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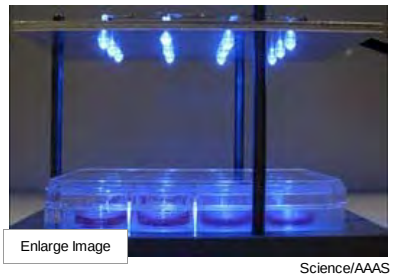
Scientists Cast Light Onto Roots of Illness Deep in the Brain

By ROBERT LEE HOTZ

Scientists are learning how to turn neurons on and off at will by shining light into caverns of the mind, a technique that someday might allow the precise treatment of people suffering psychiatric problems and other ailments.

By blending gene therapy, neural engineering and fiber optics, experimenters at more than 800 laboratories world-wide are making neurons into switches they can directly control by beaming a selected wavelength of laser light to a targeted cell in a living brain. In specially-wired lab animals, these researchers can trigger bursts of brain activity in the specific cells responsible for a movement, a mood, or disease.



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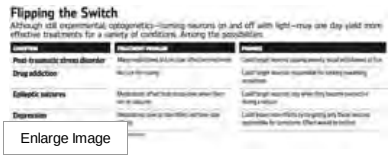
Light-activated neurons were first cultivated by researchers as layers of cells in Petri dishes, as shown above with mouse cells and blue light. Researchers are now able to make the technique work in flies, worms, zebrafish, mice, and monkeys.

The technique, called optogenetics, hasn't been tried yet in people, and treatments that work well in mice and other lab animals often fail in humans. But the researchers have found they can instantly modify animals' behavior, suppress memories and lay bare the biological underpinnings of psychiatric disorders—all by illuminating neurons primed with light-sensitive proteins.

"People are using this to turn on and off all sorts of parts of the brain," said bioengineer Edward Boyden, head of the synthetic neurobiology group at the Massachusetts Institute of Technology, who helped invent the technique with neuro-psychiatrist Karl Deisseroth at Stanford University in 2005. "You can play the brain like a piano."

While still only experimental, the technique is transforming basic brain research. Despite dramatic strides in recent decades, researchers until recently had no way to tease apart the complexity of so many different kinds of neurons in the brain. A cubic millimeter of brain tissue can house 100,000 neurons or more, sending signals across a billion connections in thousandths of a second. There are easily dozens of cell types intermingled. For the first time, researchers can activate the exact ones they want.

Eventually, such experiments might lead to better treatments for psychiatric


Flipping the Switch

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problems, medications with fewer side effects, and more effective brain implants, like those currently used to help control symptoms in thousands of Parkinson's disease patients.

In a series of animal experiments published over the past year, university-based neuroscientists genetically engineered mice and monkeys with different types of neurons primed to be uniquely responsive to shades of laser light, so that a single type of activity or behavior could be altered instantly without affecting anything else.

Here are some of the results.

Light on: Mice freeze in fear. Light off: They scamper freely. Researchers at Stanford University and MIT's Picower Institute for Learning and Memory had activated light-sensitive neurons in the brain's hippocampus involved in the memory of fright.

Light on: Addicted mice lose their taste for cocaine. Light off: They avidly seek the drug. Researchers at the Medical University of South Carolina in Charleston and the University of Iowa had targeted neurons in a part of the cortex—the brain's outer layer associated with seeking a reward.

Light on: Epileptic seizures stop. Light off: The spasms resume. Researchers at Stanford and at the Pierre and Marie Curie University in France had targeted neurons in the mouse brain's cortex and thalamus known to be overactive during seizures.

Light on: Depressed mice become more socially active and more eager for sugar. Light off: Listlessness and indifference to sweets return. Scientists at Stanford and MIT had targeted the dopamine neurons, which make a chemical thought to elevate mood in a reward circuit located in the midbrain.

"Most of the cells in the brain don't respond to light. They are locked in the dark in the skull," said Dr. Deisseroth at Stanford. "We can bathe the whole brain tissue in millisecond pulses of light and we only affect the cells we made sensitive to light. The effect achieved is instantaneous."

It is a research revolution that began with pond scum.

For generations, microbiologists had known that single-celled bacteria, fungi and algae survive thanks to proteins that respond to visible light. When illuminated, these "opsin" proteins change the flow of electrically charged ions within the cell, to help the cell turn light into energy or as a sensory cue. In 2002, German researchers isolated one from green algae—a class of proteins called channelrhodopsins—that responded only to blue light.

Taking advantage of that find, Dr. Deisseroth and Dr. Boyden attached the gene to a virus that targets brain cells. Then they wanted to see if that altered virus would insert the light-sensitive protein into a neuron, so that the brain cell would become responsive to light. "We gave it a try in neurons and it worked the first time," said Dr. Boyden. "It is important to be lucky."

The first light-activated neurons were cultivated as layers of cells in Petri dishes, but researchers were quickly able to make the technique work in flies, worms, zebrafish, mice, and monkeys.

Depending on just how researchers tailor the virus that carries the light-sensitive protein, they now can target almost any type of neuron they want to study. To activate the altered neurons, they usually use a laser tuned to the proper wavelength and pipe the beam through a fiber-optic cable implanted in the brain tissue. They can make the selected cells more active or less.

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"It revolutionized research," said Harvard Medical School researcher Wim Vanduffel, who uses optogenetics to study the primate brain. "If you shine the right wavelength, you can perturb a specific cell type. That's the beauty."

Write to Robert Lee Hotz at sciencejournal@wsj.com

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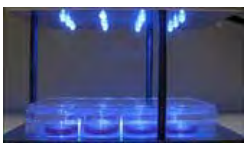

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