Optogenetics: A Conversation with Ed Boyden

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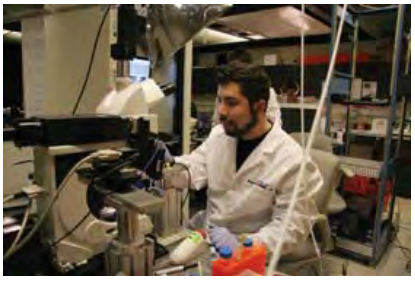
In a few short years, optogenetics has gone from a glimmer in the eye in a handful of researchers to a viable technique used worldwide to study information processing in the brain. We recently caught up with one of the originators of the technique and talked about his role in its development while also exploring future avenues of research.

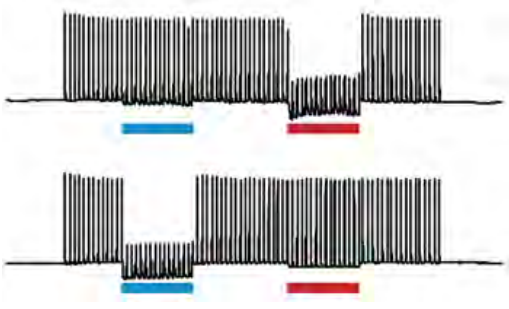
Ed Boyden is a well-known figure in the field of optogenetics: a pioneer of the technology and, in 2008, one of *Discover Magazine's* top 20 scientists under 40. Now head of the Synthetic Neurobiology Group at MIT in Cambridge, he traces his role in devising the technology to his days studying electrical engineering at this same school on the banks of the Charles River, when he was trying to understand how the laws of physics could lead to the ability to compute, to transform information in the service of a particular goal.



Ed Boyden, head of the Synthetic Neurobiology Group at MIT, is one of the originators of the technique known as optogenetics. Courtesy of Paula Aguilera, MIT Media Lab.

"I was very interested in developing new physical methods for perturbing the brain," he said recently in an e-mail from Japan, where he was giving a series of talks, "because if we could drive specific neurons, we could see what they were sufficient for controlling. If we could silence specific neurons, we could see what they were necessary for."

When he began studying neuroscience, around 2000, Boyden started collecting genes that encode for light-sensitive proteins, particularly those that might be able to convert light into electrical energy. "These are important because neurons are electrical devices. So if we express these proteins in neurons, we can perturb their electricity."



Optogenetics relies on the optical silencing or driving of particular patterns of neural activity. Shown is a demonstration of multicolor silencing of two neurons; one (bottom) expresses Mac and thus is silenceable by blue but not red light, whereas the second neuron (top) expresses Halo and is silenceable by red but not blue light. Courtesy of Brian Chow, Xue Han and Ed Boyden.

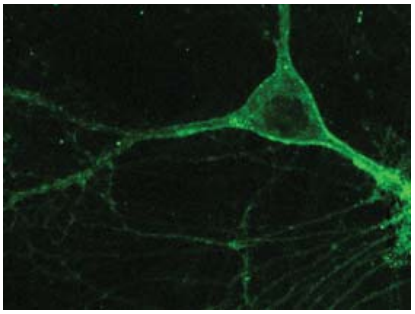
The breakthrough came in 2004, when he was collaborating with Karl Deisseroth at Stanford University in California. A psychiatrist, Deisseroth decided early in his career that the tools available to study the mechanisms of brain disease were not nearly precise enough to elucidate how groups of neurons talk to one another using electricity. So, drawing on his additional training as a bioengineer and a neuroscientist, he set out to develop tools that are precise – tools that could help shed light on what goes wrong with neural circuitry in mental illness and other brain disorders.

"The goal is to march through the disease circuitry and understand how the dynamics of neurons talking to each other is broken and how that can be tweaked to correct the disorder," he explains in his bio on the website of Howard Hughes Medical Institute, which is based in Chevy Chase, Md.

Working with Georg Nagel and others, Boyden and Deisseroth showed that one of the light-sensitive proteins – channelrhodopsin-2, a blue-light-driven ion channel from green algae – could be expressed in mammalian neurons, and the neurons activated through high-speed optical switching. Thus, they achieved noninvasive control of neural activity on the necessary millisecond timescale.

This neuron is expressing the Arch gene and generating light-activated proteins that are then localized to the outside of

and Ed Boyden.



Their findings were published in September 2005 in *Nature Neuroscience* and, in an Oct. 11, 2006, *Journal of Neuroscience* paper, Deisseroth coined the term "optogenetic" to describe a technology that "combines genetic targeting of specific neurons or proteins with optical technology for imaging or control of the targets within intact, living neural circuits." The term and the optogenetic approach both quickly caught on, and the technique is widely used today to study information processing in the brain.

But what is it? In traditional genetics, researchers seek to understand the role of specific proteins in development and behavior in organisms by controlling the proteins, through either "loss of function" or "gain of function" changes. Optogenetics professes a similar goal, although here investigators want to learn more about the role of neural circuits in particular behaviors; for example, those underlying brain disorders such as Alzheimer's and Parkinson's disease. Similar to traditional genetics studies, researchers in optogenetics achieve this by silencing or driving particular neural activity patterns.

There is an important difference between the two fields of study, however. Whereas in traditional genetics, manipulations occur on a timescale of days to weeks or even months, investigations of neural activity demand millisecond precision. This is where optics comes in. By taking light-activated proteins – channelrhodopsin-2, for example – and adding them to neurons, researchers can effectively switch the neural activity patterns on and off, adding or deleting the patterns in the brains of intact animals.

I asked Boyden what enabled the development of optogenetic approaches. Was there some technological advance, perhaps, that made it all possible?

"Initially, it was chiefly due to careful observation and a bit of good luck," he said. For example, in 2004, he and Deisseroth and colleagues found that channelrhodopsin-2 could operate in mammalian neurons without chemical supplements of any kind. This, of course, made it very easy to use – and thus very popular. At the same time, they noted that the protein could mediate currents large enough to activate neurons.

More recently, he added, his group at MIT has been using new technological methods to further the optogenetic approach – mining genomes, for instance, looking for novel molecules. (They published a *Nature* paper on this topic in January 2010.)

To be sure, for all the successes in optogenetics' still-brief lifetime, challenges remain to be overcome. A number of groups are working to address these.

One obstacle, Boyden said, is how to use these techniques in the three-dimensional, densely wired brain. His group currently is developing new hardware, he added, that better facilitates optical silencing or driving of neural activity in complexly shaped brain circuits. In March, at the Cold Spring Harbor (N.Y.) Laboratory Meeting on Neuronal Circuits, they presented a suite of hardware technologies capable of multiscale optical neural control. This included an array of LED-coupled 200-µm optical fibers allowing delivery to tens of sites in the brain of a mouse; a modular fluidic cooling system, enabling operation for very long periods of time; and 10 LEDs for 30 continuous seconds or three LEDs indefinitely. The arrays and cooling systems are light enough to be kept to the head of a freely moving mouse.

This combination of technologies can enable high-throughput screening of neural circuits associated with particular behaviors, thus identifying neural targets for optical manipulation. Noting the potential of such a systematic screen, the researchers showed that they could eliminate Pavlovian fear conditioning by manipulating selective cortical targets in a freely moving mouse outfitted with the technology.

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