A 'traffic light' for neurons means 'go' for improving brain research

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Every thought, feeling and action originates from the electrical signals emitted by diverse brain cells enmeshed in a tangle of circuits. At this fundamental level, scientists struggle to explain the mind. Worse yet, they have lacked tools to understand what's going wrong in patients with ailments such as depression or Parkinson's disease. New Stanford-led research published in the April 5 issue of *Nature* describes a technique to directly control brain cell activity with light. It is a novel means for experimenting with neural circuits and could eventually lead to therapies for some disorders.

"This accomplishment is a key step toward the important goal of mapping neural circuit dynamics on a millisecond timescale to see if impairments in these dynamics underlie severe psychiatric symptoms," said National Institutes of Health (NIH) Director Elias A. Zerhouni. "The work is also a prime example of the highly innovative approaches to major challenges in biomedical research that we support through the NIH Director's Pioneer Award program."

Karl Deisseroth, an assistant professor of bioengineering and of psychiatry who led the research group that authored the paper, received the NIH award in 2005.

"This research provides a tool that we didn't have before, which is precise on-or-off control over specific neural cells in living creatures and intact circuits," says Deisseroth, whose Stanford research group collaborated with researchers at the Max Planck Institute of Biophysics, the Johann Wolfgang Goethe University in Frankfurt and the University of Würzburg in Germany. "This gives us the power to ask what the causal role of specific cell types is in neural circuit function."

Knowing the effects that different neurons have could ultimately help researchers figure out the workings of healthy and unhealthy brain circuits, explains graduate student Feng Zhang, a lead author of the paper along with Stanford postdoctoral scholar Li-Ping Wang. If use of the technique can show that altered activity in a particular kind of neuron underlies symptoms, for example, this insight will allow development of targeted genetic or pharmaceutical treatments to fix those neurons. Conceivably, direct control of neuronal activity with light could someday become a therapy in itself.

A neural traffic light

To selectively take control of neurons, the researchers used a virus to insert genes for producing light-sensitive proteins into cells of interest. The gene ChR2 is derived from an algae that makes affected neurons more active when exposed to blue light. Deisseroth and collaborators first showed this in a paper in *Nature Neuroscience* in 2005. In this week's paper, they demonstrate that another gene, NpHR, which is borrowed from a microbe called an archaebacterium, can make neurons less active in the presence of yellow light. Combined, the two genes can now make neurons obey pulses of light like drivers obey a traffic signal: Blue means "go" (emit a signal), and yellow means "stop" (don't emit).

In the new paper, the group shows this technique can have immediately observable effects in living creatures. The Stanford team's collaborators in Germany were able to cause tiny worms called C. elegans to stop swimming while their genetically altered motor neurons were exposed to pulses of yellow light focused through a microscope. In some experiments, exposure to blue light caused the worms to wiggle in ways they weren't moving while unperturbed. When the lights were turned off, the worms resumed their normal behavior.

Meanwhile, in experiments in living brain tissues extracted from mice at Stanford, the researchers were able to use the technique to cause neurons to

signal or stop on the millisecond timescale, just as they do naturally. Other experiments showed that cells appear to suffer no ill effects from exposure to the light. They resume their normal function once the exposure ends.

Potential applications

The most direct application of optical neuron control is to begin experimenting with neural circuits to determine why unhealthy ones fail and how healthy ones work.

In patients with Parkinson's disease, for example, researchers have shown that electrical "deep brain stimulation" of cells can help patients, but they don't know precisely why. By allowing researchers to selectively stimulate or dampen different neurons in the brain, the new Stanford technique could help in determining which particular neurons are benefiting from deep brain stimulation, Deisseroth says. That could lead to making the electrical treatment, which has some unwanted side effects, more targeted.

Another potential application is experimenting with simulating neural communications. Because neurons communicate by generating patterns of signals-sometimes on and sometimes off like the 0s and 1s of binary computer code-flashing blue and yellow lights in these patterns could compel neurons to emit messages that correspond to real neural instructions. In the future, this could allow researchers to test and tune sophisticated neuron behaviors. Much farther down the road, Deisseroth speculates, the ability to artificially stimulate neural signals, such as movement instructions, could allow doctors to bridge blockages in damaged spinal columns, perhaps restoring some function to the limbs of paralyzed patients.

Finally, the technique could be useful in teasing out the largely unknown functioning of healthy brains.

"One day we'd like to be able to understand the organization of the brain," Zhang says. "How do different types of cells communicate with each other to carry out very complex things like emotion or how people make decisions?"

Source: Stanford University