CONTROLLING THE BRAIN WITH LIGHT

Ed Boyden has come a long way since 2004, when he co-developed the barrier-smashing neuroscience technology, optogenetics, as a side project while in graduate school at Stanford. At the time, researchers were daunted by the challenge that truly understanding the brain would require precisely controlling discrete sets of neurons to learn what they do. Optogenetics does just that, by exploiting light-sensitive proteins, called opsins, found in algae and similar organisms. Late one night with borrowed equipment, Boyden showed that a pulse of blue light nearly instantaneously activated neurons he had engineered to express one of these opsins. Later he and others found opsins that silence neurons with yellow light.

Neuroscientists quickly recognized that optogenetics solved a huge problem. Every brain region has intermingled, heterogeneous neurons that respond to different stimuli, produce different signals, and connect to assorted neurons in different brain regions. With optogenetics, researchers can selectively control just one type of neuron to dissect elusive neural pathways and learn how neurons initiate or sustain behaviors, or malfunction in brain disorders. Typically, researchers implant minuscule optic fibers that deliver light to an animal's brain region with the modified neurons. Optogenetics' first human application may be to treat some forms of blindness, by endowing retinal neurons with opsins. Eventually, optogenetics may improve brain stimulation techniques for treating epilepsy, Parkinson's disease, and other disorders.

Boyden, who joined the MIT Media Lab in 2006 and the McGovern Institute for Brain Research at MIT in 2010, and is associate professor in the Departments of Brain and Cognitive Sciences and Biological Engineering, is continuing to develop and enhance optogenetic techniques — most recently a noninvasive means of control and a "multiplexed" control method for the study of more complex patterns of neural activity.

"My bigger goal, though, is to build tools that help solve the brain," says Boyden. Reflecting his MIT undergraduate training in physics, computer science, and electrical engineering, Boyden thinks of the brain as a 3-D structure, with a parts list, a wiring diagram, and integrated components. "I want to map the brain to understand how it works as a network of neurons, and how neurons work as networks of molecules. When we stimulate a neuron, how does it alter the rest of the neural circuit? What is that circuit's wiring diagram? How does a neural circuit generate a thought or feeling, and can we simulate it and learn how to fix brain disorders?" To that end, his lab is developing many more tools besides optogenetics.

One such tool is whole-brain imaging of all the neural activity in an organism as it responds to a stimulus or initiates a behavior. For a test, Boyden and his collaborators modified all the 302 neurons in the worm *Caenorhabditis elegans* to express fluorescent proteins that glow when neurons fire. But even the worm's tiny nervous system is a three-dimensional structure. A scanning microscope can gather 3-D images, but too slowly to capture individual neurons firing. So Boyden and his collaborators adapted a light-field microscope with multiple lenses, which mimics a human visual trick: Just as each eye gathers light rays from different angles that are then integrated into three-dimensional images, these microscopes gather rays from different angles as the firing neurons fluoresce. The resulting 3-D video shows what upstream and downstream neurons are doing as the worm goes about its business. Boyden's lab is also developing a novel microscope to map the connectivity of the neurons — and a genetic tool to discover the protein "recipe" for individual neurons.

Eventually, Boyden wants to build a brain from scratch (i.e., from stem cells). "We could see how brains naturally develop their wiring. We could create replacement parts for diseased brains, and we could create a personalized diagnostic platform to test how a patient's 'mini brain' responds to a potential treatment." Such a construct would also satisfy the engineering maxim that Boyden embraces: "What I cannot build, I cannot understand."

— CATHRYN DELUDE

Ed Boyden aims to build tools to help solve the mystery of the brain. Photo illustration: Len Rubenstein