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A Light Bulb Moment in the Brain

The new science of optogenetics is amending neuroscience's focus on cutting and chemicals to shine a light directly on the brain.

By Lauren Ware

The new science of optogenetics is shedding new light on how the brain works. (Istockphoto.com)

In a clear Plexiglas laboratory cage, a mouse sleeps. A thin fiber optic cable projects upward from the top of its head and out through the cage's lid. ' light. The mouse continues to sleep; the light continues to pulse. After a few more pulses, the mouse wakes up. It rubs its face, stretches its legs and eat voraciously, as though it were starving. It keeps eating as the blue light pulses.

The optical fiber that carries the blue light goes directly into the mouse's brain. It targets a specific group of brain cells that have been modified to re technique called optogenetics, developed seven years ago, which can selectively activate or silence groups of nerve cells, or neurons, in real time. Ar brain and begin to map how it works with a degree of detail that was previously unimaginable.

That's what Scott Sternson has done with the apparently starving mouse at Janelia Farm in Ashburn, Va., an interdisciplinary biomedical research ce Medical Institute.

In fact, this mouse was well fed and should not have been hungry. Sternson's research group targeted a type of cell called the agouti-related peptide hypothalamus and have been linked to feeding behavior in other studies. The scientists used a virus to insert the DNA of a light-sensitive protein fro AGRP neurons. Some of the AGRP neurons take up the DNA and begin to produce the protein and send it to the cell membrane. When the blue ligh the optical fiber, the protein causes the neurons to move ions across the cell membrane, effectively stimulating them to fire an electrical signal, the ac communicate with each other. Sternson found that the more AGRP neurons are stimulated, the more the mouse eats. And as soon as the light stops,

"It's unexpected that a single neuron population has the capacity to orchestrate such a complex behavior," says Sternson.

The lab also looked at a related neuron group, the POMC neurons, which, when stimulated, caused the mouse to eat less, losing 7 percent of its bod

"The next step for us is to map the connectivity between those two neuron populations. We can look at the target regions, where the neurons in thes technique to evaluate the contributions of specific cell populations to this behavioral effect. We are essentially reverse engineering the brain to unders recently published the results of this study in *Nature Neuroscience*.

Sternson is one of a growing group of researchers using optogenetics to study behavior. It is the first tool to reliably allow scientists to manipulate ne which neurons' potentially fire, and it allows for precision because it uses genetic manipulations, such as the virus insertion described above, to targe traditional way to do this would be with electrical stimulation, which would stimulate all the neurons together," explains Sternson. "This is a major st allows us to test how circuits work in the brain."

Optogenetics was born at Stanford University in 2004, when postdoc Karl Deisseroth and doctoral student Ed Boyden conducted the first experimer channelrhodopsin-2 (ChR2) could be used to stimulate neurons. Deisseroth and Boyden happened upon this solution after several years of collabora for understanding the workings of the brain. They had considered various ideas, including using magnetic beads to control neurons, but light-sensitiv appeal. Opsins had been studied since the 1970s, but in 2003, Georg Nagel and colleagues published research about ChR2 that suggested particular p cells.

Deisseroth and Boyden gave ChR2 a try. They took the gene, inserted it into a virus, and infected neurons with the virus. The infected neurons took the protein, inserting it into their cell membranes. When a brief pulse of light was flashed, the neurons activated, or fired, producing a spike in memb some serendipity involved," says Boyden. "There is no real reason why this molecule had to work perfectly in neurons on the first try, but it did."

In 2005, Boyden and Deisseroth published a paper on their findings in *Nature Neuroscience*. "We instantly realized that for something of this broad as many people as possible, because one cannot possibly do all the different experiments on one's own," says Boyden, now at the Massachusetts Ins

Since that first experiment, many research groups have used optogenetics to study the brain. Boyden, Deisseroth and others continue to test new ligh different characteristics than ChR2. Halorhodopsin, for example, silences neurons in response to yellow light. And Boyden's group published researc using two kinds of molecules to turn off two different populations of neurons.

Sternson's group is interested in studying behavior and feeding, but other researchers are investigating different behaviors. Deisseroth's research tean and bioengineering at Stanford — has isolated a specific cell type responsible for Parkinson's symptoms in a rodent model; this might lead to more p treat Parkinson's patients. They also reversed symptoms of anxiety in mice by stimulating a set of neurons in the amygdala.

Christopher Moore and colleagues at MIT have identified a circuit that controls gamma oscillations in the brain, which are connected with a state of
used to study the bases of perception, fear, aggression, reward, and even to regenerate vision. "We've taken mice that have lost their photoreceptors
Boyden, by using opsins to photosensitize cells in the retina that were previously not light-responsive — essentially creating a new camera for the ey
still being conducted in mice, the techniques have also been shown to work in rhesus macaques.

"The ability to control defined events in defined cell types at defined times in behaving animals is absolutely essential if we wish to move from mere
Koch. Koch, a professor of cognitive and behavioral biology at the California Institute of Technology, focuses his research on the neural bases of co
the word 'science' in neuroscience is finally being realized."

As experiments in mapping brain circuits continue to advance, what's the next step? Scientists envision a future where this information can lead to m
neurological disorders. Instead of bathing the brain in a psychotropic chemical that might have unintended side effects, imagine being able to target th
responsible for the disorder, to essentially "fix" the broken neural circuit.

This might be done pharmacologically, with electrical stimulation or with light itself. Of course, such developments are years away, but the possibiliti
globe.

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