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Keeping the Brain Well Fed: The Role of Capillaries and Arterioles in Orchestrating Functional Hyperemia

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Cerebral blood flow increases in regions of increased brain activity. In this issue of *Neuron*, Rungta et al. (2018) characterize the contribution of different vascular compartments in generating this increase and outline the time course of arteriole and capillary dilation in generating functional hyperemia.

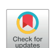
The brain is a hungry organ, consuming 20% to 25% of the total oxygen and glucose utilized by the body. Many mechanisms have evolved to ensure that the brain receives adequate nourishment to maintain its health and proper function. When a region of the brain is active, blood flow to that region increases via a process termed functional hyperemia, bringing additional nutrients to the active neurons and removing metabolic byproducts. This coupling between neuronal activity and blood flow allows imaging techniques, such as blood-oxygen-level-dependent functional magnetic resonance imaging (BOLD fMRI), which use the functional hyperemia response to determine regions of brain activity based on changes in blood flow and oxygenation.

Fundamental questions about the nature of functional hyperemia remain unsolved, complicating interpretation of fMRI. One such question concerns whether capillaries, as well as arterioles, actively dilate in response to neuronal activity (Nippert et al., 2018). The question is critical, as it determines whether blood flow increases can be targeted precisely to regions of activity and defines the limits of spatial resolution achievable by BOLD imaging. Traditionally, it was believed that increases in blood flow were regulated entirely by arteries and arterioles on the pial surface of the brain and penetrating arterioles within the brain parenchyma. Recently, however, several laboratories have reported that capillaries also dilate actively following neuronal activation and contribute to functional hyperemia (Hall et al., 2014; Kornfield and Newman, 2014; Tian et al., 2010). This observation is controversial, as one report claims that pericytes, the vascular mural cells that surround capillaries and are analogous to arteriolar smooth muscle cells (SMCs), do not express contractile proteins (Hill et al., 2015). A recent publication (Alarcon-Martinez et al., 2018) has demonstrated, however, that pericytes express alpha-smooth muscle actin and can constrict and relax. Furthermore, pericytes may also express actin isomers other than alpha-smooth muscle actin (DeNofrio et al., 1989).

In this issue of *Neuron*, Rungta et al. (2018) make a major contribution to resolving the problem of which vessels generate functional hyperemia. Working in the mouse olfactory bulb *in vivo*, they demonstrate that capillaries, as well as arterioles, actively dilate in response to neuronal activity and contribute substantially to functional hyperemia. In this elegant study, Rungta et al. (2018) use a variety of imaging techniques to simultaneously monitor several aspects of functional hyperemia. Using two-photon microscopy, they monitor activation of neuronal terminals by imaging Ca^{2+} signals in oligodendrocyte precursor cells, which they demonstrate faithfully follow presynaptic activity. They then monitor vascular responses by imaging Ca^{2+} within SMCs surrounding arterioles and within pericytes surrounding capillaries, an innovative and powerful method, as these Ca^{2+} responses occur faster than the dilation of vessels and show individual mural cell activation state independent of changes in vessel diameter or blood velocity. They simultaneously monitor vessel diameter and blood velocity with two-photon line scans.

Rungta et al. (2018) divide the vasculature into four functional units (see Figure 1): (1) pial arterioles, (2) parenchymal arterioles and the first-order capillaries branching from them, which they define as the primary functional unit, (3) the downstream, higher-order capillaries (the secondary functional unit), and (4) the smallest, highest-order capillaries, which are juxtaposed to the olfactory nerve terminals. They find that olfactory stimuli induce a decrease in intracellular Ca^{2+} in pericytes and SMCs throughout the vascular tree and that this decrease in Ca^{2+} occurs fastest and synchronously in the first three functional compartments compared to the fourth juxta-synaptic compartment. Yet, there is a difference in the evoked dilation of the vessels: the arterioles and capillaries of the primary functional unit dilate first while the pial arterioles and capillaries of the secondary functional unit dilate more slowly. The smallest juxta-synaptic capillaries (those 5 to 8 branches from parenchymal arterioles) do not actively dilate to olfactory stimuli despite the decrease in Ca^{2+} observed in the thin-strand pericytes contacting them. Rather, they dilate passively due to an increase in upstream perfusion pressure. Counterintuitively, while the primary functional unit dilates fastest, increases in blood velocity are fastest and largest in the smallest capillaries.

The persuasiveness of Rungta et al. (2018)'s findings is buttressed by an



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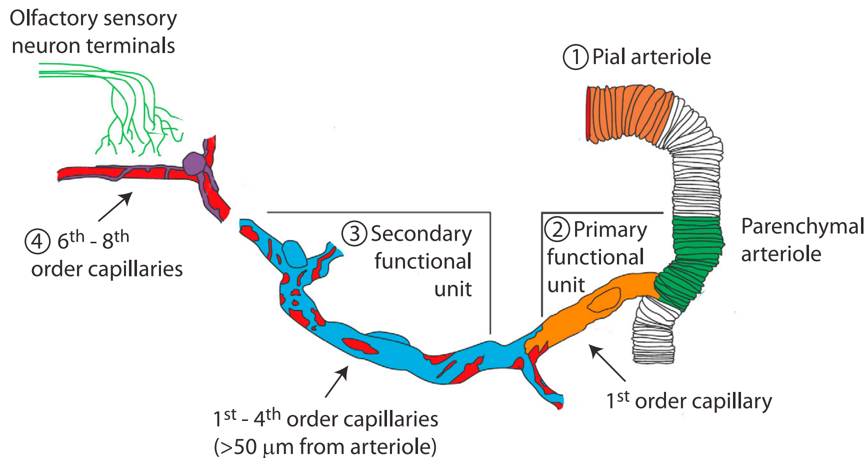

Figure 1. Vasculature of the Olfactory Bulb

Rungta et al. (2018) divide the vasculature of the olfactory bulb into four compartments: (1) the pial arterioles, (2) the primary functional unit comprising the parenchymal (penetrating) arterioles and first-order capillaries, (3) the secondary functional unit comprising first- to fourth-order capillaries that are at least 50 μm removed from the parent arteriole, and (4) higher-order small-diameter capillaries, which are closest to the nerve terminals activated by olfactory stimuli. The pial and parenchymal arterioles are enveloped by a continuous layer of SMCs. Capillaries of the primary and secondary functional units are largely covered by enwrapping pericytes while higher-order capillaries are surrounded by thin-strand pericytes. Modified from Rungta et al. (2018).

associated modeling study, which simulates the experimental results. The model predicts blood flow changes in response to experimentally measured changes in vessel diameter in the four vascular compartments. As observed experimentally, the simulations demonstrate that blood velocity increases should be delayed in the primary functional unit because of the large volume increase in that compartment produced by vessel dilation. The same effect accounts for the transient decrease in blood velocity sometimes seen in this compartment. The simulations also indicate that the largest blood velocity increases should occur in the smallest capillaries, which only dilate passively.

Additional important insights are derived from the modeling study. The simulations indicate that active dilation of capillaries in the secondary functional unit contribute to blood flow increases. More surprisingly, the smallest, highest-order capillaries also contribute substantially to functional hyperemia. When the passive dilation of these capillaries is removed from the simulation, the blood flow increase is reduced by almost half. This finding is in line with previous studies indicating that a large fraction of the total vascular resistance in the brain resides within the capillary network (Blinder et al., 2013). The observation that these capillaries do not actively dilate but that pericytes around them nonetheless display Ca^{2+} decreases suggests that Ca^{2+} in these pericytes may contribute to the stiffness of the capillary wall.

The work of Rungta et al. (2018) raises important additional questions. The smallest high-order capillaries are closest to the synaptic terminals activated by olfactory stimuli. Yet, the pericytes associated with these capillaries respond more slowly than pericytes and SMCs associated with upstream vessels of the primary functional unit. Why do the contractile cells farther from the site of neural activity respond faster? Rungta et al. (2018) suggest that a vasodilating signal (cell hyperpolarization) is propagated rapidly upstream through the vascular endothelial cells. This supports the idea that endothelial cells, rather than pericytes and SMCs, detect neuronal activity, as suggested previously (Chen et al., 2014). However, this still does not explain why pericytes surrounding the smallest capillaries respond more slowly. Perhaps, as Rungta et al. (2018) suggest, these pericytes are less closely coupled to the endothelial cells than are the upstream pericytes. Or perhaps the molecular machinery generating the Ca^{2+} decreases in these pericytes is weaker or slower. Further, these data do not exclude the possibility that the juxta-synaptic pericytes hyperpolarize first in response to neuronal activity and transmit this signal to the endothelial cells. The question of whether endothelial cells, pericytes, or SMCs are the first responders in functional hyperemia can only be determined by future experiments comparing the time course of hyperpolarization of each cell type.

Other questions arise from the work of Rungta et al. (2018). Is blood flow regulated by the same vascular compartments in other brain regions as in the olfactory bulb? One study in the rodent barrel cortex indicates that first-order capillaries dilate before the penetrating (parenchymal) arterioles (Hall et al., 2014), while another study in the somatosensory cortex shows that penetrating arterioles dilate slightly before first-order capillaries (Tian et al., 2010). By comparison, Rungta et al. (2018) observe near-simultaneous contractile cell Ca^{2+} decreases and vessel dilation in the capillaries and arterioles of the primary functional unit. Some of these discrepancies may be explained by differences in layer-specific vascular responsiveness in different cortical regions (Tian et al., 2010).

In summary, Rungta et al. (2018) make major contributions to our understanding of how blood flow is regulated in the brain. Their work is a technical tour de force, simultaneously monitoring neuronal activity, responses of pericytes and SMCs, vessel dilation, and blood velocity and further utilizing computational modeling to interpret their observations. This is an important advance over previous studies, which limited their scope to only a few of these responses. Using these imaging techniques, Rungta et al. (2018) determine which vascular compartments generate functional hyperemia and characterize the dynamics of the responses in greater detail than previously possible. This study adds to an accumulating body of work demonstrating the importance of capillaries in generating functional hyperemia.

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Primate Social Communication Goes Interactive

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Social communication has traditionally been studied from the point of view of an isolated spectator not participating in social interaction. In this issue of *Neuron*, using advanced functional imaging, Shepherd and Freiwald (2018) explore the functional neuroanatomy of social communication in the brain of socially interacting nonhuman primates and discover three large-scale brain networks dedicated to the process.

Communication is the process of transmitting information from a sender to a receiver. In this definition, only the sender is active, whereas the receiver passively perceives information. In everyday social communication situations, however, the receiver reciprocates the exchange of information. We all know the greeting ritual in the morning when someone asks "How are you?" If we were not to reply, we would immediately suffocate from the attempt to communicate in a rude way. Instead, we reply "Awesome!" if we are feeling alright and are having this encounter in the United States (in Germany, we may less enthusiastically mumble "Okay"). Social communication becomes "social" and alive if we not merely observe others, but interact with them.

Although interaction is a key aspect to social communication, social cognition has traditionally been studied from a third-person stance, from the point of view of an isolated spectator that is required to merely observe others rather than participate in social interaction with them. However, this approach can only elucidate the impoverished passive, or perceiving, side of communication. It neglects the irreducible reactive side of social communication required for an involved, second-person stance that emphasizes the importance of dynamic, real-time interactions with others (Schilbach et al., 2013). Currently, it is unknown which networks in the brain may be required once a subject becomes involved in an ongoing interaction.

In this issue of *Neuron*, Shepherd and Freiwald (2018) set out to tackle this question and explored social communication networks in the brain of interacting rhesus monkeys. Using functional magnetic resonance imaging (fMRI), they measured regional blood flow in the brains of rhesus monkeys that watched video clips of other rhesus monkeys inside a scanner (Shepherd and Freiwald, 2018). The videos displayed the real moving faces of conspecifics in two different social contexts: the first context simulated a third-person context in which the monkey in the video was looking away from the subject (averted-gaze context). This provided Shepherd and Freiwald (2018) to explore the neural processes in the subject as a detached spectator that simply observes the faces of a conspecific from a third-person stance. In the second context, the monkey in the video was looking and grimacing straight at the subject (direct gaze context) (Figure 1). This condition prompted the subject to make face and mouth movements directed at the conspecific in the video. The most common facial movement exhibited by the subject was "lipsmacking," an affiliative and affective signal often observed during face-to-face social interactions in advanced nonhuman primates. Because the subject reciprocated social signals and thus attempted to interact with the monkey in the video clip, this second context sufficed a second-person context. This condition opened a window into deciphering the brain's networks engaged in involved and reactive social