A 3-D light switch for the brain

EurekAlert!

New device for delivering light to individual neurons could one day help treat Parkinson's disease, epilepsy; aid understanding of consciousness, how memories form

A new tool for neuroscientists delivers a thousand pinpricks of light to a chunk of gray matter smaller than a sugar cube. The new fiber-optic device, created by biologists and engineers at the Massachusetts Institute of Technology (MIT) in Cambridge, is the first tool that can deliver precise points of light to a 3-D section of living brain tissue. The work is a step forward for a relatively new but promising technique that uses gene therapy to turn individual brain cells on and off with light.

Scientists can use the new 3-D "light switch" to better understand how the brain works. It might also be used one day to create neural prostheses that could treat conditions such as Parkinson's disease and epilepsy. The researchers describe their device in a paper published today in the Optical Society's (OSA) journal Optics Letters.

The technique of manipulating neurons with light is only a few years old, but the authors estimate that thousands of scientists are already using this technology, called optogenetics, to study the brain. In optogenetics, researchers first sensitize select cells in the brain to a particular color of light. Then, by illuminating precise areas of the brain, they are able to selectively activate or deactivate the individual neurons that have been sensitized.

Ed Boyden, a synthetic biologist at MIT and co-lead researcher on the paper, is a pioneer of this emerging field, which he says offers the ability to probe connections in the brain.

"You can see neural activity in the brain that is associated with specific behaviors," Boyden says, "but is it important? Or is it a passive copy of important activity located elsewhere in the brain? There's no way to know for sure if you just watch." Optogenetics allows scientists to play a more active role in probing the brain's connections, to fire up one type of cell or deactivate another and then observe the effect on a behavior, such as quieting a seizure.

Unlike the previous, 1-D versions of this light-emitting device, the new tool delivers light to the brain in three dimensions, opening the potential to explore entire circuits within the brain. So far, the 3-D version has been tested in mice, although Boyden and colleagues have used earlier optogenetic technologies with non-human primates as well.

Targeting neurons with light

One of the advantages of optogenetics is that this technology allows scientists to focus on one particular type of neuron without affecting other types of neurons in the same area of cortex. Probes that deliver electricity to the brain can manipulate neurons, but they cannot target individual kinds of cell, Boyden says. Drugs can turn neurons on or off as well, he continues, but not on such a quick time scale or with such a high degree of control. In contrast, the new 3-D array is precise enough to activate a single kind of neuron, at a precise location, with a single beam of light.

In an earlier incarnation, Boyden's device looked like a needle-thin probe with light-emitting ports along its length; this setup allowed scientists to manipulate neurons along a single line. The new tool contains up to a hundred of these probes in a square grid, which makes the device look like a series of fine-toothed combs laid next to each other with their teeth pointing in the same direction.

Each probe is just 150 microns across – a little thicker than a human hair, and thin enough so that the device can be implanted at any depth in the cortex without damaging it. The brain lacks pain receptors, so the implants do not cause any discomfort to the brain itself. As in the earlier model, several light-emitting ports are located along the length of each probe. Scientists can illuminate and change the color of each light port independently from the others.

Adding a third dimension to the probe's light-delivery capabilities has allowed researchers to make any pattern of light they want within the volume of a cubic centimeter of brain tissue, using a few hundred independently controllable illumination points.

"It's turning out to be a very powerful and convenient tool," says MIT professor of electrical engineering Clifton Fonstad, co-lead author of the paper.

Blue for on, yellow for off

Neurons in the brain are not naturally responsive to light, so scientists sensitize these cells with molecules called opsins, light-detecting proteins naturally found in

algae and bacteria. Genes for an opsin are transferred to the neurons in a mouse's brain using gene therapy, a process in which DNA is ferried into a cell via a carrier such as a harmless virus. The carrier can be instructed to deliver the DNA package only to certain types of cells.

Different colors of light turn different flavors of opsin on – blue might cause one opsin to activate a cell, while yellow might cause another opsin to silence it. Neurons that are sensitized with opsins gain these abilities to respond to light.

The response of an individual neuron – whether to turn on or turn off – depends on the type of opsin it was sensitized with, and the color of light used to illuminate it. In this way, the tool gives neuroscientists an unprecedented level of control over individual neurons in the brain.

Teams from around the world are currently using the technology developed by Boyden's group to study some of the most profound questions neuroscience tries to answer, such as how memory works, the connections between memory and emotion, and the difference between being awake and being asleep.

"I'm really excited about how the brain computes – the ebb and flow of consciousness," Boyden says. "We know so little about the brain."

A better understanding of the brain may lead to another benefit of this technology: therapy. If a particular type of cell malfunctions in a particular disease, scientists may be able to use a modified 3-D array as a neural prosthesis that could help to treat neurological conditions. Using light to stop overactive cells from firing might alleviate the uncontrollable muscle action of Parkinson's disease. Cells that cause seizures in the brain could be quieted optically without the side effects of anti-seizure medications. Implants that correct hearing deficiencies are also being explored with this technology.

Although the new device is effective in bringing light to the brain, other challenges remain before optogenetics can be used for medical therapy, Boyden says. Scientists do not yet know for certain whether the body will detect the opsin proteins as foreign molecules and reject them. Gene therapy will also have to prove itself if neurons are to be sensitized with opsin effectively.

"It's a long road," Boyden admits.

Meanwhile, he continues, the demand for the tool is currently higher than his team can supply. Boyden says his group is excited about the possibility of commercializing the new 3-D array, as one potential route that would make the devices available as quickly as possible to the neuroscience community.

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