FEATURE

Brain Control

Ed Boyden is learning how to alter behavior by using light to turn neurons on and off.

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Seeing lights: In his MIT lab, Ed Boyden studies how photosensitive proteins can be used to affect the workings of the brain. Credit: Dana Smith

The equipment in Ed Boyden's lab at MIT is nothing if not eclectic. There are machines for analyzing and assembling genes; a 3-D printer; a laser cutter capable of carving an object out of a block of metal; apparatus for cultivating and studying bacteria, plants, and fungi; a machine for preparing ultrathin slices of the brain; tools for analyzing electronic circuits; a series of high-resolution imaging devices. But what Boyden is most eager to show off is a small, ugly thing that looks like a hairy plastic tooth. It's actually the housing for about a dozen short optical fibers of different lengths, each fixed at one end to a light-emitting diode. When the tooth is implanted in, say, the brain of a mouse, each of those LEDs can deliver light to a different location. Using the device, Boyden can begin to control aspects of the mouse's behavior.

Mouse brains, or any other brains, wouldn't normally respond to embedded lights. But Boyden, who has appointments at MIT as eclectic as his lab equipment (assistant

professor at the Media Lab, joint professor in the Department of Biological Engineering and the Department of Brain and Cognitive Sciences, and leader of the Synthetic Neurobiology Group), has modified certain brain cells with genes that make light-sensitive proteins in plants, fungi, and bacteria. Because the proteins cause the brains cells to fire when exposed to light, they give Boyden a way to turn the genetically engineered neurons on and off.

This neuronal trick has placed Boyden at the center of optogenetics, one of the newest fields in biology research--one he helped to invent, and one that could influence much of what happens in neuroscience in the coming decades. He seeks to answer a very basic question: how does the electrical activity of specific groups of neurons affect thoughts, feelings, and behavior? Obvious as that question may sound, it is one that has gone unanswered since brain cells were first observed over a century ago, for the simple reason that there has never been a precise way to know which neurons are doing what during a particular thought or behavior. Relatively new technologies like functional magnetic resonance imaging (fMRI) can show average activity levels among regions encompassing millions of neurons, and not-so-new technologies such as implanted electrodes can detect activity in a more specific area, but neither can trace the simultaneous or sequential firing of a particular set of neurons that may be strung through different regions of the brain. Yet these patterns of neural activity are the very essence of brain function, controlling cognition and behavior.

By using light to get specific sets of genetically modified neurons to fire, neuroscientists can observe how this activity is associated with specific stimuli and behaviors, as well as with brain disorders such as epilepsy and Parkinson's disease. Electrical engineers have developed principles by which various individual electronic circuits can be assembled into a fully functioning computer; similarly, Boyden hopes to uncover the principles by which individual groups of simultaneously firing neurons--brain circuits, as he likes to call them--work together to allow the brain to function.

Boyden's ultimate goal: to find ways to repair misfiring brains, much as electrical engineers analyze and alter electronic circuits when debugging computer hardware. "For the vast majority of treatments for human neurological problems, the mechanisms of the treatments aren't understood, which means there isn't really a logical way to continuously improve them," he says. "Our overarching goal is to figure out ways of controlling neural circuits so that we can avoid pathological states and engineer better treatments." And though he is well aware of the ethical issues that might surround a technology capable of precisely controlling certain aspects of human thought, mood, and behavior, he is confident that optogenetics--exactly because it *is* so precise--is far more likely to help than to hurt. "All drugs and other treatments for neurological disorders modulate thought and behavior in some way, and they all have side effects, some of them quite serious," he says. "The more we can target just those brain circuits involved in the pathology, and leave others alone, the fewer side effects we're likely to see. We may have to confront new risks at some point with this technology, but the precision of the technology by itself shouldn't be seen as a problem."

Optogenetics is starting to have an enormous impact on neuroscience, says John Byrne, chairman of the neurobiology and anatomy department at the University of Texas Medical School at Houston. "We know a lot about how individual neurons function, and how regions of the brain process certain types of information, but the final frontier is

how regions of the brain process certain types of information, but the final frontier is learning how groups of neurons communicate in circuits to perform specific functions," he says. "That's what optogenetics is going to let us do with fantastic specificity."

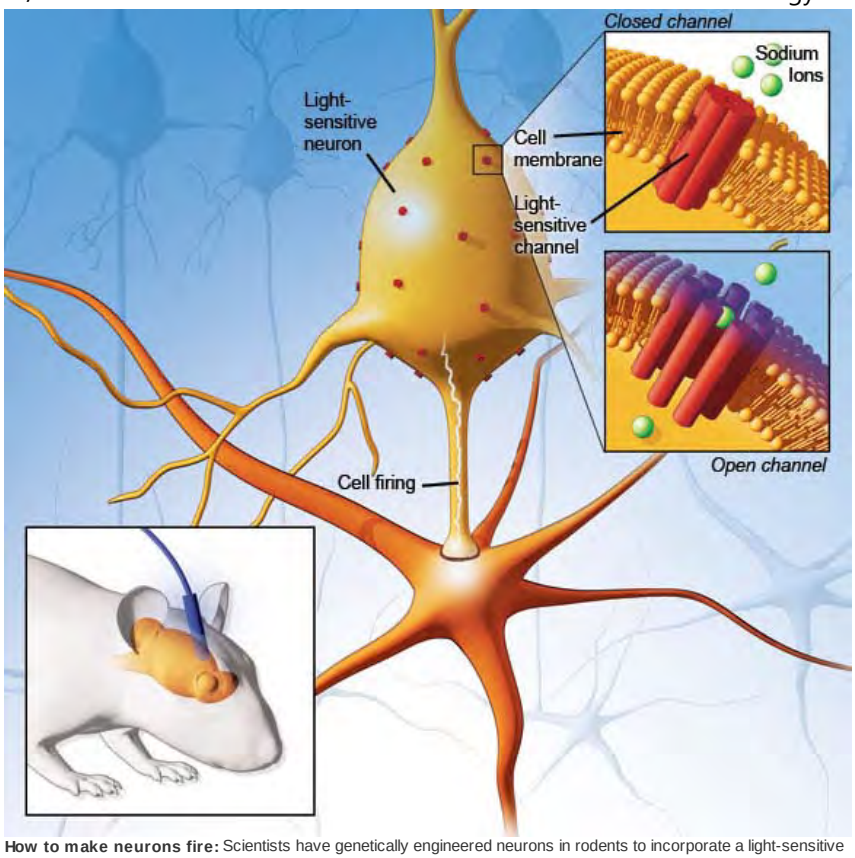
FIRE AWAY

When Boyden enrolled at MIT, at the age of 16, he quickly focused on exploring the principles of system control. Early on, he helped design a system that allowed a user to control a computer program through hand movements. But such problems felt a little too solvable--he was merely finding better ways to control systems that had already been proved controllable. The quantum-computing work getting under way in one corner of MIT's Media Lab seemed to pose the tougher kind of challenge that he sought, and Boyden spent his fourth year at the university trying to help develop a technique for taming the behavior of atoms that temporarily exist in multiple quantum-mechanical states. Unfortunately, the atoms proved too unruly to control, but that itself gave Boyden a new insight. "If the problem is impossible, you never get to the fun of controlling anything," he explains. "I needed to tackle a problem that was *nearly* impossible."

For Boyden, that was controlling the brain. After MIT, he earned a PhD in neuroscience at Stanford, where he collaborated with the neuroscientist Karl Deisseroth. Deisseroth's group, which wanted to isolate and analyze memory circuits, started working on a project that promised to provide a tool for exploring other brain circuits as well. Scientists had previously demonstrated ways that bursts of light could be used to coax brain cells into firing, but the techniques weren't refined enough to probe specific brain circuits. The Stanford researchers knew, however, that the cells of many plants and bacteria, as well as some of the cells in the eye, are photoreceptive: when light is shined on them, they generate a small voltage through the action of various forms of a protein collectively called opsins. Could opsins be used to make those methods more precise?

The answer, it turned out, was yes. Deisseroth, Boyden, and Boyden's fellow graduate student Feng Zhang chose microbial opsins that were especially efficient at converting light to electrical energy and pinpointed the genes that coded for those proteins. Then, in a technique that's standard in gene therapy, they used a virus to insert the opsin-producing genes into neurons. Once inside the neurons, the genes started producing opsins, with the result that the neurons fired when exposed to light. Boyden and his coworkers had found a precise, reliable way to stimulate specific groups of neurons and observe what happened when they fired.

Being able to link specific groups of neurons to a behavioral change, whether the change is related to cognition, motor control, emotion, or sensory perception, is crucial to treating brain disorders. If the specific neurons that are causing a problem can be identified, then researchers know where to aim potential therapies. But scientists aren't able to probe, monitor, and record the individual circuits that make up memories and thoughts, says Christian Wentz, a former graduate researcher in Boyden's MIT lab who has gone on to cofound Cerenova, an early-stage company in Cambridge, Massachusetts, that is developing optogenetic applications. "There's never been a way to establish connections between what happens on the cellular level in the brain and how we behave and think, and that's part of the reason why cognitive functions aren't well addressed by existing drugs or devices," he explains. That's why it's been so difficult to understand and treat disorders of higher-order cognition and memory, such as Alzheimer's disease.



How to make neurons fire: Scientists have genetically engineered neurons in rodents to incorporate a light-sensitive channel (right inset, top). When exposed to blue light delivered by a fiber-optic cable, the channel opens, allowing positively charged sodium ions to rush into the cell (right inset, bottom). This in turn triggers the cell to fire, transmitting a signal to cells downstream in the neural circuit. Credit: Tami Tolpa

By allowing researchers to make specific groups of neurons fire on cue, Boyden's tooth-shaped bundle of optical fibers and LEDs provides a way to investigate those connections. After opsin-producing genes have been inserted into the neurons in a mouse so that the cells react to light, researchers implant Boyden's device into the part of the rodent's brain under study. Then they can control whether the neurons around the end of each optical fiber are firing. They target different sets of neurons in the mouse's brain and observe any behavioral changes that result when those neurons fire.

Boyden has been using this technique to experiment on mice that exhibit symptoms of anxiety, fear, memory loss, and even post-traumatic stress disorder (PTSD). As the optical-fiber device stimulates different groups of neurons, he looks for signs that the mouse's symptoms are getting better or worse. If the symptoms worsen when a particular group of neurons fire, then finding ways to prevent them from firing is a promising avenue for treatment; if the symptoms improve on stimulation, then it might be therapeutic to facilitate their firing.

Labs around the world have begun using the tools of optogenetics to study virtually every major brain-related disorder, including Alzheimer's, Parkinson's, schizophrenia, epilepsy, sleep disorders, vision loss, and chronic pain. Consider epilepsy, which Jeffrey - Noebels, a neuroscientist at Baylor College of Medicine in Houston, likens to some familiar computer problems. "We just don't know why the epileptic brain fails to sync properly at times, leading to a denial-of-service attack and a blue screen," he says. "We've been stymied in trying to learn more because we've had to interrogate the brain an entire region at a time, which is like trying to figure out what's wrong in a circuit board by blasting the entire board with an electric current. With optogenetics we can focus on the neurons that are playing a critical role, which is more like looking at the individual transistors." Treatment for severe epilepsy can involve surgically removing extensive chunks of the brain's cortex in order to prevent seizures, Noebels says, but that can lead to cognitive impairment and other problems. "If we can pick out the neurons that are the rabble-rousers, we might be able to sculpt the cortex into firing in a healthier way with drugs or stimulation," he says.

Boyden sees an even bigger role for optogenetics: not only can it help reveal the roles of individual brain circuits and potentially point to ways of fixing neural misfiring, he

believes, but it can help researchers determine how all the different circuits fit together to create a fully functioning brain. How is a memory formed, lost, or altered? How does a thought trigger movement in a finger? How do we interpret visual images?

Many thousands of circuits will probably have to be matched to specific functions before the big picture emerges, and researchers will have to pick up their pace dramatically if they hope to match up most of them within a decade or two. To that end, Boyden envisions enlisting computers to automate the process. For example, a computer might investigate a circuit by sending light to a particular location in an animal's brain. To "read" what happens in response, it could look for glowing neurons or record how the animal moves or how its heart rate changes. Then it could quickly and repeatedly adjust the location of the light to try to maximize that response.

By thus probing brain circuits in mice, Boyden hopes to eventually "reverse-engineer" the neural networks that make up a brain, the way an electrical engineer might measure the *0*s and *1*s that are the outputs of an electronic chip to derive the software code programmed into the chip's circuitry. "The information in the brain is hard to understand if you don't know how it got computed," he says. "We want to uncover the original algorithm that is underlying function."

KEEPING QUIET

One of the most immediate and perhaps most important payoffs of Boyden's techniques is likely to be in drug development. "If we could use optical fibers to turn specific brain circuits on and off in an awake, behaving animal that has been given a drug, we could test which circuits are being affected by the drug and what the behavioral consequences are," says Boyden. "That would allow us to look for drugs that are more specific and effective to the right circuits, instead of just bathing the brain in a substance."

One surprising and important discovery that came out of Boyden's early studies involved a sort of "antistimulation" effect in brain circuits. Something odd happens when a group of neurons that tend to fire together is stimulated by light: while most of the cells fire more frequently, about a third actually fire less frequently. The effect has proved astonishingly consistent for all regions of the cortex, and for all types of behaviors and functions, in all animal species that have been tested. "The fact that a significant percentage of the neurons were completely inhibited told us there was an important principle of neuronal control to consider here," says Boyden. "If we want to make a brain circuit do something, we have to consider not just which neurons we excite but also which neurons we quiet downstream." That's likely to be especially important in developing new drugs. For example, a drug that aimed to relieve a symptom by stimulating one group of neurons could end up making things worse by indirectly silencing other neurons. On the other hand, silencing certain neurons could be beneficial--for example, if they had been causing epileptic seizures by firing uncontrollably.

Not only could optogenetic techniques reveal which neurons a treatment should aim to turn on or off, but they could become useful as treatments in themselves. For example, they could offer an improvement over the implantable devices that now deliver electrical jolts to treat Parkinson's and other disorders. Those devices tend to activate all the neurons near an implanted electrode, but an implanted fiber-optic device would activate only those neurons that had been altered with opsins--only the defective portions of a motor-control circuit or a mood-related circuit--while properly functioning neurons would be left alone. That, of course, would require using gene therapy on human patients, and such techniques, despite years of research, are still experimental. Eventually, however, if gene therapy proves safe, physicians could use optogenetics to repair faulty brains, perhaps by applying optical or electrical stimulation at precisely selected locations.

Will the public welcome implantable optical devices that could do such things, or will they fear that the techniques could be used to trigger or suppress particular thoughts, sensations, emotions, or behaviors? "People already have very different opinions about which psychiatric drugs are worth it and which ones aren't," Boyden says. "Those questions will be raised about this approach, too, and that's not a bad thing. There should always be an open dialogue between scientists, clinicians, regulatory agencies, and the public about the risks and benefits of new types of treatments."

David H. Freedman is freelance journalist who has written for the *Atlantic* and the *New*

York Times. His latest book, *Wrong*, explores why experts and scientists often don't get things right.

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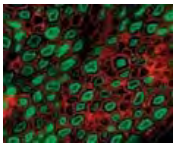

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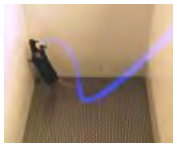

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