Seeing the light: Ed Boyden's tools for brain hackers

By Ed Yong (/search/author/Ed+Yong) | 20 November 12

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Ed Boyden, an engineer turned neuroscientist, makes tools for brain hackers. In his lab at MIT, he's built a robot that can capture individual neurons and uses light potentially to control major diseases -- all in his quest to 'solve the brain'. To break into a neuron within a living brain, you need a good eye, extreme patience, months of training, and the ability to suck with gentle care. A mouse lies in front of you, brain exposed. Your mission is to impale one of its neurons with the micrometre-wide tip of a glass pipette.

An electrode in the pipette measures the resistance at its tip, and relays the signal to a monitor. You're watching out for the subtle spikes that tell you that the tip has struck cellular gold. When it is in place, you suck on a rubber tube connected to the pipette - gently at first, to form a seal, and then slightly harder to create a small hole.

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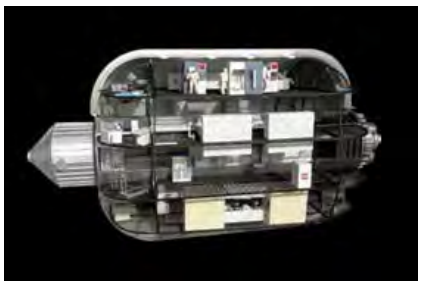

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If it works, you now have full access to the neuron's inner workings. You can inject a dye through the hole to map the cell's many branches. You can measure its electrical activity as it communicates with its neighbours. You can suck out its contents to analyse the chemicals inside it. If you did that for hundreds of connected neurons, you could start to understand the molecules and electric pulses behind the rodent's thoughts, emotions and memories.

Or at least you could if this technique, known as patch-clamping, were not so frustratingly hard. Getting an electrode to impale a single neuron is difficult enough in a dish. Doing it on a living animal is so tedious and arcane that only a few dozen people in the world can pull it off. And forget about studying networks -- to date, the record for the most individual cells patch-clamped in a live brain is two. In an age when brain scanners can produce vivid portraits of mental activity (http://www.wired.co.uk/news/archive/2011-09/23/reconstructingvision) and 3D printers can fabricate organs (http://www.wired.co.uk/magazine/archive/2012/07/start/how-3d-printing-built-a-new-face), patch-clamping seems like an anachronistic relic from a different time. But no more -- a technique that has stayed the same for over 30 years is being brought into the 21st century by Ed Boyden (http://edboyden.org/).

Boyden, 33, makes tools for brain hackers. From his lab at MIT, he is building technology that will vastly expand the range of experiments that other scientists can pull off. His latest invention is a classic example: a robot that patch-clamps as well as a human scientist, with none of the fatigue or variability. It works all day. It does not need lunch breaks. It has transformed a technique that had only been mastered by an elite few into something that anyone can do, and hundreds of labs are queuing up to buy or make an auto-patcher of their own. Boyden published a description of the robot in May this year. He says, "After our paper came out, I got an email saying, 'I just spent a year learning how to do that. Thanks. There goes that'."

Boyden has a gentle demeanour but speaks so rapidly that he keeps a treasury of tea at hand to soothe his throat. "I tend to forget to breathe," he says. His ideas flow as quickly as his words. "Even among that elite group [at MIT], Ed stands apart. His ambition is audacious," says Craig Forest from the Georgia Institute of Technology (http://www.ibb.gatech.edu/craig-forest), Boyden's partner on the auto-patcher project. Other colleagues agree. "It's regular to hear him say something like, 'I want to solve the brain.' Period. Nothing after that," says Anthony Zorzos, one of Boyden's graduate students. "But for a guy who says things like that, he's pretty down to earth."

"Solving the brain" is as difficult as it sounds. A cubic millimetre of brain tissue can house 100,000 neurons, sending signals across a billion connections in mere thousandths of a second. This cross-talk is what turns a lump of spongy tissue into the most sophisticated computer in existence. It is also impenetrable to modern methods. We can zoom out to scan broad regions encompassing millions of cells, or zoom in to dissect the traits of individual ones, but the intermediate world of circuits still eludes us. Boyden likens our current technology to studying one pixel on a computer screen at a time. "Even if you buy a million screens, you won't understand how a computer works by looking at that one pixel," he says. "I'd rather have one computer and look at everything in it." The auto-patcher is one of the tools that Boyden is developing to observe neural circuits in detail, to better understand how the brain computes.

But voyeurism is not enough. Boyden is also designing tools to tweak, trigger and silence neural circuits, offering a degree of control that neuroscience has always lacked. For a long time, studying the brain meant finding correlations. Scientists measured how blood flow or electrical activity changed as we carried out mental tasks, and they noted how injuries and disease affected those abilities. But to establish causality, you have to stimulate neural circuits, as

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well as watch them. A movie, drug or electric shock will do the trick, but we need tools to stimulate specific sets of cells, not vast swathes of neurons.

The most famous of these is the one that made Boyden's name: optogenetics (http://www.stanford.edu/group/dlab/optogenetics/). By implanting neurons with light-sensitive proteins called opsins, harvested from algae, microbes and other creatures, scientists can stimulate or silence them with a simple optic fibre. Boyden pioneered optogenetics in 2005, with Karl Deisseroth from Stanford University. Now, it is used by thousands of scientists around the world.

The opsins can be loaded into neurons within just one part of the brain, or into neurons that secrete a certain type of signalling chemical. Flash the right set and you can steer an animal's movements, send it to sleep or make it aggressive. Silence the right ones and you could potentially calm the hyperactivity that accompanies epilepsy and Parkinson's disease. "I'm wary of using the term revolutionary but I don't think it's an overstatement for optogenetics," says Robert Desimone, director of MIT's McGovern Institute for Brain Research (http://mcgovern.mit.edu/) and one of Boyden's collaborators. "It has affected virtually every lab working in neuroscience."

In Boyden's endgame, neuroscientists will use these tools to observe and control large networks of neurons at once. Imagine recording the activity of thousands of cells as a memory is formed, and then triggering the same pattern of activity to see what happens. These are the experiments that Boyden is working towards. With a background in physics and electronics, he brings an engineer's mindset to the messy world of brain science. "The premise I put to people who start in my group is: assume the brain is solved in 50 years, and that we'll need to invent lots of new tools to get there. What are those tools, and which one should we work on now?"

The tools he builds are varied, but all of them are meant to be easy to use, and to accelerate the process of discovery. Many scientists are content to slowly chisel away at the bounds of our knowledge, but Boyden is building jackhammers for them to wield. "Imagine all possible neuroscience experiments," he says. "You could pick a brain region, a type of cell, a behaviour and a disease. You might study how the interneurons of the cerebellum are involved in spatial memory or Alzheimer's. There are billions of such experiments. If you're going to solve the brain in 50 years, doing billions of PhD theses isn't how you go about it."

That is exactly the kind of attitude that neuroscience needs, according to Desimone. "Ed comes in from the outside and shakes things up," he says. "You keep on asking yourself: why didn't people in the field come up with that?"

Boyden was interested in big philosophical questions from an early age, and he knew that to answer them, he needed a solid scientific training. Fortunately, his high school -- the Texas Academy of Mathematics and Sciences -- was connected to the University of North Texas, and all the students could attend lectures and labs in their final two years. Boyden spent a few days a week working with Paul Braterman, a chemist obsessed with the origin of life.

"It was eye-opening that someone with a beaker and a fume hood could try to test these theories about how life began billions of years ago," he says.

By the time he joined MIT as an undergraduate in 1995, Boyden's interests had shifted to include engineering, physics and computer science and, in particular, how the world computes and processes information. In his final year, Boyden spent a few weeks at Bell Labs. Surrounded by former physicists who had switched to neuroscience, he spent several weeks trying to develop

ways of understanding the brains of singing birds. "It was total immersion in a community that was trying to hack the brain," he says. The brief encounter set Boyden on his path. "At MIT, I was interested in the physics of computation, but that seemed too broad," he says. "Neuroscience was a subset of that." This, then, is all you really need to know about Boyden -- he decided to try to "solve the brain" because it seemed like a more tangible and realistic problem.

Supreme confidence, not arrogance, is Boyden's hallmark. "I once let him borrow my car," says Jennifer Raymond from Stanford University, one of his PhD supervisors. "It was pretty new, and had manual transmission. I gave him the keys and 15 minutes later, he came back and said, 'How do I do the shifting?' I said, 'You can drive a stick, right?' He said, 'I've read about it.' I asked for the keys back."

It was this fearlessness about jumping into new areas that led Boyden to Raymond's group in the first place. Bell Labs had inspired him, but he realised that he needed some hardcore biological training to bolster his engineering nous. In 1999, he joined Raymond and Richard Tsien as a graduate student, to look at how the brain stores memories of movements. "I wanted to do my time," he recalls. "A lot of my friends who did engineering wanted to do neuroscience, but went back to start another dotcom company after a year. Biology is so messy, slow and painful. You need to learn to be patient and tolerant of extreme failure." Raymond and Tsien taught him those qualities, and gave Boyden the freedom to pursue the many side projects bubbling inside his brain. A good thing too, for one of these would change the field.

At Stanford, Boyden bonded with Karl Deisseroth (http://www.stanford.edu/group/dlab/about_pi.html), another of Tsien's students, who was about to finish his PhD and start a psychiatric residency. They spent several late nights brainstorming ways of mapping and controlling specific circuits in the brain. It would not be enough to electrify thousands of neurons into action; they wanted a way of exciting specific cells of their choosing.

In 2002, Gero Miesenböck at the Memorial Sloan-Kettering Cancer Center (http://www.mskcc.org/) in New York showed this could be done with light-sensitive molecular machines. He infused mammalian neurons with three proteins from a fruit fly's eye, so that a burst of light would make them fire. His technique was the first true example of optogenetics, and proved light could drive neural activity. But it was unwieldy. The three proteins had to be balanced at exactly the right levels, and took seconds to influence neurons -- a glacial pace in the millisecond-fast world of the brain. Boyden and Diesseroth knew that to create a tool others would use, they needed a fast, self-contained machine.

As it happened, a freshwater alga called *Chlamydomonas reinhardtii* has been using just such a machine for billions of years. *Chlamydomonas* looks like a microscopic green marble, and it relies on sunlight to make its own food. It tracks the nearest light with an eyespot, containing an opsin called channelrhodopsin-2 (ChR2). Like other opsins, ChR2 is a machine for converting light into electricity. It consists of seven tightly clustered columns that open into a pore when they are hit by blue light. The pore stays open for just a few milliseconds, long enough to let in a flood of positively charged ions. This creates a voltage.

Here was the neural controller that Boyden and Deisseroth wanted and the timing could not have been better. ChR2 was discovered in 2002, just as Deisseroth was about to start his own laboratory and Boyden was finishing his PhD. The duo had languished upon their dreams of neuron control for a few years, but Miesenböck's paper showed that others were thinking along similar lines. "It kicked us back into the game," says Boyden. The duo got a copy of the ChR2 gene, and used a harmless virus to smuggle it into mammal neurons. The infected neurons manufactured copies of ChR2 and became sensitive to

blue light.

In hindsight, there were many reasons why this should not have worked. But it did, and on the very first go. At 1am on 4 August 2004, Boyden patch-clamped a ChR2-infused neuron, shone blue light on it and watched it fire. Somehow, an algal protein had just the right qualities to turn on a mouse neuron. "All the stars aligned evolutionarily," he says. But Boyden is modest about his contribution and notes that other labs published similar and more extensive papers in the following months. "The idea was very much in the air," he says. "If we hadn't made the discovery, someone else would have."

Eventually the duo published their results, and the publication of that first paper in August 2005 triggered a huge interest in both optogenetics and Boyden himself. He spent just a year as a postdoctoral researcher in two Stanford labs ("No single lab can contain Ed," says Raymond) before returning to MIT in 2006 to launch his own group. He became a professor a year later. These days, his team -- the Synthetic Neurobiology Group (http://syntheticneurobiology.org/) -- is around 30-strong, and involved in dozens of collaborations.

His current academic home at MIT's Media Lab looks like a standard molecular biology lab where engineers have run amok. Benches full of the usual beakers, plastic tubes and pipettes, also have screwdrivers protruding from them. Every piece of equipment has been jerry-rigged. On a whirlwind tour, Boyden points to a simple microscope riddled with accessories. "Laser, more lasers, a monochrometer, a xenon lamp," he says. Then, after a pause: "I don't even know what these are."

Boyden's laboratory spaces are scattered around two floors and a dozen rooms. He walks between them at a brisk stride, taking in a playground of high-pressure water-cutters, 3D printers, holograms, X-ray microscopes and gardens of robotic flowers. "There's a lot of very thought-provoking stuff around," he says. "If I'm writing, I try to walk around every hour or so. I walk past these flowers and, for a few minutes every day, I'm thinking about robots."

Boyden's former partner Deisseroth is also at the top of his game. His Stanford lab has become a conveyor belt for high-impact publications, where optogenetics is used to study everything from fear to memory to mental health. Post-docs emerge from it plated in academic gold. With Deisseroth's background in psychiatry, the goal of using optogenetics to treat mental disorders is never far from his mind. Boyden, meanwhile, has focused more on improving the tools he helped to create. He sees clinical work as important, but also as slow and expensive. "If we did both invention and clinical work, we'd keep on improving tools and the in-house clinical people would always play catch-up," he says. "Instead, we really focus on making the best tools possible, and collaborating with others on their application."

These tools include an expanded palette of light-sensitive opsins. Together with Xue Han -- then his partner, now his wife -- he showed that two microbial opsins, halorhodopsin (Halo) and archaeorhodopsin (Arch), can silence neurons when exposed to yellow light. Combine these with ChR2 and you can flip neural circuits on or off with bursts of blue and yellow. Boyden is still mining the tree of life for more opsins, especially those that respond to red light. Red penetrates deeper into the brain and it's less likely to accidentally trigger a blue-sensitive opsin such as ChR2 by mistake, since it sits at a far end of the visible spectrum. And Boyden has just received a grant from the US Defense Advanced Research Projects Agency (DARPA) to scour the genomes of plants for other light-activated proteins -- not just gates like the opsins, but also hinges, motors and other molecular machines.

Boyden also moved optogenetics from rodents, flies and worms into primates.

Together with Han and Desimone, he was the first to successfully load ChR2 and Arch into the brains of macaque monkeys. A monkey's immune system is more likely to tell us if our body would launch harmful offensives against these microbial and algal proteins. Their brains are much also larger than a rodent's, making them tougher to impregnate with opsin genes and harder to illuminate with optic fibres.

The delivery of light is a big issue. It is cumbersome enough to have a mouse tethered to a laser by an optic fibre, and it is downright unfeasible to expect the same of a human. Again, Boyden is on the case. Together with his former student Christian Wentz, he has developed a wireless optogenetics helmet. It weighs less than a gramme, contains 16 LEDs for flashing opsin-infused neurons, and is powered by magnetic fields produced by a distant transmitter, which can plug into a laptop's USB port. If you talk to scientists about optogenetics, words such as "transformative" and "Nobel" get bandied around a lot. If you talk to Boyden about it, you realise that he would be dissatisfied with pioneering just one revolutionary technique in his lifetime. "Optogenetics is a great tool but by itself it won't solve the brain," he says. "You can control things, but if you can't observe what's going on, you won't fully understand it."

Observing the brain is the goal of the auto-patcher project. Patch-clamping is the ultimate technique for neural voyeurs -- a way of connecting the dots between the electricity coursing through a neuron and the biochemistry going on inside it. Boyden and Craig Forest's student Suhasa Kodandaramaiah spent four months learning how to patch-clamp a single neuron in a living brain (making him the only person at MIT who can) and just under two years writing a script that would do the same.

The robot can clamp single neurons as well as a skilled human can, and the team have already upgraded it to deal with several cells. It is still a challenging task, but the team have already doubled the previous record by clamping four neurons at once. Boyden adds, "I like to think of 'dynamic connectomics', where we can see how connections change, second by second, minute by minute, throughout changes in attention, learning, diseases and so on."

Others have been quick to realise the robot's potential. "At the Society for Neuroscience meeting in Washington DC in November, over 100 people left me their email and asked me to contact them as soon as this is commercially available," says Forest. "We also talked to Pfizer and they said this could allow them to test how drugs affect neurons in a living brain." Forest has created a start-up called Neuromatic Devices to sell the patch-clamping robots, but Boyden has no ownership of this or any other company that has spun out of his work. He has made the instructions for building an auto-patcher, like those for his optogenetic techniques, freely available online. "I just want to move the field along as fast as we can," says Boyden.

Boyden is also working on other ways of mapping the connections between neurons, by delivering precise bursts of light to optogenetically enhanced cells. One such tool, known as the waveguide array, is the work of his student, Anthony Zorzos. It is a grid of 100 needles mounted on a stamp-sized square. Each one funnels light from a central laser down parallel tracts and beams them outwards at ten individual points, shining on the neurons nearby.

In Boyden's dreams, all of these tools would eventually converge in a " brain co-processor (http://www.technologyreview.com/news/420884/brain-coprocessors/)" -- a mechanical sidekick for the mind. "Imagine you had a stroke or Alzheimer's and lost a fraction of your brain," he says. "Could you have a machine that would read out info from the brain, compute what the missing part should have done and enter that information back in?" All of his tools fit within this framework, including techniques for reading information from neural circuits (the waveguide and auto-patcher) and entering data back into them (optogenetics). This is what "solving the brain" looks like: we would

know so much about neural computations that we could duplicate them. We could stop epileptic seizures in their tracks by detecting telltale patterns of brain activity and blocking the neurons involved. We could abate the risk-taking urges of drug addicts or the long-term fears of people with post-traumatic stress disorder. We could boost our problem-solving abilities.

Such goals may be distant and optimistic, but they keep Boyden excited. In the meantime, he has more pressing concerns. His wife has just given birth to their second child, Athena. She is on newborn duty, while Boyden looks after their two-year-old son, Edward. Even by his standards, it is a busy and chaotic time. By day, he is building tools that allow us to engineer the brain. By night, he is caring for the two brains that he personally helped to build.

How does optogenetics work?
Optogenetics techniques enable researchers to activate or silence specific neurons using pulses of light. Here's how they do it.

1. Build a synthetic ChR2 gene: A synthetic version of the ChR2 gene, found in green algae, is built. This opsin gene codes for a light-sensitive channel that responds to blue light.

2. Put the gene into a virus: Next, the synthetic gene, which has a DNA "postcode", is inserted into a virus, which acts as a messenger when injected into an animal's brain.

3. Infect your subject: Once inside the brain, the (harmless) virus infects multiple neurons. The gene is expressed only in a subgroup of these, as marked by the postcode.

4. Fire blue light into the brain: A pulse of blue light can now be fired into the brain. Neurons containing the light-sensitive channel open up and start firing electrical impulses.

5. Measureneuron response: When specific neurons are active, behavioural and physiological responses can be measured. Different opsin genes vary the responses.

Ed Yong wrote about mapping the Amazon (http://www.wired.co.uk/magazine/archive/2012/03/features/logging-the-amazon) in 03.12

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