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Connecting the dots

Understanding the exact link between functional magnetic resonance imaging (fMRI) and neural activity is critical to bridge the widening gap between neuroimagers and cellular neuroscientists.

"An image is worth a thousand words," which may explain why the images produced by techniques such as fMRI have been so effective at capturing the imagination of the public and of neuroscientists. A recent study quantified just how convincing explanations derived from neuroimaging can be: non-experts were more likely to believe a bad explanation for a phenomenon when it was accompanied by an extra few lines saying that the effect was localized to a certain brain area, even though this additional information was entirely irrelevant[1]. However, these images are the output of an extended analysis and several steps removed from neural activity, so much so that many scientists who study activity at the level of the cell feel that fMRI studies have little that is of interest to them. With the increasing complexity and subspecialization in the techniques now required of modern neuroscience, this ghettoization is perhaps inevitable. To really understand how the brain works, however, it is important that scientists working at the levels of the cell and of the system communicate with each other and that findings at one level can be translated and understood at the other. In particular, an understanding of how the signal tracked in brain imaging studies relates to neural activity is crucial.

Specifically, fMRI measures changes in the blood oxygenation level–dependent (BOLD) signal. The relationship between the BOLD signal and neural activity is necessarily indirect: because neurons do not have internal energy reserves in the form of glucose and oxygen, their firing causes more energy uptake. Oxygen release from blood is therefore greater for active than for inactive neurons and this difference in levels of oxygenated and deoxygenated blood is what drives the BOLD signal.

Of course, fMRI is not the only method to track the activity of groups of neurons in behaving animals. Electrophysiology studies, measuring changes in multi-unit spiking activity and local field potentials (LFPs), fulfill a similar purpose. However, the results from electrophysiology and imaging studies are clearly not equivalent, even though they are often treated as such. For one thing, the link between electrophysiological measures and neural activity is much better understood, with LFPs being thought to reflect perisynaptic activity and spiking activity being thought to reflect the firing of action potentials.

In contrast, the link between the BOLD signal and neural activity is much less clear. One way to get around this problem is to work out how electrophysiological measures such as spiking activity and LFPs correlate with BOLD activity. Because the relationship between these electrophysiological measures and underlying neural activity is relatively clear, tying BOLD activity to either LFPs or multi-unit spiking would be an indirect, but valid, way of connecting fMRI results to activity at the level of the neuron. Although there are other issues that affect the interpretation of the BOLD signal, this has been an area of much recent interest, with some studies attempting to link hemodynamic changes to electrophysiological measures.

One such study[2] used dual microelectrodes to simultaneously record colocalized tissue oxygen measurements (a proxy for the BOLD signal), spiking and LFP activity in the cat visual cortex. Changes in tissue oxygen were more closely coupled to LFPs than spiking activity, leading to the conclusion that the BOLD signal represents perisynaptic, rather than spiking, activity.

These results are by no means universally accepted, however, and there has been debate about them, including in the pages of this journal[3]. This is partially because it is difficult to ensure that the effects of multi-unit spiking and LFPs are directly comparable and also partially because it is difficult to ensure that these effects are completely separable. Neither LFPs nor multi-unit spiking may completely account for the BOLD signal, but it should be possible to discover which of them makes the greater contribution to the BOLD signal, and the resolution to this debate will be interesting.

Another major issue that arises when connecting neural activity to fMRI maps is the question of how the activity of a heterogeneous population of neurons is reflected in the BOLD signal. For example, the release of inhibitory neurotransmitters at synapses is still energy consuming and inhibitory neural activity could therefore still result in a localized increase in BOLD signal at the site of inhibition, despite a decrease in the responses of excitatory neurons. If the BOLD signal is more affected by perisynaptic than firing activity, as suggested by the study described above[2], inhibitory neural activity may well show up as positive activation in fMRI maps, indistinguishable from that caused by excitatory activity. The link between inhibitory neural activity and BOLD also seems to be modulated by the exact brain area being scrutinized and is probably affected by the net energy consumption resulting from the combination of inhibitory and excitatory processes.

The mystery of what information about neural activity is encoded by the BOLD signal is only deepened by reports of a negative BOLD signal, but the discussion about the interpretation of negative BOLD signals and how inhibitory neural activity relates to the BOLD signal has been muted in comparison with the lively debate on the relationship between electrophysiological and blood oxygenation measures.

It has now been nearly two decades since the first fMRI paper was published, and despite a huge increase in the number of papers using fMRI as a tool (from just four in all of 1992 to eight in one day in 2007), only 5% of the over 19,000 fMRI papers published since the 1990s have looked at the neural basis of the fMRI signal[4]. A mechanistic understanding of the BOLD signal is essential if we are ever to connect up the dots between systems and cellular neuroscience. ■

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