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Researchers validate, extend fMRI research on brain activity

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Like a motorist who knows that the "check engine" light indicates something important but ill-defined is happening, neuroscientists have relied heavily on an incompletely understood technology called functional magnetic resonance imaging to show them what the brain is doing when people respond to different stimuli. The non-invasive technology offers a window into the physiology of human cognition and emotion, but — without a satisfying explanation of how some common fMRI signals are produced — the ability of researchers to draw conclusions has been limited.

Now a Stanford University-led team has solved the mystery, and in doing so has discovered a new way to make fMRI signals based on increased blood flow even more useful. Combined with optogenetics (a technology developed at Stanford that employs genes from microbes to allow neurons to be controlled with pulses of light), blood-flow fMRI can now be used to study the brain-wide impact of changes in neural circuitry, such as ones that may underlie many neurological and psychiatric diseases.

The team's research will appear May 16 in the online version of *Nature*.

A 'BOLD' finding

The study is the first to prove what neurologists could only hope was true: that fMRI signals based on elevated levels of oxygenated blood in

specific parts of the brain are caused by an increase in the excitation of specific kinds of brain cells. For example, in the past researchers could only assume that when they showed subjects a picture of someone they knew, stronger fMRI signal in a part of the brain that possibly deals with face recognition was caused by the excitation of neurons, rather than some other factor.

These signal increases are measured using the blood oxygenation level-dependent, or BOLD, technique.

Because researchers have published more than 250,000 papers using or building upon the BOLD technique, clarifying its true meaning is very important, said senior author Karl Deisseroth, MD PhD, associate professor of bioengineering and of psychiatry and behavioral sciences.

"It was often assumed that a positive fMRI BOLD signal can represent increased activity of excitatory neurons, but this was never really known and, in fact, became much more controversial over the years," said Deisseroth. Now, the new study confirms those earlier assumptions.

The key experiment involved turning on genetically engineered excitatory neurons in an experimental group of rats in the presence of blue light delivered via a fiber optic cable. The researchers then anesthetized the rats and looked at their brains with fMRI. They found that exciting these defined neurons with the optogenetic light produced the same kind of signals that researchers see in traditional fMRI BOLD experiments — with the same complex patterns and timing. In the control group of rats, which were not genetically altered, no such signals occurred. This showed that true neural excitation indeed produces positive fMRI BOLD signals.

The broader brain

To see what else this new understanding of optogenetically-enhanced fMRI BOLD might yield, the team took the research a few steps further, led by co-first authors Remy Durand, a Stanford bioengineering graduate student, and Jin Hyung Lee, PhD, a University of California-Los Angeles assistant professor and alumna of Deisseroth's lab at Stanford. They found that they could use optogenetics to produce activity in specific kinds of cells in neural circuits, and then read out the far-reaching effects with fMRI BOLD over a substantial distance in the brain.

In one experiment, for example, the team could see how activity they stimulated in the thalamus, a key relay center deep in the brain, could affect circuits stretching into the somatosensory cortex, a surface brain region important in processing sensation.

"We can now ask what the true impact of a cell type is on global activity in the brain of a living mammal," Deisseroth said. "A key to scientific inquiry is developing tools that allow us to intervene and experiment with brain circuits — engineering a reversible gain or loss of function — rather than simple observation of correlations. This points to new approaches for understanding and treatment."

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