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NEUROSCIENCE: fMRI under the spotlight

David A. Leopold

Unit on Cognitive Neurophysiology and Imaging, Laboratory of Neuropsychology, National Institute of Mental Health, Bethesda, Maryland 20892, USA

David A. Leopold: leopoldd@mail.nih.gov

Abstract

Analysis of a selected class of neuron in the brain of living animals using functional magnetic resonance imaging (fMRI) opens up a new horizon for mapping genetically specified neural circuits.

Advances in modern brain research are such that sometimes the line between science and science fiction is blurred. In the past decades, two advances have redefined the limits of experimental neuroscience. The first is functional magnetic resonance imaging, or fMRI, which is widely used to map brain activity in humans. The second is genetic reprogramming of brain cells using molecular genetics. In an elegant study (page XXX of this issue), Lee *et al.*¹ combine these methods to demonstrate that, within the rat brain, the direct activation with light of a genetically defined subclass of neuron leads to robust fMRI responses. The study demonstrates a tight link between neural firing and fMRI responses, and at the same time introduces a powerful new tool for mapping the function and dysfunction of large-scale circuits in the brain.

Functional MRI has had an enormous impact on modern science, with neuroscientists, psychologists, clinicians and even economists routinely basing their conclusions on stunning images of brain activity obtained using this technique. But critics argue that, because fMRI measures changes in blood flow (haemodynamics), rather than information-carrying electrical signals within neurons, its results are often open to interpretation. Indeed, although it is tempting to interpret positive fMRI signals as increased rate of action-potential firing by neurons, this 'one-size-fits-all' interpretation is unlikely to be correct. For instance, some electrophysiological experiments have shown that the simmering, subthreshold activity of neurons is better correlated with haemodynamic fluctuations detected by fMRI than are action potentials². Other evidence^{3,4} suggests that the local coupling between action potentials and haemodynamic signals varies with the behavioural context.

At the heart of the problem are the many complex cellular and molecular mechanisms governing blood flow⁵. Lee *et al.*¹ therefore measured fMRI responses to the direct activation of a certain subtype of neuron manipulated by the technique of optogenetics. For this, they introduced two genes using a viral vector into a class of rat brain cells called excitatory principal neurons. One of the genes encoded a fluorescent protein of a glowing jellyfish origin⁶, which served as a marker to verify precisely which cells were manipulated. The other gene's product was channelrhodopsin, a light-sensitive, membrane-associated protein from a species of green algae⁷. Thus, by making a restricted class of cell sensitive to light, the authors could selectively manipulate the activity of those cells, while leaving other circuit elements unperturbed.

This group has previously used⁸ such an approach to demonstrate exquisite, moment-by-moment control over a mouse's running behaviour by illuminating neurons in an area of the

motor cortex, the brain region responsible for voluntary movements. What makes the present study a technical tour de force is their measurement of haemodynamic and electrical responses to optogenetic stimulation in the brains of anaesthetized rats inside an fMRI scanner.

In the vicinity of the optical fibre with which the authors illuminated the rats' motor cortex, they find robust neural and fMRI responses within a conventional time course. This indicates that the direct activation of excitatory cortical neurons had somehow triggered changes in local blood flow. Such stimulation of a well-defined subclass of neuron goes a step farther than previous sensory stimulation and electrical microstimulation approaches, in which activation was less specific. What's more, Lee *et al.* predict that emerging tools will soon allow targeting cells based not only on genetic markers, but also on their morphology and tissue topology⁹. If so, a further dissection of the cells that are particularly important for neurovascular coupling should be possible in the future.

While optically stimulating the motor cortex, Lee *et al.* also detected robust fMRI responses in the thalamus, a structure in the middle of the brain to which neurons of the motor cortex project axonal processes (Fig. 1a). Both the neural responses and fMRI responses in the thalamus were more sluggish than in the cortex, which the authors attribute to network delays; this point, however, requires further study.

Intriguingly, direct illumination of the thalamus also resulted in fMRI responses, despite its distance from the cell bodies of the manipulated neurons of the motor cortex (Fig. 1b). These responses reflect the expression of light-sensitive channels in the cortical axons projecting into the thalamus. Remote optical stimulation of axons — which has previously been combined with electrophysiological recordings¹⁰ to study long-range connections in brain slices — thus offers a new and powerful way to probe the anatomical and functional connectivity using fMRI.

The finding that direct excitation of principal neurons leads to positive hemodynamic responses will be important for the functional brain imaging community, as it shows a causal link between firing of a class of neurons and the fMRI signal. However, this observation should be interpreted with caution: the downstream neural and non-neural elements probably also make a complex contribution to the vascular response (see authors' discussion).

The main impact of Lee and co-workers' study will be in providing alternative ways for mapping neural circuits. The combination of optogenetics and fMRI, for the first time permits investigation of genetically specified, large-scale networks in the brain of living animals, such as networks that may be disrupted in mental illnesses. This method may, for example, allow researchers to track the unfolding of neural circuits during development, as connections are steered and regulated by their patterns of gene and protein expression. When applied to models of neurological and psychiatric disease, this approach may help determine when and how certain regions of the brain fail to connect properly. Finally, the anticipated use of optogenetics as a tool for human deep brain stimulation⁹ can readily be combined with fMRI scanning, extending the methods introduced here to the mapping of activity in the human brain. Specifically, this approach may soon allow researchers to visualize the responses to stimulation of well-defined cells or axons that are thought to underlie positive therapeutic outcomes in a range of patients.

References

1. Lee JH, et al. Nature. 2010 **XXX**, XXX–XXX.
2. Logothetis NK. Philos Trans R Soc Lond B Biol Sci 2002;357:1003–1037. [PubMed: 12217171]

3. Maier A, et al. *Nature Neurosci* 2008;11:1193–1200. [PubMed: 18711393]
4. Sirotin YB, Das A. *Nature* 2009;457:475–479. [PubMed: 19158795]
5. Iadecola C, Nedergaard M. *Nature Neurosci* 2007;10:1369–1376. [PubMed: 17965657]
6. Tsien RY. *Annu Rev Biochem* 1998;67:509–544. [PubMed: 9759496]
7. Boyden ES, Zhang F, Bamberg E, Nagel G, Deisseroth K. *Nature Neurosci* 2005;8:1263–1268. [PubMed: 16116447]
8. Gradinaru V, et al. *J Neurosci* 2007;27:14231–14238. [PubMed: 18160630]
9. Gradinaru V, et al. *Cell* 2010;141:154–165. [PubMed: 20303157]
10. Petreanu L, Huber D, Sobczyk A, Svoboda K. *Nature Neurosci* 2007;10:663–668. [PubMed: 17435752]

Figure 1. fMRI responses to stimulations near and far

Lee *et al.*¹ genetically modified rat cortical neurons to produce light-sensitive, membrane channels. They find that selective optical stimulation of cell bodies in the cortex (**a**) or axons in the thalamus (**b**) lead to fMRI responses in both regions. The strongest and most abrupt responses, however, were detected in the cortex after its direct stimulation.