Optogenetics Research Opens New Approaches for Brain Mapping, Repair

Combining the use of light and genetics to control the behavior of cells in living tissue, optogenetics may lead to a more precise understanding of the brain's hugely complex neural network.

18 June 2015 Earl Lane

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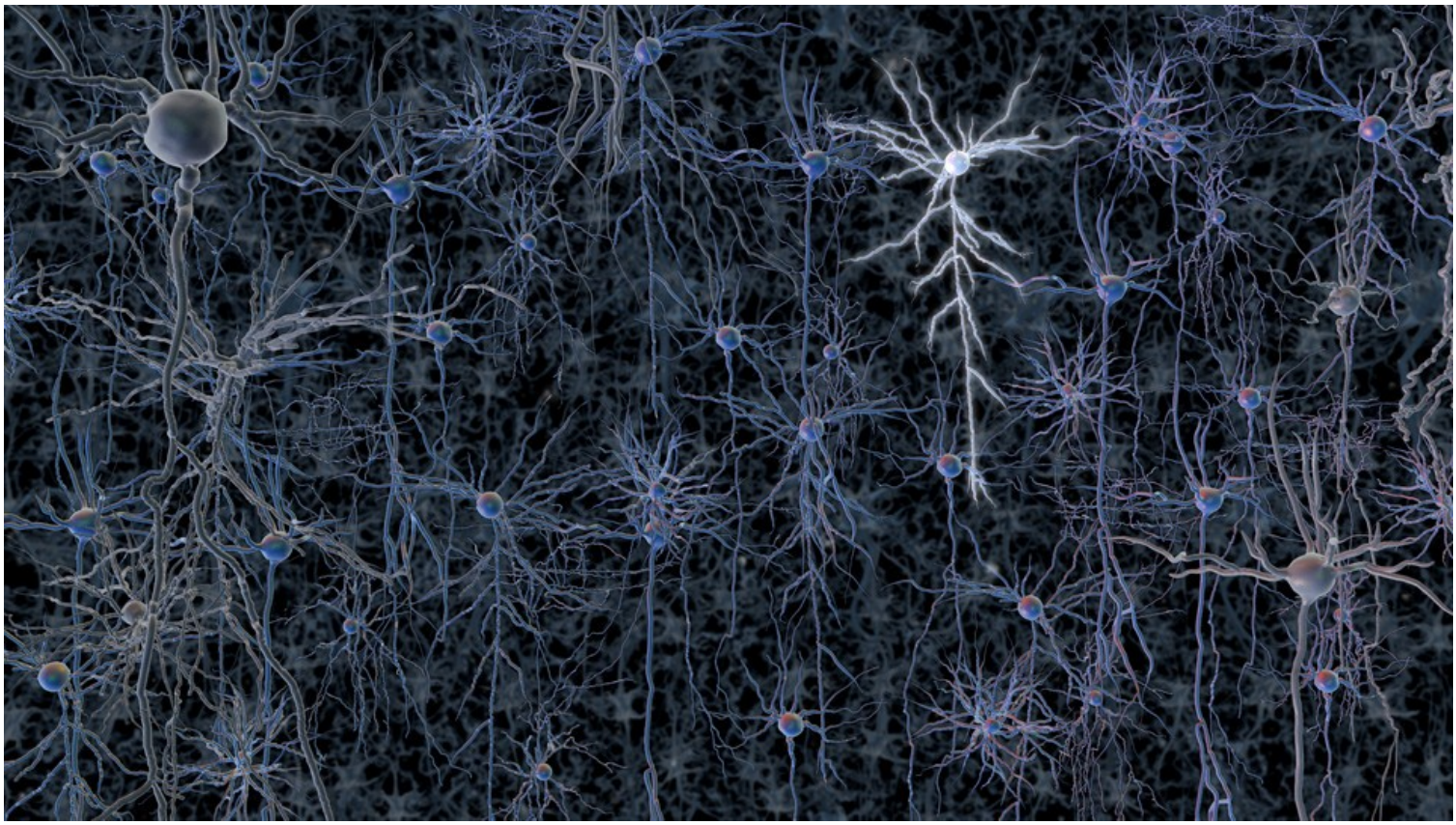

IN OPTOGENETICS, LIGHT-SENSITIVE PROTEINS ARE GENETICALLY TARGETED TO SPECIFIC CELLS, WHICH CAN THEN BE ACTIVATED OR SILENCED BY LIGHT. | SPUTNIK ANIMATION, ED BOYDEN, AND THE MCGOVERN INSTITUTE FOR BRAIN RESEARCH AT MIT

Basic research on how to turn brain cells "on" and "off" with pulses of light may someday lead to better understanding and treatment of disorders such as Parkinson's disease, epilepsy, and schizophrenia, specialists said at a 9 June briefing organized by AAAS.

Hundreds of research labs have entered the rapidly developing field of optogenetics, which combines the use of light and genetics to control the behavior of cells in living tissue such as neurons in the brain.

The effort, as yet confined to animal studies, is only about a decade old but has become one of the hottest areas of neuroscience research because it promises a more precise understanding of the hugely complex network of cells in the brain.

EDWARD BOYDEN | AAAS

As MIT's Edward Boyden, one of the co-developers of optogenetics, noted at the briefing, the brain is incredibly dense and varied. Each cubic millimeter contains perhaps 100,000 cells connected by 1,000,000,000 synaptic connections. Understanding how networks of cells in circuits work together to give rise to behaviors, thoughts, and emotions requires new technology, he said, and optogenetics is starting to provide new approaches for mapping and repairing the brain.

"You build new tools to drive the science," Boyden said, "and from the science, you can build new treatments."

Boyden, director of the MIT Media Lab and McGovern Institute's Synthetic Neurobiology research group, spoke at a luncheon briefing on Capitol Hill, the latest in a series of neuroscience briefings hosted by AAAS in conjunction with Rep. Chaka Fattah (D-Pa.), and through the support of the Dana Foundation. Boyden was joined by Dayu Lin, assistant professor of psychiatry and neuroscience at the New York University School of Medicine, and Brian Chow, assistant professor of bioengineering at the University of Pennsylvania.

Researchers have known for decades that some microorganisms, such as single-celled green algae, have proteins that respond to light by opening a channel in the microbe's membranes, allowing the passage of electrically charged ions (such as calcium and sodium).

CHAKA FATTAH | AAAS

During the past decade, Boyden and others have found ways to snip the microbial genes that code for the light-sensitive proteins and insert them into brain cells, thus making those neurons also responsive to light. By shining pulses of light on the altered cells, scientists can switch them "on" or "off," resulting in the same flow of ions that occurs when neurons fire naturally in the brain.

"If you shine light on the cells, they are able to respond at great speed, causing the same kind of electrical pulses that neurons use when they are communicating," Boyden said.

Optogenetics has been able to activate single neurons in living animals in milliseconds and reverse the intervention just as rapidly. Since the pulses of light exert highly precise control over the neurons, it opens the possibility of very selective studies of firing patterns in brain regions of interest. Researchers want to activate or inhibit classes of neurons and study the effect on connected cells or regions. "We want to perturb and monitor individual cell types in highly specific ways," Brian Chow said.

Boyden said there is considerable interest in brain regions that are important for learning or addiction — learning gone wrong — with particular attention to small groups of neurons deep in the brain that manufacture dopamine, a chemical transmitter involved in regulating communication between neurons.

BRAIN NEURONS IN THIS MOUSE CAN BE STIMULATED BY LIGHT. | ED BOYDEN/MCGOVERN INSTITUTE FOR BRAIN RESEARCH AT MIT

He mentioned mouse studies by Chris Fiorillo, now at the Korea Advanced Institute of Science and Technology (KAIST), who inserted genetic sequences that code for a light-sensitive protein called channelrhodopsin-2 into dopamine-producing neurons of mice. He then inserted fiber optic wires into the mice's brains so those neurons could be stimulated with light.

In a box, a mouse was offered the opportunity to poke its nose into a hole where it would receive a pulse of light or a hole where no stimulation was offered. When brief pulses of light stimulated the mouse's altered neurons, Boyden said, it quickly returned for another pulse and another after that. In the experiment, Fiorillo was able to connect events involving individual dopamine neuron stimulations with how the animals learned to seek rewards. Pinpointing the exact neurons in the brain that drive the reward process also reveals potential new targets for treating addiction, Boyden said.

Similarly, using light to stimulate atrophied neurons that may be associated with schizophrenia could someday allow clinicians to repair cognitive function, Boyden said, and enhance the flow of information through disordered brain circuits that otherwise may be giving rise to delusions and paranoia.

Certain light-sensitive molecules also can be used to inhibit the activity of brain cells, a finding that has implication for disorders such as epilepsy. Animal studies have shown that "you can turn off a seizure by shutting down the activity of neurons" associated with epilepsy, Boyden said.

Optogenetics also has been used to mimic the underlying mechanisms in narcolepsy, a disorder that causes patients to fall asleep at inopportune times. Researchers have engineered the genomes of mice so they have a light-sensitive inhibitory molecule that can shut down the wakefulness-promoting properties of neurons called hypocretin cells. When laser light is shined through optical fibers into the mice's brains, "They're all passed out in about a half minute," Boyden said. "Turn the light off, they wake back up." Such experiments suggest that deletion of cellular activity, even for a brief time, "is causally involved with a pathological process like

DAYU LIN | AAAS

narcolepsy," Boyden said. In turn, that means researchers may be able to pinpoint circuits that cause the disorder and map possible therapeutic targets.

Optogenetics also may provide an improved understanding of Parkinson's disease, which involves haywire processing in certain motor-control circuits in the brain. Patients already are being treated with some success by deep-brain electrical stimulation of nerve cells. If electrical energy can be used to modulate cell response, why not optical energy as well, Boyden asks.

Karl Deisseroth (http://www.aaas.org/news/karl-deisseroth-brains-and-behavior-are-revealed-light-and-clarity), an optogenetics pioneer at Stanford University, has used the technique with animals to learn more about the nature of the disordered brain circuitry in Parkinson's. His work suggests that deep-brain stimulation — whether electrical or optical — may be most effective when it targets not the neurons themselves but the connections between cells, thereby affecting the flow of activity between brain regions.

Dayu Lin described her work with mice to better understand the neural basis for aggressive behavior. She showed some striking videos in which docile mice can be turned into attack rodents with pulses of light to their brains. She did so by activating neurons in a specific region of the hypothalamus, deep in the center of the brain. She used a virus to ferry light-sensitive channelrhodopsin-2 proteins into neurons of the region called the ventrolateral subdivision of the ventromedial hypothalamus, or VMHvl. This brain region appears to be closely associated with aggressive behavior.

Lin showed that the mice, when stimulated with light, would attack an inflated surgical glove, a behavior they never do when left to their own devices. Conversely, Lin said that if the VMHvl is inhibited, it suppressed natural aggression between males. "VMHvl cells also are found in other species, including primates and humans, and offer a possible target for interventions to manage aggression" Lin said.

A PULSE OF LIGHT CAUSES A MOUSE TO ATTACK THE GLOVE IN ITS CAGE. | COURTESY OF DAYU LIN, ASSISTANT PROFESSOR, NEUROSCIENCE INSTITUTE, NEW YORK UNIVERSITY SCHOOL OF MEDICINE

While such basic research can suggest new treatment targets, the speakers noted that there are many obstacles before clinical treatment of brain disorders with optogenetics becomes a reality. In the United States, these include the lack of an approved vector for transporting DNA segments for light-sensitive proteins into human brain tissue. (Adeno-associated virus or AAV has been approved in Europe as a vector for gene therapy, and is being explored in the United States for clinical trials.) Since optogenetic therapies would require invasive genetic and optical interventions, with a permanent impact on a person's brain, the risks and benefits of such procedures must be carefully weighed. There also are tricky ethical considerations. For example, if a mouse's aggression can be switched on and off, will there be attempts to do the same with humans, and who will decide whether such intervention is medically or legally acceptable? (Lin noted that existing methods of electrical deep brain stimulation for aggression control are prohibited in the United States but approved in some European countries.)

BRIAN CHOW | AAAS

Still, Chow said there are new opportunities through optogenetic approaches. "The power of the method is its specificity and speed," he said, adding that it combines the advantages of drugs, which are quite specific to certain types of proteins and their signaling pathways but act slowly, and electrical stimulation methods, which are much faster but not as biochemically specific.

Boyden noted that it now takes about nine years for development and approval of a brain drug, at a cost of $850 million or more. And about 90% of the time, he said, the drug fails to ultimately win FDA approval. With an estimated 1 billion people worldwide suffering from some form of brain disorder, he argues, there is a very real need for new approaches, including optogenetics, to reveal more precise targets in the brain.

But Boyden said the primary clinical impact of optogenetics will arise, almost certainly, from the science that it enables. "Direct usage of optogenetics in humans will only work in a few circumstances currently, because we just don't know enough about the brain to know where to target the gene and the light," Boyden said. "That will change in the coming decades, but it will take some time." Chow agreed that optogenetics will likely provide much better insight into how to use existing treatment modes and interpret existing biomarkers of disease.

In at least one area, however, a therapeutic result is on the horizon. Many research groups, including Boyden's and Chow's, have been exploring ways to treat forms of blindness in which photoreceptor cells in the eye have been degraded or are non-existent. Boyden said three commercial firms now are developing optogenetic methods to insert light-sensitive molecules into other cells in the eye that would transmit visual information directly to the brain. If successful, the technique could provide a form of vision to potentially hundreds of thousands of patients, Boyden said.