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## Seeing the Brain in a New Light

Researchers have devised a clever way to activate neurons in a living mouse by shining light on the surface of the animal's brain. The light switch that turns neurons on is actually a light-sensitive protein that is produced by algae. When this protein is genetically engineered into the neurons of living mice, researchers can precisely trigger those neurons with light, causing them to generate electrical impulses.

The scientists who developed the new method believe it will change how researchers map the function of brain circuits in living animals. We believe that this light-induced activation technique is a major technical breakthrough in the functional analysis of neural circuitry, said the leader of the research team, Michael Ehlers, a Howard Hughes Medical Institute researcher at Duke University Medical Center. This technique will soon become the standard method for these types of experiments.

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The researchers published a research article describing the new technique in the April 19, 2007, issue of the journal *Neuron*. The research team included Ehlers and Duke colleagues Benjamin Arenkiel, Guoping Feng and George Augustine. Other co-authors were from the University of Coimbra and the Gulbenkian Science Institute in Portugal, and from Stanford University.

In developing their technique, the researchers drew on work by other scientists studying channelrhodopsin-2, a protein found in green algae. One of the unique features of the protein is that it enables algae to migrate toward light. The researchers found that when they introduced the gene for channelrhodopsin-2 into neurons in culture, the protein rendered the neurons light-sensitive. When the scientists exposed those neurons to light, they found that the light stimulated neural activity in the neurons in culture. Co-author Karl Deisseroth at Stanford was among those who demonstrated that the channelrhodopsin-2 could render neurons light-sensitive in culture.

A major question was whether this algal protein could be expressed in animals throughout development and still remain functional and not cause

any problems, said Ehlers. When Guoping Feng produced the transgenic mice in his laboratory, he found that they developed normally and showed no obvious neurological or behavioral problems, he said.

In our laboratory, we then studied the effect of using a fiber optic light source to illuminate the brains of these animals with light pulses, said Ehlers. We found that the light-evoked activity response was very rapid, and it corresponded precisely to the pulse location of the light, he said. By repeating light pulses at one-thousandth-of-a-second intervals, the researchers showed that they could trigger repeated trains of electrical signals in the neurons. The light beams they used were as fine as 100 microns in diameter, said Ehlers. By comparison, a human hair is about 200 microns in diameter.

The new light-activation technique has advantages over other methods that are being used in functional mapping of neural circuitry, said Ehlers. One widely used method involves presenting a sensory stimulus such as an odorant to an animal and recording the electrical activity the stimulus triggers in the sensory neural circuitry. This method is slower and less specific than the light-activation method developed by Ehlers and his colleagues. Another approach researchers have used involves introducing chemical receptors into neurons genetically and then using them to trigger specific neurons. This technique is very useful for some applications but is slower and can be experimentally difficult, Ehlers said.

In a related study published April 15, 2007, in an advance online publication of *Nature Neuroscience*, Karel Svoboda and colleagues also took advantage of channelrhodopsin-2, using the protein in brain slices to map functional brain wiring across great distances. Svoboda is a group leader at HHMI's Janelia Farm Research Campus.

To demonstrate the utility of their new technique, Ehlers and his colleagues used it to map how nerve signals from the olfactory bulb travel to a brain structure called the olfactory cortex. The olfactory bulb is the neural relay station that receives impulses from odor receptors, and the olfactory cortex in the brain initially processes odor information into odor perception.

The researchers used different light patterns to activate various neurons in the olfactory bulb structures called glomeruli in the mouse brain. During these experiments, they used recording electrodes to measure the resulting electrical activity of neurons in the olfactory cortex. Their goal was to see if the new technique would help them understand how signals from the structures in the olfactory bulb converge on the olfactory cortex. After analyzing the pattern of electrical responses they observed in their experiments, they concluded that cortical neurons require input from a distributed array of neurons in the olfactory bulb in order to fire. We could never find a single glomerulus or clump of glomeruli that would strongly activate a neuron in the cortex, said Ehlers. Distributed input from many glomeruli was required to cause a cortical neuron to fire.

To improve their light-driven mapping technique, the researchers plan to apply additional genetic techniques that will enable them to insert the

channelrhodopsin-2 gene into specific neuronal subtypes. While their current transgenic method is specific for neurons, it introduces the channelrhodopsin-2 gene into many subtypes of neurons. Also, the researchers will explore methods for light stimulation of parallel brain regions using computer-driven patterns of illumination, which could be a precursor to new technologies for neural activation in the brain and spinal cord.