

Shedding light on how the brain works

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Emerging optogenetics field could explain things like memory, mental illness

By By Carolyn Y. Johnson, Globe Staff | November 23, 2009

More than two centuries ago, the Italian scientist Luigi Galvani found that electricity could make a dead frog's leg kick, as if it were alive. Today, using the same basic principle but new tools, scientists are employing light to trigger brain cells - looking not for a kick, but for the origins of emotions, behaviors, and diseases in the brain.

Advanced imaging technologies have given neuroscientists new ways to peer into the working mind, but a precise understanding of how 100 billion brain cells create everything from memories to mental illness has remained elusive.

Now, by using gene therapy to insert light-sensitive proteins from algae and other organisms into brain cells, scientists are able to control specific brain circuits with light, and then watch what happens.

It's a big shift, said Dr. Karl Deisseroth, a neuroscientist and psychiatrist at Stanford University, who compares the difference between imaging the brain and triggering individual cells to learning the rules of football by watching the game on a high-end TV or by controlling players.

"It wouldn't matter how good your video camera was or your TV was; it would still be very mysterious, and that's imaging," Deisseroth said. The new technology, on the other hand, "allows you to play the role of coach and understand things."

Scientists start with algae, ancient forms of bacteria, and other organisms that contain proteins sensitive to light. They isolate the genes containing the instructions for making those proteins, insert the genes into a virus, and "infect" specific brain cells with the virus. The brain cells then start making the light-sensitive protein - essentially creating a switch that can turn a cell on or off when exposed to light. That's earned the field the name optogenetics.

Scientists were not sure what to expect when they first did the experiment in mice. There were three possibilities when they flipped on the light: Nothing would happen, the animals might have seizures or other problems, or they would start seeing a measurable behavior.

But it worked. When the researchers threaded a fiber-optic cable into the brain of one of these mice and flashed a blue light, the animal ran in a circle. Other researchers found that fruit flies that had been genetically modified to carry a light-sensitive trigger in brain cells would jump up and fly away when they were hit with a laser beam.

Those experiments proved the concept would work, and the emerging field is now offering neuroscience the tantalizing possibility of being able to probe things like emotion and disease in a systematic way, said Ed Boyden, head of the synthetic neurobiology group at the Massachusetts Institute of Technology Media Lab.

"Typically in neuroscience, most of us focus on one region or pathway or one circuit or one part of the brain," Boyden said. "But except for fairly slow imaging technologies, we can't get a global picture of the brain yet - we can't see how the whole thing works." Optogenetics, he added, raises the prospect of mapping the brain.

Scientists have begun to use the technique to investigate complex behaviors and disease. This year, Deisseroth's group published the results of an investigation into a rodent model of Parkinson's disease that found it could reduce symptoms by using light to stimulate nerve cells that connect to a part of the brain called the subthalamic nucleus.

Last month, at the annual meeting of the Society for Neuroscience, Herbert Covington, a postdoctoral researcher at Mount Sinai School of Medicine in New York, presented data showing that using light to stimulate cells in the prefrontal cortex relieved symptoms of depression in mice.

"In a brain area, you have this heterogenous population of cells, and it's hard to imagine which ones are really important and which ones are not," Covington said. The strength of the new technique is that it can be used to see what specific cells do, providing hints at the neural basis of a disease or behavior.

Earlier this year, Boyden published the results of experiments in a nonhuman primate, a first step to showing that the technique would work outside the mouse. The study found that genes carrying instructions for light-sensitive proteins could be activated in brains of rhesus macaque monkeys, with no safety issues over many months.

Boyden has cofounded a start-up company, called Eos, that is developing a potential therapy for vision loss. One of the reasons people lose their sight is because of the death of photoreceptor cells, which are sensitive to light. Boyden's company is working on using some of the fundamentals of optogenetics to make other cells in the eye sensitive to light to potentially restore vision.

While it is possible that light therapy could one day be used on people, the biggest near-term opportunity will be in better understanding the brain.

"If you identify the neurons that control appetite, you have a drug target; if you identify the neurons that regulate fear, you have a drug target," said Gero Miesenböck, a professor at the University of Oxford who did pioneering work on fruit flies.

Mice and flies may seem a far cry from people, but the idea is that understanding these basic functions in other organisms might give scientists new ideas about how the human brain works, and where to focus in people when designing a drug or other therapy.

"There's a very fertile intermediate ground here," Deisseroth said. "You can take the insight from the animals and design better treatments for people, without actually going to the level of directly putting light into human brains."

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