

The Hemo-Neural Hypothesis: On The Role of Blood Flow in Information Processing

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Abstract

Brain vasculature is a complex and interconnected network under tight regulatory control that exists in intimate communication with neurons and glia. Typically, hemodynamics are considered to exclusively serve as a metabolic support system. In contrast to this canonical view, we propose that hemodynamics also play a role in information processing through modulation of neural activity.

Functional hyperemia, the basis of the fMRI BOLD signal, is a localized influx of blood correlated with neural activity levels. Functional hyperemia is considered by many to be excessive from a metabolic standpoint, but may be appropriate if interpreted as having an activity-dependent neuro-modulatory function. 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.

These hemo-neural mechanisms should alter the information processing capacity of active local neural networks. Here, we focus on analysis of neocortical sensory processing. We predict that hemodynamics alter the gain of local cortical circuits, modulating the detection and discrimination of sensory stimuli.

This novel view of information processing—that includes hemodynamics as an active and significant participant—has implications for understanding neural representation and the construction of accurate brain models. There are also potential medical benefits of an improved understanding of the role of hemodynamics in neural processing, as it directly bears on interpretation of and potential treatment for stroke, dementia and epilepsy.

Introduction

The brain contains a remarkably rich and inter-dependent network of neurons, whose activity is well correlated with information processing. The study of this network has been the focus of modern neuroscience (Cajal 1996). The brain also contains a rich and inter-dependent vascular network, whose ‘activity’—blood flow—is typically well correlated with neural activity. Based primarily on knowledge of anatomy, Aristotle believed that the vasculature was the biological system that manifested its activity in intelligence, emotion and action (Gross 1998). In contrast, the standard modern view of blood flow is that it serves a physiological function unrelated to information processing, such as bringing oxygen to active neurons, eliminating ‘waste’ generated by neural activity or regulating temperature. Except in extreme cases of cell damage or death, current hypotheses do not include blood flow as a contributor to shaping neural activity. Realistic computational models of brain function do not include blood flow as a component, and neurophysiologists do not consider it as a regressor to explain variance in their data.

In contrast to this canonical position, we propose the hypothesis that hemodynamics play a role in information processing, through modulation of neural activity by blood flow. We predict that functional hyperemia, the ‘overflow’ of blood to a brain region during neural activity, provides a spatially- and temporally-correlated source of regulation, modulating the excitability of the local circuit. This shaping of the neural response will, in turn, impact representation.

The goal of this paper is to describe this alternative view of information processing, and to argue for the importance of incorporating this potential class of mechanism into our understanding of how different systems in the brain act in a synthetic manner. We focus our comments on the role that hemodynamics may play in sensory neocortex, as this brain region is widely studied with regard to its information processing role and a great deal is known about its hemodynamic regulation. This focus is not meant to detract from the potential importance of hemo-neural interactions for processing in other brain areas, or in other contexts, as noted throughout.

A ‘Turing Test’ for Biological Information Processing Systems

In what is commonly regarded as the ‘Turing Test’ (Turing 1950), the capacity of a computer for intelligent, autonomous thought is judged by whether the machine can lead a blinded human observer, unbiased by direct knowledge of the correspondent, to judge it as intelligent. Borrowing this logic to begin our argument, we provide a ‘Turing Test’ for biological information processing systems. We ask whether, given the following list of traits, a scientist would predict that this ‘anonymous’ system plays a role in representation in the brain. The traits of this system are as follows:

- The system possesses a complex anatomical network in the brain
 - This system shows micro-scale structure in all brain areas
 - This system shows regional anatomical specializations that reflect information processing, such as layer-specific localization of pathway density in different neocortical areas.

- Activity in this system is co-modulated synergistically with activity in the known information processing network—the major neuromodulators such as acetylcholine (ACh), serotonin (5-HT) and norepinephrine (NE), for example, are key regulators of this system, and almost all factors that impact activity in this system also impact neural activity.
- Fine regulation of activity in this network is not tightly coupled to metabolic need
- Fine regulation of activity in this network is tightly coupled to neural information processing:
 - The spatial and temporal pattern of activity in this system shifts with perceptual input, motor output, attention and cognitive performance.
 - The spatial resolution of differential activity in this system can be as precise as single cortical columns or olfactory glomeruli.
 - The temporal onset of activity in this pathway is within hundreds of milliseconds of the onset of neural information processing, with a duration similar to the time scales for neural phenomena considered important for information processing such as adaptation and synaptic depression
 - Localized damage in this system leads to specific and predictable information processing deficits

Without the predisposition to view hemodynamics as only a mechanism for meeting metabolic need or other physiologic function, this anonymous description suggests that the vascular system, and its ‘activity’ expressed as blood flow, is poised to play a role in information processing through the directed modulation of neural activity.

The validity of this hypothesis depends on three points. First, whether the anatomy and physiological regulatory mechanisms can position hemodynamic signals spatially and temporally to have an impact on neural activity. Second, whether there are known correlations between information processing and changes in blood flow. Third, whether there are mechanisms by which changes in hemodynamics in the normal range of function can impact neural activity. In the following sections, we suggest that these basic criteria are met, and begin to present hypotheses as to the information processing role that such regulation may play.

The Interleaved Anatomy and Physiology of Hemodynamic and Neural Systems

Anatomical Specificity

The vascular pathways that regulate blood flow are finely articulated and inter-digitated with the neural architecture. These anatomical vascular patterns are not uniform, and in many cases reflect the information processing functionality of the brain area. In the neocortex, capillary density shows specificity in the ‘vertical’ dimension through enhanced concentration in specific layers, such as layer IV of primary sensory areas (Patel 1983; Woolsey et al. 1996; Zheng et al. 1991), in contrast to the flat laminar profile in the entorhinal cortex (Michaloudi et al. 2005). Further, the system shows ‘horizontal’ specificity within a cortical area, such as the segmentation of capillary beds to the ‘barrels’ of rodent somatosensory cortex or ‘blobs’ and ‘stripes’ of V1 (Patel 1983; Riddle et al. 1993; Woolsey et al. 1996; Zheng et al. 1991). Subcortical structures show similar apparent principles of distribution, as the striatum of the basal ganglia shows enhanced capillary density in the matrix as compared to the striosomes (Feekes and Cassell 2006). The olfactory bulb also shows localization of capillary density in the glomeruli (Borowsky and Collins 1989). Peripheral nerves

and vessels are known to follow anatomically similar paths (Vesalius) with recent studies showing that nerves and peripheral vascular supply employ similar developmental guidance mechanisms (Carmeliet 2003; Eichmann et al. 2005).

Overlapping Physiological Regulation

When local populations of neurons are active, they recruit increased blood flow and volume to the activated region, a process known as ‘functional hyperemia’ (Grubb et al. 1974; Hoge et al. 2005; Kong et al. 2004; Martin et al. 2006; Roy and Sherrington 1890). Functional hyperemia can be induced and modulated by a variety of mechanisms, with the relaxation of smooth muscle around arteries and arterioles a principal final common pathway leading to changes in blood flow and volume. As discussed below, astrocytes are believed to be a primary route for detecting neural activity and engaging the vasculature. Recent evidence has also implicated neurons in the direct control of blood flow. In neocortex, interneurons directly contact vascular processes, and intracellular electrical stimulation *in vitro* of interneurons adjacent to vessels can evoke dilation or constriction (Cauli et al. 2004; Hamel 2006; Hirase et al. 2004; Vaucher et al. 2000).

The mechanisms that induce functional hyperemia typically also impact neural activity. Almost all chemical factors that are known to modulate blood flow directly or indirectly regulate neuronal function. Prime examples of this overlap are the major brainstem neuromodulatory inputs, such as ACh, 5-HT and NE. Single cholinergic projections, for example, target pyramidal neurons, local interneurons (which in turn impact vasculature), astrocytes and smooth muscles around vasculature, and modulate activity in each within a restricted zone (see (Hamel 2006) for a review). Dopamine is believed to play a similar role in frontal and somatosensory neocortex, with contacts targeted to vasculature within the cortical mantle, implying local synergistic regulation (Krimmer et al. 1998). Other factors known to directly regulate both networks include the freely diffusing molecule nitric oxide (NO), which relaxes smooth muscle (Palmer et al. 1987) and modulates neural activity in a variety of ways (see below). Processes from single interneurons and from astrocytes contact and impact neighboring neurons and nearby microvascular processes (Hamel; Haydon and Carmignoto 2006; Oberheim et al.; Zonta et al. 2003). These examples of local co-regulation imply fine-scale synergy in the function of neural and vascular networks.

These observations, that the anatomical organization of vascular networks map to known information processing subdivisions, and that blood flow ‘activity’ and neural activity share a wide range of local regulatory mechanisms, are obviously not arguments that compel an additional role for blood flow. Rather, they suggest that the anatomy and physiology of these two networks are positioned to function synergistically in information processing. As discussed in the next section, changes in blood flow correlate strongly with neural activity, but these correlations are not closely tied to fine-scale metabolic need.

Functional Hyperemia: Spatial and Temporal Correlation with Information Processing

Spatial Precision

The spatial resolution of functional hyperemia is widely debated, and likely varies as a function of context and brain area. In the somatosensory and visual neocortex, a general consensus exists that the pattern of increased blood flow is similar to that of subthreshold neural activity, with a peak in

signal that is localized to a cortical column (~400 μm), and an extent spanning several columns (Dunn et al. 2005; Hess et al. 2000; Lauritzen 2001; Sheth et al. 2004; Vanzetta et al. 2004; Yang et al. 1998). This correlation is strongest when better localized comparisons are made between the flow delivered to the neocortical layers through small arterioles and capillaries. Large vessels that run over the surface of the cortical mantle, which contribute prominently to many imaging techniques, will typically provide artifactually large estimates of the spread of blood delivered to the tissue (Disbrow et al. 2000; Dunn et al. 2005; Duong et al. 2001; Sheth et al. 2004; Vanzetta et al. 2004).

Vertical specificity in the cortical pattern of functional hyperemia has also been observed. In the somatosensory neocortex, the peak flow rate evoked by sensory stimulation is localized to specific laminae (Gerrits et al. 2000; Norup Nielsen and Lauritzen 2001; Silva and Koretsky 2002). Evoked response amplitude and peak flow have also been correlated within cerebellar laminae (Akgoren et al. 1997). In other brain areas, evidence for more precise delivery has also been observed, as flow can be localized to a single glomerulus in the olfactory bulb during stimulus presentation (i.e., $\leq 100\mu\text{m}$) (Chaigneau et al. 2003; Yang et al. 1998). Several potential mechanisms exist for fast and localized regulation of this type, ranging from direct neural control due to interneuron activation (Cauli et al. 2004; Hamel 2006) to pericyte control of vascular diameter in capillaries (Peppiatt et al. 2006).

Temporal Precision

Functional hyperemia is also temporally locked to neural activity onset. In the somatosensory neocortex, blood flow increases measured using laser Doppler have been observed less than 200 milliseconds after the onset of sensory-evoked neural responses (Matsuura et al. 1999; Norup Nielsen and Lauritzen 2001). Similarly, optical imaging techniques that integrate over local volumes at somewhat slower temporal resolution typically record a significant increase in flow within ≤ 500 msec of sensory stimulus presentation (Dunn et al. 2005; Malonek et al. 1997; Martin et al. 2006). The subsequent duration of these increases is often viewed as ‘poorly correlated’ with neural activity, as functional hyperemia can sustain for seconds after the onset and offset of a stimulus. As discussed in a later section, this sustained temporal pattern may not be a mismatch between activity and flow, but rather may be consistent with the information processing role of blood flow.

Functional Hyperemia is not Well Correlated with Oxygen Consumption

This increased supply of blood during functional hyperemia does not match most estimates of metabolic need. As first shown by Raichle, Fox and colleagues (Fox and Raichle 1986), the increase in oxygenated hemoglobin recruited by neural activity exceeds the oxygen delivery needs of the tissue. While there is ongoing debate as to the mechanisms of energy use during neural activity, and as to the role that glucose demand plays in setting blood flow levels, there is general consensus that functional hyperemia, as the name suggests, overshoots the oxygen requirements of the tissue several fold (see (Kida and Hyder 2006) and (Raichle and Mintun 2006) for recent reviews).

Several hypotheses have been proposed to account for this significant ‘uncoupling’ between the predicted metabolic need for blood and the actual levels observed, ranging from temperature regulation to metabolite (waste) removal (Hayward and Baker 1968; Woolsey et al. 1996; Yablonskiy et al. 2000; Zhu et al. 2006). While these alternative physiological processes may be one role of functional hyperemia, several recent reviews have concluded, in concurrence with the

original conclusions of (Fox and Raichle 1986), that a much stronger correlation exists between processes associated with signal processing, such as neurotransmitter release and subthreshold electrophysiological activity, than with other metabolic or physiologic ends (see (Lauritzen 2005; 2001; Peppiatt and Attwell 2004)).

Potential Mechanisms Linking Functional Hyperemia and Neural Activity

We propose an alternative explanation for functional hyperemia, beyond an exclusively metabolic account. This spatially and temporally directed process may play an active role in modulating neural activity, and the observed changes in blood flow and volume may not be overly exuberant, but rather may meet a different goal. Under this hypothesis, functional hyperemia is not the over-delivery of oxygenated blood for metabolism, but rather the targeted regulation of neural processing.

We emphasize that while uncoupling of metabolic need and functional hyperemia is an argument for positing an alternative hypothesis, the proposed information processing role of blood flow is not exclusive of other physiological roles for increased blood flow. Even if oxygen supply were proportional to need in the brain, the localized process of functional hyperemia could still shape neural activity and impact representation, and would still need to be included in any complete account of the processing machinery that supports information processing.

In this section, we discuss a variety of mechanisms through which functional hyperemia could impact neural activity. We have grouped these into two broad categories, *indirect* mechanisms, where astrocytes play a mediating role between vascular and neural networks, and *direct* mechanisms, in which astrocytes do not play an explicit role.

Direct Hemo-Neural Interactions

Diffusible Factors

Diffusible messengers that freely cross the blood-brain barrier represent one class of agent that can directly impact neural activity and that likely increase in concentration with increased blood volume. Within this class of modulators, nitric oxide (NO) is the best understood. This molecule diffuses across cellular membranes and can likely freely traverse the blood brain barrier (Kitagami et al. 2003). There are at least two vascular sources of NO that could impact neural activity: transport from the blood and production in vascular tissue. The blood carries NO, much of which is bound to oxygenated hemoglobin. With deoxygenation under physiologic conditions, the affinity of hemoglobin for NO decreases, leading to its release (Pawloski and Stamler 2002; Singel and Stamler 2005). While the impact of the blood-derived NO concentration on vasodilation is a topic of ongoing debate (Pawloski and Stamler 2002; Stamler et al. 1997), an increase in blood flow and/or blood volume should lead to an increase in the NO concentration in the surrounding tissues (Kitagami et al. 2003; Kubes et al. 1991; Vallance et al. 1989). Further, NO is produced in endothelial cells which could be stimulated to release this factor by shear stress due to enhanced flow (Charles 1999; Garthwaite et al. 2006; Iadecola et al. 1993).

The impact of increased NO concentration on neural activity could take many forms. In the presence of increased NO concentration, thalamic sensory relay neurons *in vitro* show depolarization and modulation of voltage-dependent metabotropic G-protein coupled channels, leading to dampened oscillatory activity and a more tonic mode of transmission (Budde et al. 1992). In the somatosensory

and visual thalamus *in vivo*, increased NO concentration leads to enhanced stimulus-evoked firing rate, thought to occur through a distinct, NMDA-dependent mechanism (Cudeiro et al.; Do et al. 1994; Shaw and Salt 1997). In the primary visual cortex, both suppression and facilitation of evoked firing rate have been observed following local increases in NO concentration, potentially indicating sub-populations of neurons with distinct responses in V1 (Kara and Friedlander 1999). Analyses based in signal detection theory suggest that the cumulative effect of these interactions is an enhanced signal to noise ratio of sensory transmission (Kara and Friedlander 1999). Various forms of synaptic plasticity such as long-term potentiation and depression are also modulated by NO (see (Hardingham and Fox 2006) for a recent review). The presence of enhanced blood flow, when coupled with specific patterns of spike timing or bursting activity, could combine to induce modifications of synaptic efficacy.

Direct support for the view that vascular NO impacts neural activity comes from recent findings by Garthwaite and colleagues (Garthwaite et al. 2006). They provide evidence that endothelial NO production leads to a net depolarization in proximal nerve fibers. This tonic depolarization is thought to be mediated by guanylyl-cyclase coupled receptors in the axons, whose production of cGMP engages hyperpolarization-dependent depolarizing ion channel receptors, leading to an increase in membrane potential. While these observations have yet to be tested *in vivo*, they provide strong initial reinforcement for the NO aspect of the Hemo-Neural hypothesis.

Mechanical Engagement

Functional hyperemia within a local region of cortex (e.g., a cortical column) could shape neural responses through its mechanical impact on the tissue. Increased flow, volume, pressure and the local expansion or motion of vascular processes may lead to the deformation of neural membranes. In somatosensory cortex, sensory afferent stimulation evokes a 30-40% increase in the diameter of single pial arterioles, on average a net increase of 10-15 microns, with individual examples showing expansion in excess of 15 microns (Hughes and Barnes 1980; Koralek et al. 1990; Ngai and Winn 1996).

These local mechanical signals could modulate neural activity through the engagement of mechano-sensitive ion channels. Two channels positioned to translate hyperemia into depolarized membrane potentials are the amiloride sensitive Na⁺ channel and stretch-activated cation channel, as both types are present in high concentration in the rodent neocortex (Lein et al. 2007). A further example of a neural channel positioned to sense these events in the neocortex is TRAAK, a stretch-activated potassium channel (Honore et al. 2006; Maingret et al. 1999). This channel is present in high concentrations across all neocortical layers, and shows peak density in the soma and proximal dendrites of neurons (Reyes et al. 2000; Talley et al. 2001). Mechanical engagement of this potassium channel would lead to hyperpolarization, presumably inducing a net suppression of the firing probability across a local neural population, or modulating firing modes of neurons, e.g., bursting in a subset of pyramidal cells (Silva et al. 1991).

Temperature Change

Almost all cellular processes are sensitive to temperature. Ion channels show several varieties of temperature dependence, and the impact of temperature on the driving force across a membrane is predicted by the Nernst equation. Blood flow largely dictates brain temperature, transmitting changes in core body temperature to the brain and maintaining temperature in the context of the

cooler extracranial environment (Baker et al. 1994; Hayward et al. 1966; Zhu et al. 2006). While there is substantial species-specific variation in the regulation of brain temperature (Baker et al. 1994), changes in behavioral and metabolic state regularly induce fluctuations in mammalian brain temperature of $>2^{\circ}\text{C}$ (Andersen and Moser 1995; Kiyatkin 2004; Kiyatkin et al. 2002). A dorso-ventral gradient of temperature (from cooler to warmer) exists across the brain, with higher temperatures in the ventral regions determined by the large basal arteries (Melzack and Casey 1967; Serota and Gerard 1938), and a steeper gradient in the neocortex (Zhu et al. 2006).

One hypothesis invoked to explain functional hyperemia is that it provides temperature regulation of the brain, removing heat due to neural activity (Hayward and Baker 1968; Yablonskiy et al. 2000). Preliminary studies suggest that tactile stimulation (e.g., of vibrissae or skin) can induce increases in temperature from an unidentified source in somatotopically appropriate cortex or thalamus of $>.1^{\circ}\text{C}$ (Gorbach 1993; Melzack and Casey 1967; Trubel et al. 2006), while different dynamics (and cooling) can be observed with sustained sensory stimulation (McElligott and Melzack 1967; Trubel et al. 2006; Yablonskiy et al. 2000). While a potentially important role for enhanced flow, the effects of functional hyperemia on temperature in a local region (e.g., a cortical column) have not been directly measured, and these effects may vary as a function of relative depth (Zhu et al. 2006). Recent studies using magnetic resonance imaging as a probe for temperature change have reported decreases in temperature correlated with sensory-enhanced flow on the order of 1°C in visual cortices (Yablonskiy et al. 2000). Direct measurements of brain temperature changes during hypercapnia, a condition that transiently increases flow and arterial blood pressure, have shown decreased brain temperature, on the order of $.25^{\circ}\text{C}$, in the non-human primate (Hayward and Baker 1968).

If functional hyperemia has even a relatively small impact on local temperature, there are several mechanisms through which it could affect neural activity. Evoked hippocampal field potential responses show increased latency with decreasing temperature changes of less than 2°C (see (Andersen and Moser 1995) for a review), and decreasing temperature from 37 to 32°C doubles the amplitude of the after-hyperpolarization and enhances spike frequency adaptation (Thompson et al. 1985; Thompson and Prince 1986). Neurons in rodent parietal cortex show substantial temperature dependence in the physiological range. Decreases of 1°C from 36° to 35°C can lead to a complete suppression of ACh-induced action potential firing (Mednikova and Pasikova 2005). In layer II pyramidal neurons in the primary somatosensory cortex, a 2°C decrease in temperature (from 35° to 33°C) induces a 50% decrease in the mini-EPSC rate, a 50% increase in the input resistance, and a decrease in the current-injection evoked firing rate (Simkus and Stricker 2002).

The changes in synaptic response observed with small changes in temperature in the physiological range in parietal cortices suggest that these effects could have a substantial impact on the net output of a cortical column. For example, within the rat barrel cortex, a difference in the rise time of excitatory conductances on the order of 1 millisecond can determine whether or not a vibrissa deflection will evoke a spike (Moore and Nelson 1998; Moore et al. 1999; Simons and Carvell 1989; Wilent and Contreras 2005). Many of these changes associated with temperature could modulate conductance and evoked release on this time scale, altering sensory signal transmission.

Indirect Mechanisms: Astrocyte-Mediated Hemo-to-Neural Signaling

Anatomically, astrocytes are positioned between neurons and vasculature, and play a key role in neural-to-hemodynamic signaling. However, many recent studies have demonstrated that astrocytes also modulate neural activity (for reviews, see (Araque et al. 2001; Nedergaard et al. 2003; Newman 2003; Volterra and Meldolesi 2005)). In this section, we propose that glia may mediate hemo-to-neural interactions, translating functional hyperemia-related vascular signals into changes in neural activity and, in turn, information processing.

The Anatomical Interconnectivity and Range of Impact of Astrocytes

Astrocytes have multiple processes that are interconnected with glial, neural and vascular elements. Astrocytes are densely interconnected with other astrocytes, communicating through gap junctions and chemical signals. As first observed by Golgi ((Golgi 1885)), astrocytic end-feet form a dense net of multiple discrete contacts with vessels (Nedergaard et al. 2003). Astrocytic end-feet also overlap axonal-dendritic connections in the central nervous system, forming the ‘tripartite synapse’ (Araque et al. 1999; Nedergaard 1994; Nedergaard et al. 2003). In the hippocampus, 57% of synapses form this kind of anatomical and functional unit (Lehre and Danbolt 1998).

Individual astrocytes are proposed to have physiological impact over ‘micro-domains’ spanning ~ 300 - 400 microns in diameter (Nedergaard et al. 2003; Oberheim et al. 2006). Within this extent, a given astrocyte contacts up to thousands of neurons (Fellin et al. 2004; Oberheim et al. 2006), and their end-feet line microvessels at the ‘border’ of a putative microdomain (Simard et al. 2003). Signal transmission in astrocytes is triggered by traveling calcium oscillations that induce the release of several factors (Charles et al. 1991; Cornell-Bell et al. 1990). One support for the ‘microdomain’ view is that spreading calcium waves and the related process of ATP diffusion extend approximately this distance. Evidence also exists for the selective induction of calcium waves in sub-zones within an astrocyte. Spontaneous calcium oscillations in hippocampal slices can occur in single astrocytic processes (Pasti et al. 1997; Taylor-Clarke et al. 2002) and electrical stimulation of the cerebellum can recruit activation in sub-regions of glia (Grosche et al. 2002; Grosche et al. 1999). Local expression of calcium waves may provide a more precise and more rapid means of communication between vasculature and neurons via astrocytes.

Role of Astrocytes in Neural-to-Hemodynamic Communication

Several theories predict that astrocytes play a major role in translating neural activity into enhanced blood flow (Araque et al. 1998a; Paulson and Newman 1987; Pellerin and Magistretti 1994; Rossi 2006; Takano et al. 2006; Zonta et al. 2003). Calcium signaling in astrocytes can be induced by a variety of factors released by neurons, including glutamate, GABA and ACh (Fellin et al. 2006), and this increased calcium signal may trigger enhanced blood flow through vascular end foot contacts. Initial support for this view came from the observation that glutamate application in culture induces the production of vasodilatory substances in astrocytes (Fellin et al. 2006). Direct support comes from *in vitro* and *in vivo* studies, in which either electrical stimulation of local neurons or direct stimulation of astrocytes causes dilation of local vessels in a fashion correlated with increased astrocytic calcium concentration (Filosa et al. 2004; Mulligan and MacVicar 2004; Takano et al. 2006; Zonta et al. 2003).

Astrocyte-to-Neuron Communication

Astrocytes can regulate neural activity through a variety of mechanisms. A prominent mechanism is the release of neuro-active factors, including but not limited to steroids, neuropeptides, growth factors, aspartate, prostaglandin E2, and D-serine (Haydon and Carmignoto 2006; Volterra and Meldolesi 2005). The potentially most important member of this class is glutamate. In culture and slice preparations, glutamate release from astrocytes can cause large, NMDA-dependent depolarizations in adjacent neurons (Araque et al.; Hassinger et al. 1995; Parpura et al. 1994; Parri et al. 2001; Pasti et al. 1997). Further, direct stimulation of adjacent astrocytes enhances the rate of spontaneous miniature excitatory post-synaptic currents (EPSCs) and net depolarization in neighboring neurons (Araque et al. 1998a). In some circumstances, the net effect of astrocytic stimulation is the potentiation of presynaptic neural inputs (Jourdain et al. 2007), while in others the effect of the astrocyte-induced increase in spontaneous release is synaptic depression, decreased evoked response amplitudes and increased failure rate (Araque et al. 1998a). At the neuromuscular junction, glial regulation is responsible for ~50% of the synaptic depression observed during repetitive stimulation (Newman 2003; Rochon et al. 2001). Similarly, astrocytic release of adenosine is believed to play a role in heterosynaptic suppression of transmission (Manzoni et al. 1994; Zhang et al. 2003). Some evidence also suggests a role for astrocytic glutamate release in maladaptive excitatory activity, specifically in the generation of epileptogenic-like activity in pyramidal neurons (Kang et al. 2005).

Astrocytic glutamate release can also impact local circuit function through influence on inhibitory interneurons. Release of caged calcium in hippocampal astrocytes increases the rate of spontaneous activity in inhibitory interneurons, and the rate of inhibitory post-synaptic currents observed in neighboring neurons (Liu et al. 2004). Further, activation of interneurons by astrocytic glutamate facilitates the potentiation of inhibitory input to pyramidal neurons, leading to a decrease in the failure rate of presynaptic release from interneurons (Kang et al. 1998).

In addition to the direct release of factors onto neurons, other astrocytic mechanisms have been shown to modulate neural activity. The uptake of glutamate is a well-established role of astrocytes, and provides a complementary mechanism for neural regulation. In the retina, the amplitude and duration of ganglion cell EPSCs are significantly increased when the glial glutamate transporter is blocked (Higgs and Lukasiewicz 1999), suggesting that glia can act to regulate the duration of excitatory signal transmission.

The Impact of Functional Hyperemia on Astrocyte Activity

While it is accepted that astrocytes can impact neural activity, thereby providing a key step in the hemo-astro-neural progression proposed here, the second essential process, the impact of functional hyperemia on signaling in astrocytes, has not been established. Functional hyperemia could cause signaling in astrocytes relevant to neural information processing through a variety of mechanisms, including all of those described above for *direct* hemo-neural modulation.

Diffusible messengers carried by blood may modulate astrocytic function. Application of NO to astrocytes *in vitro* induces an influx of calcium (Li et al. 2003) and glutamate and ATP release (Bal-Price et al. 2002). Astrocytes and endothelial cells are known to interact closely in development, in cell signaling and in the maintenance of the blood-brain barrier (see (Abbott 2002) for a review). The dense apposition of astrocytic endfeet over capillary endothelial cells (Kacem et al. 1998)

positions them to be modulated by endothelial NO release, which can be triggered by increased hemodynamic activity (Charles 1999; Garthwaite et al. 2006; Iadecola 1993).

Mechanical interactions are also a potential mechanism for vascular to astrocytic signaling leading to neural modulation. Several studies have demonstrated the induction of calcium waves with mechanical deformation in astrocytes (Charles et al. 1991; Islas et al. 1993; Niggel et al. 2000; Stout and Charles 2003). Astrocytic end feet are, as described above, in an ideal position to detect the mechanical impact of functional hyperemia, as they ensheath cerebral microvessels, and endfeet have a high density of mechano-sensitive connexin channels that trigger intracellular calcium release (Simard et al. 2003).

The Impact of Hemo-to-Astrocytic Activation on Neural Processing

As described in the above review, neural activity is modulated by astrocytic activity, and astrocytes are in a key position to be modulated by changes in blood flow and volume. As such, functional hyperemia should, through this *indirect* mechanism, modulate neural activity. Anatomical and physiological considerations suggest that these proposed interactions will occur at least within a microdomain of ≤ 300 -400 microns (Anderson and Nedergaard 2003; Oberheim et al. 2006). The calcium waves in astrocytic processes move slowly, on the order of microns per second (Mulligan and MacVicar 2004; Wang et al. 2006): However, calcium waves can occur in astrocytic processes locally opposed to neurons, and sensory stimulation recruits astrocytic processes on a faster time course (<1 s) than cell bodies (Takano et al. 2006). These findings suggest that local interactions (<10 micron) may be crucial if *indirect* mechanisms contribute significantly to a more rapid hemodynamic impact on ongoing neural activity, and more generally that the hemo-astro-neural pathway may impact longer time course state-related phenomena.

Summary

The pathways and time courses predicted by the Hemo-Neural hypothesis, and the related interactions between neurons, vasculature and astrocytes, are summarized in **Figure 1**. In the diagram, the gray arrows represent accepted interactions or those for which primary data currently exists. As reviewed above, neural activity is believed to induce functional hyperemia through direct contact with vasculature, and/or through astrocytic intermediaries. Astrocytic activity, in turn, has been shown to be able to drive vascular dilation and contraction, and also to alter neural processing.

The darker arrows in Figure 1 constitute the present hypothesis. They represent the direct and indirect pathways through which hemodynamic modulation of neural information processing is proposed to occur. The time course at the bottom of Figure 1 shows the predicted evolution of these effects. The direct pathway (black arrow) is predicted to cause rapid neuromodulation, occurring milliseconds to seconds after the onset of functional hyperemia. The indirect pathway that requires astrocytic transduction (dark gray arrows) is predicted to show delayed modulation, occurring seconds to tens of seconds after the onset of functional hyperemia.

One Impact of Blood Flow on Information Processing: Cortical Dynamics

The above evidence suggests that both direct and indirect mechanisms exist through which functional hyperemia can modulate neural activity. In the current section, we propose one kind of

impact of functional hyperemia on neural information processing, the dynamic modulation of neural excitability in sensory neocortex.

With regards to the primary somatosensory cortex, functional hyperemia has spatial structure on the order of a single cortical column (≤ 400 microns), its onset follows neural activity by ≤ 200 msec, and enhanced blood flow and volume sustain for seconds after the onset of neural activity. We predict that this signal provides a spatio-temporally targeted modulator of the gain state of neural transmission. The mechanisms defined above suggest that either enhancement or suppression of spontaneous and evoked activity can occur, and that the directionality of modulation depends on brain area and context. Facilitation of neural activation could be engaged through recruitment of mechano-sensitive cation channels, through modulation by NO or through astrocyte-mediated depolarization.

Depolarization or hyperpolarization of this type will impact the response of cortical neurons to a sensory stimulus, and dynamics of this kind have been proposed as a means of optimizing cortical function for perception. One hypothesis suggests that the transition from high cortical gain to low cortical gain represents a transition from states optimal for detection to those optimal for discrimination of sensory stimuli, respectively (see Moore et al., 1999; Moore, 2004 for reviews). High gain modes in which a broader region of a cortical map is activated by a sensory stimulus are predicted to facilitate the detection of input, but may be sub-optimal for precise stimulus representation. In contrast, low gain modes with sharper, more delimited lateral spread of signal are predicted to facilitate the precise representation and discrimination of sensory stimuli, but are less optimal for detection of weaker sensory signals. This transition could be modulated by either the pattern of ongoing sensory stimulation, reflecting the information context in which processing is occurring. For example, high-frequency sensory input leading to an adapted state is predicted to impair detection and facilitate discrimination. Similarly, internal state properties may also modulate cortical activity levels and information processing, such as ongoing activity in the thalamo-cortical loop at alpha-band frequencies (Worden et al. 2000).

Perhaps the most important context in which to consider the Hemo-Neural hypothesis is during natural behavior. In many active sensing contexts, preparatory motor or cognitive behaviors will lead to an increase in blood flow in the cortical representation that is about to process incoming signals, and may 'pre-condition' neural processing by inducing enhanced blood flow prior to the receipt of meaningful information. One example of a motor behavior that is correlated with a shift to an attentive perceptual state is the 'whisking' engaged by rodents during active sensing with the vibrissae. When a rat searches its environment, looking for an object to contact and identify, it actively whisks its vibrissae forward and backwards at a rate of 5-12 Hz (Carvell and Simons 1990; Kleinfeld et al. 2006; WI 1964). During search, whisking can begin up to seconds prior to contact with the surface. During whisking in air, both sensory feedback and input of signals from the motor system drive activity in SI (Fee et al. 1997; Ferezou et al. 2006; Kleinfeld et al. 2002), activity that should produce enhanced blood flow within 2-3 cycles of the onset of vibrissa motions (or ~ 250 msec). Under the present hypothesis, blood flow would 'anticipate' the acquisition of information, helping transform cortical circuits to more optimally represent the incoming signals prior to surface contact.

This kind of anticipatory change in blood flow is not limited to cases where active motor exploration precedes acquisition. In many ‘cognitive’ paradigms, blood flow modulation occurs in anticipation of or independent of the receipt of sensory input. One example of a context in which hemo-neural modulation of cortical dynamics may impact information processing is through enhancement of evoked responses during selective attention. A wide variety of studies have demonstrated that attention to a region of input space (e.g., a retinotopic position or body area) is correlated with enhanced evoked action potential firing of cortical neurons with receptive fields overlapping the attended region (Bichot and Desimone 2006). These effects typically emerge 100-500 milliseconds after the onset of attentional focus (Khayat et al. 2006; Khoe et al. 2006; Worden et al. 2000).

Functional hyperemia is positioned to modulate activity during attention, as enhanced blood flow is often localized to regions of the cortical map corresponding to the attended region of space. For example, in area V1, selective and divided attention to specific quadrants of the visual field is correlated with increased BOLD signal in the attended sub-regions of the retinotopic map (McMains and Somers 2004). Similarly, anticipation of contact in a specific body region is correlated with relatively greater blood volume in the corresponding part of the SI homunculus (e.g., the hand area if finger contact is predicted) as compared to non-cued body regions prior to stimulation onset (Drevets et al. 1995).

Ongoing blood flow and volume levels that impact representation may be determined by any of the many mechanisms that control functional hyperemia. Of particular interest given the current proposal is the regulation of hyperemia by neuromodulators already implicated in regulation of attention, such as acetylcholine. A wide variety of studies have suggested that ACh release may be essential to the cortical dynamics mediating attention and working memory (Feldman et al. 2005; Furey et al. 2000; Robbins et al. 2000; Sarter et al. 2005). Under the current hypothesis, ACh would have synergistic neuromodulatory and hemodynamic influences during enhanced attentional states, modulating the local vascular and neural network in the service of a common information processing goal.

Why Engage Functional Hyperemia for Neural Modulation?

This proposal begs the question as to why functional hyperemia is a ‘necessary’ aspect of neural modulation, given that other mechanisms are known to exist that recruit these dynamics. Put another way, why would such a mechanism evolve if it appears redundant to existing processes? There are several responses to this kind of teleological question applied to biology.

The emergence of a neuroregulatory role for functional hyperemia is not difficult to conceive. If one presumes any of the several possible metabolic needs for activity-driven increases in blood flow, in agreement with the existing theories for this phenomenon, then a correlation is present between blood flow and neural activity. If an ‘overflow’ of this supply also proved adaptive for the functionality of neural representation, then one would predict its evolutionary emergence through the reinforcement of this correlation. Further, there is strong evidence from invertebrates for the vascular transmission of neuromodulatory substances that regulate neural firing, neural oscillations and behavior, e.g., in control of the stomatogastric ganglion (Marder et al. 2005; Nusbaum and Beenhakker 2002).

There are also important physiological reasons why functional hyperemia may be employed to suppress neural activity. Unchecked neural activation following stimulation is a hallmark of forms of epilepsy and schizophrenia (Blum and Mann 2002), and in the limit becomes the cause of excitotoxic cell death (Tsuang et al. 2000). Metabolic ‘control systems’ such as the hemodynamic pathways could, therefore, have evolved mechanisms for neural regulation targeted to the basic health of the system that have additional benefit for the efficient representation of information. The existence of severe maladies characterized by failed neural suppression suggests, further, that mechanisms of neural gain regulation are not sufficient in a significant fraction of the population. As such, the addition of a novel mechanism (functional hyperemia) is not redundant.

A further argument for a role for functional hyperemia in information processing is its unique character. While there are several possible mechanisms through which functional hyperemia may differentially impact different neuron or synapse classes, a distinctive feature of this mechanism is that it acts on the neurons throughout a local area, ‘binding’ their function. This kind of impact would be predicted to be of particular significance in representations, like a sensory map, where spatial position within a local network is important to representation. High-resolution sensory cortices such as primary visual cortex (Hubel and Wiesel 1977) and the vibrissa barrel cortex (Andermann and Moore 2006; Andermann et al. 2004; Moore and Andermann 2005) are characterized by clustering of neurons with similar tuning in an overlapping set of columns. These interdependent columnar systems may be ideally positioned to be regulated by a modulator acting on the spatial scale currently ascribed to hyperemia.

Recent hypotheses have emphasized that energetic efficiency in brain operation is a paramount constraint, and therefore leads to sparse coding through the dynamic restriction of activity and the adaptability of networks (Laughlin and Sejnowski 2003). In such a situation, the interdependence of computation and metabolism would be adaptive. The synergistic engagement of the metabolic supply network to regulate coding is, in this context, a consistent proposal.

Perhaps the most appropriate answer to the question of why functional hyperemia ‘needs’ to exist as an information processing mechanism is that this question is ill-posed. The attempt to delineate the evolutionary necessity of any given mechanism in an existing organism is almost always an open-ended endeavor. This practice is particularly difficult when judging the importance of a newly proposed mechanism, where the nature of its interactions is only hypothesized. Analysis of the neuromodulatory role of functional hyperemia is, at present, best focused on the study of the observable impact of hemodynamics on neural processing, reserving a further discussion of the evolutionary ‘necessity’ of this mechanism until more is known about its basic biology and its impact on behaviorally-relevant information processing.

Clinical Implications of the Hemo-Neural Hypothesis

There are several potential clinical implications of the prediction that functional hyperemia modulates neural activity. Diseases that impact the vasculature and impact cognitive function may in part be operating through a failure in the hemo-neural interactions, and the loss or alteration of neuromodulatory function that results.

The negative outcomes of stroke are commonly believed to arise only from localized cell death in the focus of the lesion and the metabolic losses and stresses associated with deprived flow. Under the current hypothesis, the altered blood supply in itself, and the subsequent loss of normal functionality in a given neural circuit, may be causal in behavioral symptoms even if downstream neurons are viable. One cause of cell death in stroke is hyper-excitation of the tissue resulting from a variety of factors (Mattson 2003). A direct prediction of the hemoneural hypothesis is that decreased blood flow could induce an increase in the excitability of neural tissue, and that this loss of a suppressive mechanism could contribute to this post-traumatic response. The loss of suppression also predicts a period of enhanced hyper-excitability at the edge of the lesioned area, sustained until homeostatic mechanisms can be engaged, and leaving the tissue beyond the predicted penumbra of obvious damage in a maladaptive state for normal information processing.

Recent advances suggest that Alzheimer's disease is initially expressed as a vascular phenomenon, with impaired cholinergic dilation of blood vessels implicated in its pathophysiology (Cauli et al. 2004; de la Torre and Mussivand 1993; Geaney et al. 1990; Iadecola 2004; Sato and Sato 1995). As such, the Hemo-Neural hypothesis would predict an impact of vascular decline on hemo-neural interactions, taxing the information processing capacity of the system through loss of one form of normal modulatory control. A specific prediction is that pre-diagnosis Alzheimer's patients could show enhanced facilitation and/or the failure of tonic and phasic levels of intracortical suppression, in agreement with recent transcranial magnetic stimulation studies (Liepert et al. 2001; Pierantozzi et al. 2004).

Epilepsy can arise through a broad variety of mechanisms, including a failure in the normal mechanisms of neural suppression (Duncan et al. 2006). The Hemo-Neural hypothesis predicts that hemodynamic abnormalities could lead to these symptoms. In agreement with this prediction, abnormal vascular anatomy is a hallmark of seizure disorders (Leutmezer et al. 2003; Zaidi et al. 2000) and a compromised blood-brain barrier predicts seizure onset (Oby and Janigro 2006). Further, vagal nerve stimulation has recently been successfully employed to suppress the onset of epileptic seizures (DeGiorgio et al. 2000; Schachter 2002) and could operate at least in part through vascular regulation.

A failure in cortical dynamics is also widely predicted to be a causal factor in schizophrenia. Schizophrenic subjects show several indications of failed cortical suppressive mechanisms, including decreased prominence of gamma oscillations (Lee et al. 2003; Spencer et al. 2003). While this symptomatology has many proposed neural causes (Lewis et al. 2005; Woo and Lu 2006), vascular abnormalities in resting blood volume distribution and presumed vascular anatomy have also been observed in schizophrenic subjects (Cohen et al. 1995), and could contribute.

Other Links Between Hemodynamics and Information Processing

The interdependent nature of vascular and neural interactions suggests other hypotheses as to their combined function in information processing, beyond the suggestion that functional hyperemia regulates neural dynamics. The role of hemodynamics in shaping oscillatory behaviors—such as those expressed in EEG and MEG signals—should be considered. This suggestion is particularly salient given the potential role of NO in regulating thalamic rhythms (Pape and Mager 1992), and astrocytes in unifying activity across disparate neurons (Angulo et al. 2004; Fellin et al. 2004).

Vascular oscillations are also prominent features of the cerebral vasculature (van Helden et al. 2006), and changes in these hemodynamic state properties may interact with neural state properties. A further prediction mentioned above is that the combination of functional hyperemia and patterns of neural activity may facilitate the induction of longer-term neural plasticity. On a longer time-scale, selective regulation of the blood-brain barrier, shaped by the recent history of flow to the region, could also serve an integrative role (Krizanac-Bengez et al. 2004; Leybaert 2005).

A more radical aspect of the Hemo-Neural hypothesis than the one elaborated above is that the vasculature also plays a direct role in carrying information, beyond just modulation of neurons. If neural activity in one region (for example, a specific layer of the neocortex) were to produce a signal that was taken up by the vasculature, it could be selectively transmitted to a downstream target (e.g., other layers of the neocortex). At least two mechanisms could support this kind of communication. Peripheral and central vascular tissue is capable of electrical coupling (Segal and Duling 1987; Yamazaki and Kitamura 2003). Electrical signals can be transmitted, putatively through gap junction connections in endothelial and/or smooth muscle cells, from capillaries to their feeding arterioles, and may condition a vasodilatory response. These changes in membrane potential in vascular cells can be driven by neuromodulators (e.g., ACh) (McGahren et al. 1998) and by local changes in flow (e.g., the occlusion of a neighboring arteriole) (McGahren et al. 1997). These signals generated 'downstream' could induce voltage dependent interactions in upstream targets, from a capillary bed and the granular layers of the cortex, for example, to an arteriole and the supragranular layers. Moving in the other direction, the transport of diffusible messengers is also a possibility. Diffusible messengers produced in a superficial cortical layer could be transported down an arteriole and released in deeper layers. This view, while even further from currently accepted models of information processing, similarly bears further investigation.

Future Directions

The ideas presented have several direct implications for future research. The Hemo-Neural hypothesis argues that any computational model or broader theory that seeks an accurate and biophysical account of information processing in the brain should include hemodynamics as an explicit component. This view also suggests that the wealth of studies that have investigated hemodynamic patterns and neural-to-vascular coupling are not only informative with regards to the metabolic functioning of the brain, but are also descriptions of signals that impact representation. As such, fMRI and related techniques are not simply second-order localization tools, but probes of part of the process of information representation. If true, there are important considerations as to the logical interpretation of these hemodynamic signals, and of how they synergistically interact with the variable that most of these studies would like to track, neural activity.

The Hemo-Neural hypothesis suggests several lines of experimentation to systematically test this proposal. Understanding the impact of hemodynamics on neural activity requires the independent regulation of blood flow *in vivo*. This kind of probe is essential for systematically dissociating these effects from alternative explanations, and for ultimately addressing these predictions during active behavior. An informative frustration in attempting these experiments is the extensive overlap in factors that regulate hemodynamics that also directly or indirectly regulate neural activity through other pathways. The interdependent modulation of these two systems, while a strong argument for the Hemo-Neural hypothesis, also makes the discrete investigation of these predictions difficult. This

challenge underscores the inter-related nature of central neural and hemodynamic processes, and the likelihood that they function in tandem in the modulation of information processing.

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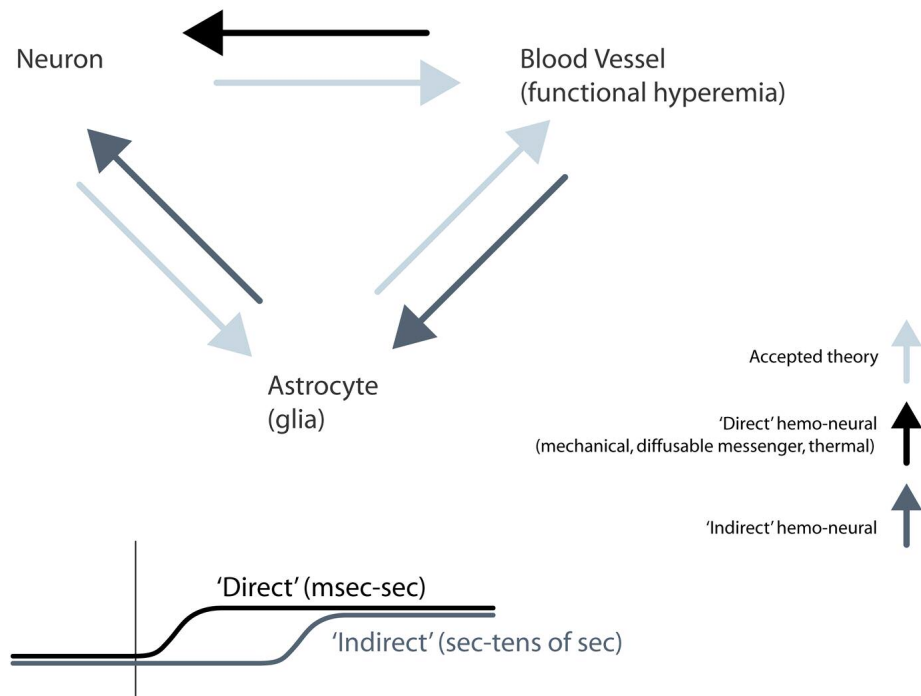


Diagram courtesy Julian Wong (artist) and Christopher Moore (McGovern Institute)

Figure 1 The Hemo-Neural Hypothesis: Bi-Directional Interactions Between Hemodynamics, Neurons and Glia Figure 1 illustrates the key concepts underlying the Hemo-Neural Hypothesis. Neural activity is known to drive functional hyperemia, and may do so through either neural inputs to the vasculature or through intermediary astrocytes (lighter gray arrows). The Hemo-Neural Hypothesis proposes that hemodynamic changes can impact neural activity through direct and indirect pathways. Direct effects (black arrow) are hypothesized to occur through the release of diffusible messengers, mechanical interactions and/or changes in temperature. Indirect effects (darker gray arrows) are hypothesized to occur through activation of astrocytes, which in turn modulate neural activity. As shown in the diagram on the bottom of the figure, direct interactions are predicted to occur within milliseconds to seconds following changes in the local hemodynamic environment, and indirect interactions to occur on a time scale of seconds.

127x108mm (300 x 300 DPI)