The New York Times
nytimes.com

August 14, 2007

The Beam of Light That Flips a Switch That Turns on the Brain

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It sounds like a science-fiction version of stupid pet tricks: by toggling a light switch, neuroscientists can set fruit flies a-leaping and mice a-twirling and stop worms in their squiggling tracks.

But such feats, unveiled in the past two years, are proof that a new generation of genetic and optical technology can give researchers unprecedented power to turn on and off targeted sets of cells in the brain, and to do so by remote control.

These novel techniques will bring an “exponential change” in the way scientists learn about neural systems, said Dr. Helen Mayberg, a clinical neuroscientist at Emory University, who is not involved in the research but has seen videos of the worm experiments.

“A picture is worth a thousand words,” Dr. Mayberg said.

Some day, the remote-control technology might even serve as a treatment for neurological and psychiatric disorders.

These clever techniques involve genetically tinkering with nerve cells to make them respond to light.

One of the newest, fastest strategies co-opts a photosensitive protein called channelrhodopsin-2 from pond scum to allow precise laser control of the altered cells on a millisecond timescale. That speed mimics the natural electrical chatterings of the brain, said Dr. Karl Deisseroth, an assistant professor of bioengineering at Stanford.

“We can start to sort of speak the language of the brain using optical excitation,” Dr. Deisseroth said. The brain’s functions “arise from the orchestrated participation of all the different cell types, like in a symphony,” he said.

Laser stimulation can serve as a musical conductor, manipulating the various kinds of neurons in the brain to reveal which important roles they play.

This light-switch technology promises to accelerate scientists’ efforts in mapping which clusters of the brain’s 100 billion neurons warble to each other when a person, for example, recalls a memory or learns a skill. That quest is one of the greatest challenges facing neuroscience.

The channelrhodopsin switch is “really going to blow the lid off the whole analysis of brain function,” said George Augustine, a neurobiologist at Duke University in Durham, N.C.

Dr. Deisseroth, who is also a psychiatrist who treats patients with autism or severe depression, has ambitious goals. Brain cells in those disorders show no damage, yet something is wrong with how they talk to one another, he said.

“The high-speed dynamics of the system are probably off,” Dr. Deisseroth said. He wants to learn whether, in

these neuropsychiatric diseases, certain neurons falter or go haywire, and then to find a way to tune patients' faulty circuits.

A first step is establishing that it is possible to tweak a brain circuit by remote control and observe the corresponding behavioral changes in freely moving lab animals. On a recent Sunday at Stanford, Dr. Deisseroth and Feng Zhang, a graduate student, hovered over a dark brown mouse placed inside a white plastic tub. Through standard gene-manipulating tricks, the rodent had been engineered to produce channelrhodopsin only in one particular kind of neuron found throughout the brain, to no apparent ill effect.

Mr. Zhang had implanted a tiny metal tube into the right side of the mouse's partly shaved head.

Now he carefully threaded a translucent fiber-optic cable not much wider than a thick human hair into that tube, positioned over the area of the cerebral cortex that controls movement.

"Turn it on," Dr. Deisseroth said.

Mr. Zhang adjusted a key on a nearby laser controller box, and the fiber-optic cable glowed with blue light. The mouse started skittering in a left-hand spin, like a dog chasing its tail.

"Turn it off, and then you can see him stand up," Dr. Deisseroth continued. "And now turn it back on, and you can see it's circling."

Because the brain lacks pain receptors, the mouse felt no discomfort from the fiber optic, the scientists said, although it looked a tad confused. Scientists have long known that using electrodes to gently zap one side of a mouse's motor cortex will make it turn the opposite way. What is new here is that for the first time, researchers can perturb specific neuron types using light, Dr. Deisseroth said.

Electrode stimulation is the standard tool for rapidly driving nerve cells to fire. But in brain tissue, it is unable to target single types of neurons, instead rousing the entire neural neighborhood.

"You activate millions of cells, or thousands at the very least," said Ehud Isacoff, a professor of neurobiology at the University of California, Berkeley. All variety of neurons are intermixed in the cortex, he said.

Neuroscientists have long sought a better alternative than electrode stimulation. In the past few years, some have jury-rigged ways to excite brain cells by using light; one technique used at Yale made headless fruit flies flap away. But these methods had limitations. They worked slowly, they could not target specific neurons or they required adding a chemical agent.

More recently, Dr. Isacoff, with Dirk Trauner, a chemistry professor at the University of California, Berkeley, and other colleagues engineered a high-speed neural switch by refurbishing a channel protein that anchors in the cell membrane of most human brain cells. The scientists tethered to the protein a light-sensitive synthetic molecular string that has glutamate, a neurotransmitter, dangling off the end.

Upon absorbing violet light, the string plugs the glutamate into the protein's receptor and sparks a neuron's natural activation process: the channel opens, positive ions flood inside, and the cell unleashes an electrical impulse.

In experiments published in May in the journal Neuron, the Berkeley team bred zebrafish that carried the artificial glutamate switch within neurons that help sense touch.

“If I were a fish, and somebody poked me in the side,” (in this case, with a fine glass tip), Dr. Isacoff said, “I would escape.” But when the translucent fish were strobed with violet light, the overstimulated creatures no longer detected being prodded. Blue-green light reversed the effect.

One advantage of the Berkeley approach, Dr. Isacoff said, is that it can be adapted for many types of proteins so they could be activated by light. But for the method to work, scientists must periodically douse cells with the glutamate string.

In contrast, Dr. Deisseroth’s laboratory at Stanford has followed nature’s simpler design, borrowing a light-sensitive protein instead of making a synthetic one.

In 2003, Georg Nagel, a biophysicist then at the Max Planck Institute of Biophysics in Frankfurt, and colleagues characterized channelrhodopsin-2 from green algae. This channel protein lets positive ions stream into cells when exposed to blue light. It functioned even when inserted into human kidney cells, the researchers showed.

Neuroscientists realized that this pond scum protein might be used to hot-wire a neuron with light. In 2005, Edward Boyden, then a graduate student at Stanford, Mr. Zhang and Dr. Deisseroth, joining with the German researchers, demonstrated that the idea worked. And in separate research published last spring, Mr. Zhang and Dr. Boyden, now at the Massachusetts Institute of Technology, each found a way to also silence neurons: a bacterial protein called halorhodopsin, when placed in a brain cell, can cause the cell to shut down in response to yellow light.

The Stanford-Germany team put both the “on” and “off” toggles into the motor neurons or muscle cells of transgenic roundworms. Blue light made the creatures contract their muscles and pull back; yellow let them relax their muscles and inch forward.

Dr. Augustine and associates at Duke next collaborated with Dr. Deisseroth to create transgenic mice with channelrhodopsin in different brain cell populations. By quickly scanning with a blue laser across brain tissue, they stimulated cells containing the switch. They simultaneously monitored for responses in connecting neurons, by recording from an electrode or using sensor molecules that light up.

“That way, you can build up a two-dimensional or, in principle, even a three-dimensional map” of the neural circuitry as it functions, Dr. Augustine said.

Meanwhile, other researchers are exploring light-switch technology for medical purposes. Jerry Silver, a neuroscientist at Case Western Reserve University in Cleveland, and colleagues are testing whether they can restore the ability to breathe independently in rats with spinal cord injuries, by inserting channelrhodopsin into specific motor neurons and pulsing the neurons with light.

And in Detroit, investigators at Wayne State University used blind mice lacking photoreceptors in their eyes and injected a virus carrying the channelrhodopsin gene into surviving retinal cells. Later, shining a light into the animals’ eyes, the scientists detected electrical signals registering in the visual cortex. But they are still investigating whether the treatment actually brings back vision, said Zhuo-Hua Pan, a neuroscientist.

At Stanford, Dr. Deisseroth's group has identified part of a brain circuit, in the hippocampus, that is underactive in rats, with some symptoms resembling depression. The neural circuit's activity — and the animals' — perked up after antidepressant treatment, in findings reported last week in the journal Science. Now the team is examining whether they can lift the rats' low-energy behavior by using channelrhodopsin to rev up the sluggish neural zone.

But human depression is complex, probably involving several brain areas; an easy fix is not expected. The light-switch technologies are not likely to be used for depression or other disorders in people any time soon. One concern is making sure that frequent light exposure does not harm neurons.

Another challenge — except in eye treatments — is how to pipe light into neural tissue. Dr. Deisseroth's spinning mouse demonstration suggests that fiber optics could solve that issue. Such wiring would be no more invasive, he said, than deep brain stimulation using implanted electrodes, currently a treatment for Parkinson's disease.

An even bigger obstacle, however, is that gene therapy, a technology that is still unproven, would be needed to slip light-switch genes into a patient's nerve cells. Clinical trials are now testing other gene therapies against blindness and Parkinson's in human patients.

But even if those succeed, introducing a protein like channelrhodopsin from a nonmammal species could set off a dangerous immune reaction in humans, warned Dr. Howard Federoff, a neuroscientist at Georgetown University and chairman of the National Institutes of Health committee that reviews all gene-therapy clinical trial protocols in the United States.

In the near term, Dr. Deisseroth predicts that the remote-control technology will lead to new insights from animal studies about how diseases arise, and help generate other treatment ideas.

Such research benefits could extend beyond the realm of neuroscience: The Stanford group has sent DNA copies of the "on" and "off" light-switch genes to more than 175 researchers eager to try them in all stripes of electrically excitable cells, from insulin-releasing pancreas cells to heart cells.