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LIGHT-SENSITIVE PROTEINS FROM ALGAE ILLUMINATE THE BRAIN, PROVIDING A MORE SOPHISTICATED VIEW OF NEURAL CIRCUITRY.

Light Mind Control
WIDE ANGLE BY **RUTH WILLIAMS** / MAY 18, 2009

Who would have predicted that researchers who spend their days teasing apart the complexities of the human brain would be indebted to pond scum? In some ways, that day has come: Thanks to light-sensitive proteins from green algae and other microorganisms, neuroscientists can now activate and record brain cells with unprecedented precision.

The algae's gift to neuroscience is a protein called channelrhodopsin. In response to visible light, the protein opens a channel in the algae's cell membrane that allows positively charged ions to surge in. This ion influx sets up a chain of events that prompts the algae to swim toward the light—the best place for photosynthesis. But psychiatrist-turned-neuroscientist-turned-bioengineer Karl Deisseroth and colleagues at Stanford University have found another use for channelrhodopsin. In neurons, an ion influx triggers impulse firing. By putting a modified version of channelrhodopsin into mouse neurons, the researchers can now activate these cells as easily as flipping a light switch.

Almost as easily, anyway. First, mice have particular neural cells engineered to contain channelrhodopsin or other similar light-sensitive channels. Then they're fitted with a long, flexible, fiber-optic cable that feeds through their skull and interfaces with the appropriate brain region. The mice are then free to run around their cages while light pulses are sent along the fiber, specifically triggering the engineered cells to generate action potentials. And switching off the light immediately switches off the neurons. "It's marvelous that we have millisecond precision in tools that effectively come from plants," says Deisseroth.

The approach is referred to as optogenetics. Deisseroth first wrote about the technique in 2005, followed by research in 2006 and 2007 showing light-induced neuron activation in living neurons and in living mammals. He and colleagues are now co-opting the approach t unravel long-standing mysteries of the brain. Before optogenetics, activating neurons in living animals relied upon crude electrical or pharmacological stimulation.

"Electrodes don't know what the different cell types are. All they do is emit a current, and that affects all the neurons that are nearby," says Deisseroth. "It's been a goal to confer specificity of stimulation to cells." Using optogenetics, scientists can deliver the light-sensitive channels to precisely the cell type they want to target.

They have been busy targeting all sorts of cell types: The Stanford lab has used the system to investigate behavioral conditioning, a treatment for Parkinson's disease, and the elusive role of brain waves. And as researchers adopt optogenetics across the world, the technique promises to revolutionize our overall understanding of neural circuitry and function. For the first time, scientists are able to establish a causal relationship between genes expressed by specific cells and the resulting changes in physiology, cognition, behavior, and mood.


Courtesy of Karl Deisseroth

Deisseroth recently collaborated with a group of neuroscientists, bioengineers, and psychiatry researchers from Stanford and University of California, San Francisco, to better understand how the brain rewards behavior. They showed that by stimulating high-frequency firing of dopamine-producing neurons in a part of the brain associated with reward, mice could be conditioned to visit one chamber in preference to a second. Scientists had suspected that this high-frequency firing increased dopamine release an triggered feelings of reward, but until now there wasn't proof. The study was published last month in *Science*.

The technique recently moved beyond the mouse cage, furthering the very real possibility that lasers may eventually be used to control the human brain. In an encouraging translational leap, a team of researchers led by Edward Boyden at MIT's Synthetic Neurobiology Group and Department of Biological Engineering just reported the successful use of similar photoactivation methods in awake macaque monkeys. Crucially, Boyden's group demonstrated that optogenetics seems t be safe: The method did not damage the areas of the brain being tested, nor did it activate an immune response in the monkeys over

eight to nine months. The rhesus macaque is an important model for understanding higher-level learning and human cognition. Boyden also sees this proof of method leading to light-emitting prosthetics (replacing electrodes) for treating neurological disorders such as schizophrenia, ADHD, and Parkinson's disease. The technology his lab is now building might one day even augment cognition in normally functioning adults. "This work has a real potential to positively impact human health," says Boyden.

In another study published earlier in April, Deisseroth's lab answered a long-standing question about deep brain stimulation (DBS), a technique used to treat Parkinson's disease. DBS activates a part of the brain called the subthalamic nucleus, but it had been unclear which of the many cell types in the nucleus confer the therapeutic benefits that had been observed. Also unclear was whether the key to the stimulation was exciting or silencing the neural pathway. Deisseroth's team found that specific neurons projecting into the subthalamic nucleus from the brain's cortex are the important target cells, and that activating these cells reduced symptoms in Parkinson's model mice. Determining that the stimulation activated neurons was no easy task prior to optogenetics. "If you're electrically stimulating and you want to electrically record, you can't do those at the same time because the electrical stimulation generates a big artifact," Deisseroth explains. Stimulation with light avoids that pitfall.

The ability to simultaneously stimulate and measure was useful in other recent experiments conducted by Deisseroth's team, and from a group led by Christopher Moore at MIT. The two groups looked at the formation and function of brain waves. The brain has a spontaneous, natural rhythm caused by oscillations in cerebral electrical activity—aka brain waves—that result from masses of neurons firing in synchrony. Two fundamental mysteries have been how and why this synchrony is generated. Deisseroth and his trainees, Vikaas Sohal and Feng Zhang, have now answered those questions for a particular type of brain wave called gamma waves (which oscillate at about 40 times a second). The pair discovered that short, locally acting neurons called fast-spiking interneurons generate gamma waves, and that they enhance the information flow in long, distantly acting neurons. These waves occur when the brain is actively engaged in processing information, such as during exploration. The two studies thus indicate that gamma waves drive such high-level cognitive processing as opposed to being merely a consequence of cognitive activity.

Since gamma oscillations occur throughout the brain's cortex, Deisseroth suggests that their function might be one of unifying information from multiple systems at once—auditory, visual, etc. "Perhaps it's the synchrony that enables the brain to respond to the person as a single entity," Deisseroth says.

Both the gamma-wave and the dopamine studies confirm established hypotheses about the brain, and optogenetic approaches might now help to confirm or debunk countless other hypotheses. "We've sent these tools out to probably more than 400 labs around the world," says Deisseroth. That's a lot of questions answered. And that's a lot of researchers who might feel a curious sense of gratitude when passing their local pond.

Front page image courtesy of Zen Shooter.