions are coupled or uncoupled to whether they are mediated by different mechanisms.

REFERENCES


