Published in final edited form as:

Nature. 2009 January 22; 457(7228): 387–388. doi:10.1038/457387a.

Pre-emptive blood flow

David A. Leopold

Abstract

Electrical signalling among brain cells summons the local delivery of fresh blood — the basis of functional brain imaging. Yet, sometimes, blood is sent in anticipation of neural events that never take place.

The brain makes only 2% of the human body mass but, owing to its high energy demands, receives over 15% of the cardiac output. When blood enters the brain, it doesn't course indiscriminately throughout its vessels; instead, it is selectively channelled to specific regions in a need-based fashion. On page 000 of this issue, Sirotin and Das¹ show that, sometimes, blood is distributed to the brain's visual cortex in the absence of any stimulus, priming the neural tissue in apparent anticipation of future events.

The physiology of the cerebral cortex — the folded sheet of densely packed grey matter covering the brain's surface — is well studied. Neurons there carry information about stimuli and events using electrical impulses, which they generate and transmit to other neurons. Arteries, arterioles, and capillaries deliver fresh blood to neurons, whereas supporting glia cells surround both neurons and blood vessels, regulating blood flow and performing various housekeeping roles.

Housekeeping in the brain is sometimes a challenge, as neurons undergo sudden bursts of activity, which consume energy and pollute their surroundings. Consider, for example, what happens in the cortex when we first direct our gaze to a bright stimulus. In the region of the cortex specialized for vision, thousands of previously quiescent neurons suddenly erupt in a cacophony of activity, each generating up to hundreds of electrical impulses per second. In response to the metabolic consequences of such activity, fresh blood is directed towards neurons and glia in active regions, flushing out waste products, delivering nutrients and restoring the local milieu. Hopefully above modification, referring to the glia, is sufficient for reader.

Brain mapping techniques such as functional magnetic resonance imaging (fMRI) measure blood flow (haemodynamics) rather than neural activity. The efficacy of fMRI in studying neural processes in the human brain depends on the precise coupling between neural activity and blood flow. Although details of how neural activity triggers changes in blood supply are a topic of active debate, the assumption that the two signals are tightly coupled in both space and time is generally a good one.

Yet biology seems to provide exceptions to every rule, and Sirotin and Das¹ seem to have tapped into a big one. Their study shows that cortical blood flow can depart wildly from what is expected based on local neural activity. They observed this mismatch while performing difficult experiments in alert rhesus monkeys, simultaneously measuring vascular and neural responses from the same region of the visual cortex. Changes in the blood supply were monitored by a sensitive video camera peering at the surface of the brain through a transparent window, while local electrical responses of neurons were measured with a microelectrode. The monkeys were oblivious to all this, focusing instead on a behavioural task that would earn them

a juice reward. The task required the animals to fixate their gaze on a tiny spot on a computer monitor for several seconds at a time.

When Sirotin and Das presented the monkeys with a conventional visual stimulus under these conditions, they observed a close correspondence between neural and haemodynamic responses to the stimulus, as expected based on much previous work². The surprising finding came on trials without a visual stimulus, when the visual cortex should be disengaged. This time, the task was carried out in complete darkness (aside from the tiny spot directing the animal where to look). In contrast to all expectation, the hemodynamic signal continued to rise and fall during these trials despite the lack of visual stimulation. This was evident in the video of the cortical surface, which continued to reveal the cyclical ebb and flow of cerebral blood, accompanied by simultaneous changes in blood oxygenation and arterial diameter. During these same trials the neural signal fell nearly silent. Individual neurons in the same patch of cortex ceased to show any changes in their rate of generating impulses, and only the faint whimper of background electrical activity, corresponding to the local cerebral field potential, indicated that cortical neurons were at all stirred by the behavioural task.

What might be the origin of this vascular priming? While the Sirotin and Das cannot rule out the possibility that subtle neural modulation of the visual cortex contributed to this response via local metabolic coupling, the robust haemodynamic responses they observed were not predictable from any of the measured neural signals. -This study, perhaps more than any previous work, highlights the potential role of direct, task-related neural control of vascular tone. Both glia and blood vessels receive signals from diverse types of neuron, including from those in brain centres controlling attention and arousal³. The task-based modulation of the vascular response may therefore represent input from a part of the brain that can anticipate the probable neural activity over the next seconds in a specific brain region, and so prime that region.

But how specific might such an anticipatory signal be? As the authors¹ found similar modulation in other systemic markers — heart rate and pupil diameter — might the observed modulation reflect an overall change in the brain's blood supply? A control experiment involving an auditory task points against this possibility. Unlike the fixation task, periodic attention to an auditory stimulus did not elicit haemodynamic modulation in the visual cortex. This control, although doing little to clarify the origin of the haemodynamic modulation, shows that such priming depends on the type of sensory stimulus that the brain expects.

The mere mismatch between blood flow and neural activity *per se* is not a great surprise. Indeed, the precise relationship between neural activity, metabolism and blood flow has always been difficult to pin down. Early functional imaging studies revealed a quantitative discrepancy between oxygen consumption by an activated brain region following a sensory stimulus and the corresponding blood-flow response to that region⁴. Simply put, far more oxygenated blood was delivered to an active region than was required based on metabolic demands. Earlier work has also shown that the correspondence between neural activity and blood-based imaging signals is inconstant and highly situation dependent^{5,6}, and has highlighted the complex relationship between neural activity, metabolism and blood flow⁷⁻⁹.

Yet the neurovascular mismatch Sirotin and Das report is extreme. The clear and rhythmic haemodynamic modulation in the visual cortex spurred by non-visual tasks is sure to raise eyebrows in the human fMRI research community. For one, most fMRI experiments involve the periodic presentation of sensory stimuli, and then rely on the temporal structure of the haemodynamic response to deduce local neural activity. The present study¹ clearly demonstrates that some of the assumptions underlying such analysis — namely that cyclical variations in blood flow reflect local, stimulus driven events — may sometimes be incorrect.

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Figure 1. Behavioural modulation of blood flow

Blood flow in the visual cortex is normally modulated in step with neural responses to visual stimuli. Sirotin and Das¹ show that the vascular response in this area of alert monkeys' brain is readily modulated by their expectation of the task, even in complete darkness and without accompanying neural modulation.