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Decoding the Brain with Light

Scientists are using genetic "light switches" to probe memory and improve disease therapy.

By Emily Singer

Molecular "light switches" can reveal exactly which neurons are involved in creating a memory, allowing scientists to trigger that memory using only light. The finding, presented at the Society for Neuroscience (http://www.sfn.org/am2009/) conference in Chicago this week, is just one example of how a novel technology called optogenetics is allowing scientists to tackle major unanswered questions about the brain, including the role of specific brain regions in the formation of memory, the process of addiction, and the transition from sleep to wakefulness.

The technology, developed just four years ago by Karl Deisseroth (http://www.stanford.edu/group/dlab/) , a physician and bioengineer at Stanford, and Ed Boyden (http://edboyden.org/) , now a bioengineer at MIT, is already being used by hundreds of labs across the globe. Thanks to molecular tinkering and new fiber-optic devices that deliver light deep into the brain via an implant, researchers can use optogenetics to study the effect of neural stimulation on different behaviors in live animals.

To make neurons sensitive to light (http://www.technologyreview.com/tr35/Profile.aspx?Cand=T&TRID=454) , scientists genetically engineer them to carry a protein adapted from green algae. When the modified neuron is exposed to light, via the fiber-optic implant, the protein triggers electrical activity within the cell that spreads to the next neuron in the circuit. The technology allows scientists to control neural activity much more precisely than previous methods, which generally involved delivering electrical current through an electrode.

Michael Hausser (http://www.ucl.ac.uk/wibr/research/neuro/mh/index.htm) 's team at University College London is using optogenetics to probe how memories are stored in the brains of mice. According to the basic model of memory formation, learning a new association--such as that a particular sound precedes an electric shock--activates a subset of neurons in part of the brain called the hippocampus. "It's thought that recall of the memory can be triggered by activating only a subset of the cells in that network," says Hausser. "But there's no clear, direct experimental evidence for any of

the steps in the process."

Hausser and his collaborators genetically engineered the light-sensitive protein so that it would only be expressed in neurons in the hippocampus that were activated during the formation of a memory. Next, they taught the mice to fear a particular sound by pairing it with an electric shock. Hearing the sound then made the animals freeze in fear--and triggered production of the protein in activated brain cells.

The next day, researchers shone blue light on the animals' hippocampi. That triggered activity in only the subset of cells that fired during memory formation the day before, causing the animal to freeze in fear in response to light, rather than to the sound. The researchers also labeled these cells with a fluorescent marker, allowing them to count the number of cells involved in the creation of the memory. "A remarkably small number of neurons in these animals [are] sufficient to drive recall, on the order of 100 to 200 cells," says Hausser.

In addition to illuminating the most basic aspects of the brain, researchers are using the technology to better understand specific maladies such as depression, Parkinson's, and addiction, in hopes of improving treatments. Parkinson's disease, for example, can be treated using deep brain stimulation, in which a surgically implanted electrode delivers pulses to a specific structure deep in the brain. But the procedure is invasive and carries risk of side effects such as depression and cognitive dysfunction. Earlier this year, Deisseroth's team published details of research using the light switches to study the brain circuits involved in Parkinson's disease. They found that they could alleviate the motor deficits in animals with Parkinson's-like symptoms by activating neural targets much closer to the surface of the brain.

The findings raise the possibility of using noninvasive methods for stimulating the brain to treat Parkinson's patients, which Deisseroth and collaborators are now exploring. Transcranial magnetic stimulation (TMS), a way to activate parts of the brain using a magnet placed over the scalp, has already been approved by the Food and Drug Administration to treat depression. But studies using TMS to treat Parkinson's have yielded mixed results, probably because "people have been poking around different parts of the brain, not being guided by this kind of knowledge," says Deisseroth. In a new study, the researchers will first use sophisticated brain-imaging methods to try to identify in Parkinson's patients the human correlate of the spot identified in animal studies--the exact area will likely vary from person to person--and then target the stimulation specifically to that region.

Scientists are also using optogenetics to study depression, another disease that can be treated with electrical stimulation. They hope to tease out the brain areas responsible for the different symptoms associated with depression, such as fatigue, hopelessness, and lack of pleasure in daily activities.

Researchers mimic clinical depression in mice by subjecting them to several days of extreme social stress. After such stress, these normally social animals refrain from social interaction for the rest of their lives. Like clinical depression in humans, this impairment generates abnormal patterns of neural activity in part of the brain called the prefrontal cortex, and it can be alleviated with antidepressants.

Herbert Covington, a researcher in Eric Nestler (http://www.mountsinai.org/Find%20A%20Faculty/profile.do?id=0000072500004647234661) 's lab at Mount Sinai School of Medicine, in New York, made neurons in the prefrontal cortex of stressed mice sensitive to light. He then stimulated the animals' neurons using light delivered in a pattern similar to that seen in healthy mice exploring a new environment. Much like antidepressants, the light treatment made the previously fearful animals socialize normally with other mice.

"Depression is a complex mix of behaviors," says Covington. "Stimulating the prefrontal cortex can restore a social behavior. Next we will look at whether it can restore activity--will mice choose to do things they find rewarding, which is often a problem in depression." The findings might ultimately enable researchers to develop treatments targeting specific aspects of the disease.

It's not yet clear whether optogenetics technology will become a treatment itself or whether its major impact will be shedding light on disease. Two groups are already focusing on potential treatments: Ed Boyden at MIT has founded a startup (http://www.technologyreview.com/biomedicine/22720/) to use optogenetics to restore sight to people with vision disorders by making damaged retinal cells sensitive to light, and a startup spun out of Case Western Reserve University in Cleveland, OH, plans to commercialize the technology to restore bladder control in paralyzed people.

Upcoming Events

The Tough Get Growing: How to Succeed in a Down Economy (http://enterpriseforum.mit.edu/network/broadcasts/200911/index.html)
MIT Campus, Cambridge, MA
Monday, November 16, 2009
http://enterpriseforum.mit.edu/network/broadcasts/200911/index.html (http://enterpriseforum.mit.edu/network/broadcasts/200911/index.html)

Global Public Policy Summit (http://www.gpps2009.com)
Bermuda
Sunday, November 01, 2009 - Tuesday, November 03, 2009
http://www.gpps2009.com (http://www.gpps2009.com)

Optimizing Innovation 2009 (http://www.connecting-group.com /Web/EventOverview.aspx?Identificador=6)
New York, NY
Wednesday, October 21, 2009 - Thursday, October 22, 2009
http://www.connecting-group.com/Web/EventOverview.aspx?Identificador=6 (http://www.connecting-group.com/Web/EventOverview.aspx?Identificador=6)

Bioengineering Insights 2009 (http://engineering.ucsb.edu/insights2009/TR)
Santa Barbara, CA
Monday, October 26, 2009
http://engineering.ucsb.edu/insights2009/TR (http://engineering.ucsb.edu /insights2009/TR)
