PERSPECTIVES

Local action for global vision

Maxim Volgushev
Department of Psychology, University of Connecticut, Storrs, CT 06269, USA

Email: maxim.volgushev@uconn.edu

Active brain cells use oxygen, but exactly how neurone activity drives brain metabolism is poorly understood. A paper by Li & Freeman (2011) in a recent issue of *The Journal of Physiology* sheds light on this important question, by demonstrating how indistinguishable patterns of local neural responses can be accompanied by distinct patterns of brain oxygen consumption. They cleverly exploit the topographic organisation of sensory cortices, using visual stimuli to manipulate the area of activated cortex, and show that global cortical activation can influence local measurements of neural and metabolic activity. The results are important for understanding the basis of non-invasive measures of brain function.

The most common brain imaging techniques are optical imaging of intrinsic signals and functional magnetic resonance imaging (fMRI). These methods measure changes of the blood oxygen level-dependent (BOLD) signal. The BOLD signal is of special importance in brain science, because it can be measured non-invasively in humans using fMRI. Put simply, increased neuronal activity increases energy consumption, producing a decrease in tissue oxygen level (measured as the 'initial dip' in the BOLD signal), followed a few seconds later by a reactive increase of blood and oxygen supply (the 'positive peak'). Herein, however, lies the problem of using BOLD signals to understand brain function: BOLD signals have slow dynamics and coarse spatial scale. The BOLD signal begins long after stimulus-evoked neuronal responses, when cognitive processes such as stimulus detection and recognition may have already been accomplished. Spatially, the initial dip probably integrates changes of tissue oxygen level over ~0.2 mm^2, and the positive peak integrates over ~2 mm^2 (Thompson *et al.* 2005; Viswanathan & Freeman, 2007), encompassing many thousands of cortical neurones. Thus, neural signals and BOLD signals provide complementary, different-scale views on how the brain operates.

Changes of the BOLD signal are known to be related to changes of neuronal activity, but the details of this relationship are controversial (reviewed in Logothetis 2008; Ekstrom, 2009). A key question remains: can similar changes of neuron activity be accompanied by distinct BOLD signals? The paper by Li and Freeman gives a positive answer to this question.

The authors recorded from the best-understood sensory cortex: the primary visual cortex of cats. They combined recordings of neuronal multi-unit activity (MUA) and local field potential (LFP) with simultaneous, co-localized measurements of tissue oxygen level. Control neurone responses and BOLD signals were first evoked with patterned visual stimuli: patches of optimally oriented moving gratings. Next, two different stimuli which suppress neuronal responses were tested. In the first protocol ('surround suppression'), neuronal responses are suppressed by increasing the stimulus diameter. In the second ('cross-orientation'), neuronal responses are suppressed by superimposing an orthogonal grating on the optimally oriented grating. Although neuronal responses decreased in both cases, the BOLD signals were affected in a strikingly different way. Surround suppression produced an increase of the initial dip, but no change of the positive peak of the BOLD signal. In contrast, the cross-orientation protocol yielded a decrease of the initial dip but an increase of the positive peak.

How can we reconcile this apparent contradiction, where one level of neuronal activity is accompanied by two distinct patterns of brain metabolism changes?

Consider what happens when stimulus diameter is increased from 4 deg to 20 deg in the surround suppression test. The strength of thalamic input from the lateral geniculate nucleus (LGN) to the local recording site in the cortex decreases only slightly because LGN neurones are barely sensitive to size change for stimuli over 2 deg diameter (Stone *et al.* 1979; Ozeki *et al.* 2009). More importantly, the large stimulus will activate about 60–70% of the cat's primary visual cortex (Tusa *et al.* 1978), including long-range projections to the recording site from regions up to several millimetres away (Kisvarday *et al.* 1997). Activity around the recording electrode will be diminished as global and local inhibitory circuits work to stabilize the cortical network (Ozeki *et al.* 2009). A magnified BOLD initial dip could result from increased local activity of the inhibitory neurones (as the authors suggest), or as part of a more general increase of oxygen consumption over a very large (hundreds of mm^2) activated cortical area (Fig. 1). The BOLD positive peak does not increase with stimulus size, perhaps in part because the effect of local vasodilatation is shunted by the simultaneous vasodilatation over large regions of visual cortex.

In Li and Freeman's second protocol of cross-orientation suppression, the neuronal activity is modified in a very different way. Responses of LGN neurons will be enhanced by addition of an orthogonal ('mask') grating (Freeman *et al.* 2002; Priebe & Ferster, 2006). However, the plaid-like spatial pattern of LGN inputs is sub-optimal

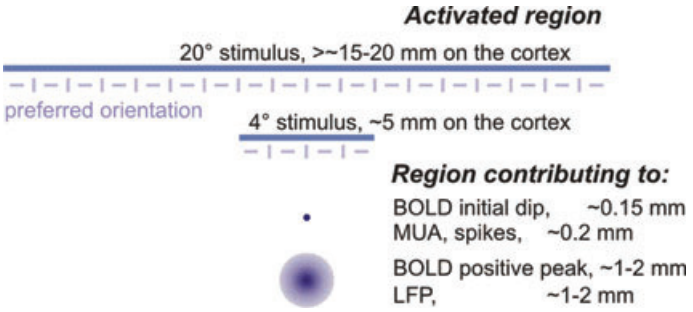

Figure 1. Spatial relation between region of primary visual cortex activated by the stimuli and regions contributing to the recorded electrophysiological (MUA and LFP) and oxygen level (BOLD) signals

DOI: 10.1113/jphysiol.2011.212670

for activation of orientation-sensitive cortical neurons at the recording site and their activity will be reduced (Priebe & Ferster, 2006), thus leading to the reduction of the initial dip. The overlapping mask stimulus will also activate cortical neurons that prefer the orientation of the mask. The spatial grain of the cortical orientation map means that these neurons would lie outside the sensitivity area of electrophysiological recording, and outside the area contributing to the BOLD initial dip. But these neurones would lie within a broader area contributing to the vasodilation response, and their activity could explain why the BOLD positive peak is increased.

The results reported by Li and Freeman provide excellent illustration of two important points. First, they clearly demonstrate the complexity of relations between neuronal activity and BOLD signals. Changes of neuronal activity may arise from activation of different circuits and be mediated via different mechanisms. Although producing the same final measured level of neuronal activity, the difference in underlying circuits may be reflected by the BOLD signals. Second, the observations show why it is essential to consider large-scale patterns of neuronal activation for understanding locally measured processes. This illustrative example shows the power of combined electrophysiological and brain imaging methods which provide complementary, fine-grain and large-scale perspectives on neuronal activity, and most importantly help to understand how they are related.

References

Ekstrom A (2009). *Brain Res Reviews* **62**, 233–244.

Freeman TCB, Durand S, Kiper DC & Carandini M (2002). *Neuron* **35**, 759–771.

Kisvarday ZF, Toth E, Rausch M & Eysel UT (1997). *Cerebral Cortex* **7**, 605–618.

Li B & Freeman RD (2011). *J Physiol* **589**, 3175–3190.

Logothetis N (2008). *Nature* **453**, 869–878.

Ozeki H, Finn IM, Schaffer ES, Miller KD & Ferster D (2009). *Neuron* **62**, 578–592.

Priebe NJ & Ferster D (2006). *Nat Neurosci* **9**, 552–561.

Stone J, Dreher B & Leventhal A (1979). *Brain Res Reviews* **1**, 345–394.

Thompson JK, Peterson MR & Freeman RD (2005). *J Neurosci* **28**, 9046–9058.

Tusa RJ, Palömer RA & Rosenquist AC (1978). *J Comp Neurol* **177**, 213–236.

Viswanathan A & Freeman RD (2007). *Nature Neurosci* **10**, 1308–1312.