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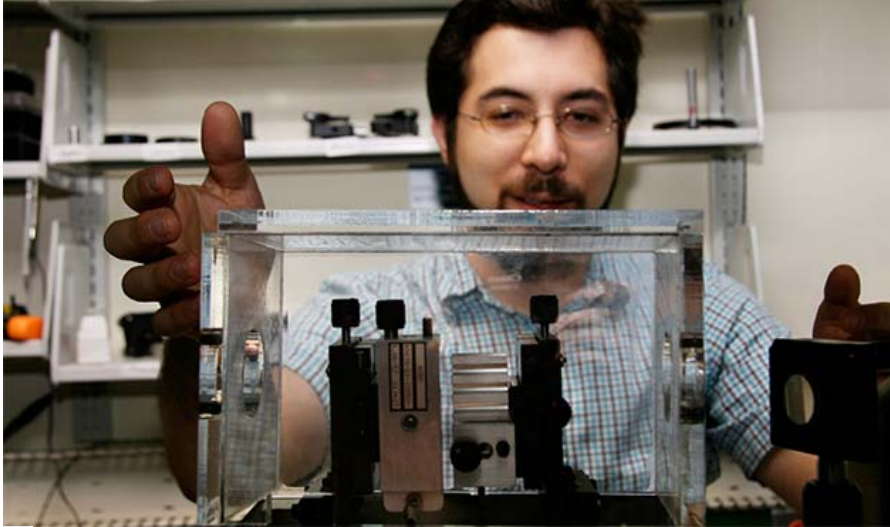
Rewiring the Brain: Inside the New Science of Neuroengineering

By Quinn Norton 2 second ago

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Dr. Boyden replaces a cover on sensitive laser equipment at the Neuroengineering and Neuromedia Lab at MIT.

Photo: Quinn Norton

First of two parts.

Dr. Ed Boyden is showing off his lab's equipment with naked delight. We've whizzed past a laser table, a 3-Dprinter and some rattling biological shakers, and come to rest beside a water cutter.

Boyden picks up a piece of scrap metal and demonstrates how the cutter uses a powerful stream of water and fine bits of garnet (nearly as hard as diamond) to slice precisely through almost any material. It can be used to build nearly anything. He pauses, and considers. "We're probably the only lab in the world that uses a water cutter to build neural interfaces."

Boyden directs MIT's Neuroengineering and Neuromedia Lab, part of the MITMedia Lab. He explains the mission of neuroengineering this way: "If we take seriously the idea that our minds are implemented in the circuits of our brains, then it becomes a top priority to understand how to engineer brains for the better."

Here, neuroscience is not merely studied, it is applied. Which is why we're off again, to see the molecular engineer's microscope, the viral growing area, and the machine where they cut micron-thin slices of mouse brains in order to evaluate what changes they've made using the rest of the equipment.

Human beings worked out a few thousand years ago that the brain is where the action is. Since then we've been trying to get it to do what we want it to.

Like a computer, the power of the brain arises out of how the many parts constantly and quickly talk to each other. But unlike the electrical circuits in a computer, brain cells aren't physically connected to one another. Neurons communicate across tiny empty spaces, called synapses, that lie between the tendrils of neuronal cell bodies. This almost-but-not-quite touching is what gives them such flexibility as those connections form and fade throughout our lives.

Most of what we think of as our ability to learn and change comes from the pattern of those synapses. In a way, history is the story of trying to manipulate those patterns through learning, faith, love, drugs, food, exercise -- in short, anything and everything. We have spent thousands of years working out indirect ways of changing the contours of our brains to change the shape of our minds.

Neuroengineers, on the other hand, take a pragmatic and direct approach. They are trying to change brains by going in and just changing them.

Boyden, a bespectacled professor with a soft smile, speaks rapidly and expansively. He has been a polymath all his life, plunging into one discipline after another. It's hard to imagine there was ever a time when he wasn't moving.

"Early in life, I wanted to be a mathematician," he says. He walked the path of the quantitative universe, studying math, then physics, then electrical engineering, trying to understand the universe -- trying to change it in precise ways. But it was birds and serendipity that brought him to the messy human brain.

"I decided to go to Bell Labs and learn lasers," Boyden says, "but the person I wanted to work with was going home to Germany, so I ended up working with his neighbor, Michael Fee, who was analyzing how the bird brain generated birdsong. That experience was my first work in biology or neuroscience." Boyden had a new all-consuming passion.

Not long after he found himself in the Stanford University lab of Dr. Karl Deisseroth, combining his abilities as an engineer with his new calling as a neuroscientist. There, Boyden was part of a team that invented a new way of controlling brain cells. Employing molecular biology, genetic engineering, surgery, fiber optics and lasers, they created a kind of "light switch" which was then used to control a group of neurons.

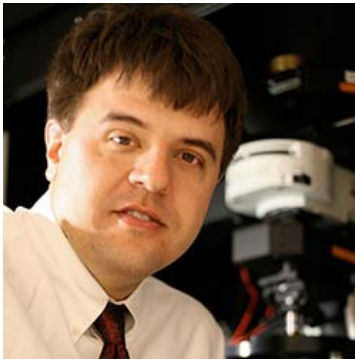
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Dr. Karl Deisseroth of Stanford's Deisseroth Lab with a powerful microscope used for molecular engineering. *Photo: Quinn Norton*
 How it works: The researcher modifies a harmless, non-reproducing virus to add genes to a particular type of cell, in this case a target type of neuron in a mouse.

The genes come from two sources: one from an algae, and the other from an archeon found only in the Sahara Desert. These genes respond to light either by switching the cell off or causing it to fire up. The archeon is as far from us as life on Earth gets. **Archaea** are unfathomably old: Our last common ancestor probably lived around 2.7 billion years ago. They are so simple they are nothing but single cells without a nucleus, but we are still relatives. We use the same system of genetic proteins and the same cellular mechanisms to read and act upon them. So if we take a bit of an archeon's DNA that responds to yellow light and transplant it into a nerve cell in the brain of the most sophisticated biological system on Earth, it just works: When stimulated with yellow light, the archeon's gene makes the nerve go quiet. The gene lifted from an algae, a distant but not-quite-so-distant relative, works in a similar way, except that it causes the cell to fire, which occurs when the gene receives a pulse of blue light. *Eureka*, the mechanics of a light switch: blue light to turn the neuron on, yellow light to turn it off. The next step is getting the switch into the brain. The body is good at killing viruses, so it's not simply a question of infecting someone with a brain control flu. The only way to get a virus like this into the brain is to put it there directly. Then there's the matter of getting the right colors of light past the skull and into the precise spot to be controlled. All of this means Deisseroth's team has to open up the mouse's head surgically, apply the virus to the desired area, then feed in a fiber optic cable that will continue to protrude out of the mouse's head after the surgery has healed up. Then they attach the fiber optic cable to lasers that can pump in the precise frequencies of light needed to control the cells. Once it's done, though, they have absolute control over the section of the brain involved. Fed into the left motor cortex, the area that controls movement, it could make someone dance to the right. Fed into the pleasure center of the brain, it could make someone happy with the press of a button. It's hard to tell if a mouse is happy, but attaching this system to its motor cortex makes a dramatic demo. Deisseroth, who is still developing this technology at Stanford, plays the video of a mouse wandering around its container. The fiber optic cable leading into its brain is barely visible until someone turns on the blue light. Then the animal runs to the left in large, almost perfectly circular loops. "You've got to wonder what he's thinking," Deisseroth muses. "It's I gotta go left, I gotta go left."



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The list of experts needed to get this done is daunting: various biologists, an ecologist, a geneticist, a neurologist, a surgeon, a laser physicist and -- whether they're invited or not -- a bioethicist or two. Making mice run in circles is one thing, but installing mood switches into human brains raises more consequential moral issues.

"If we surgically or electrically modify someone's personality... that raises many questions about personal identity, (of) who we are at our core," says Dr. Debra Matthews of The Berman Institute of Bioethics. "We place ourselves in the mind and therefore the brain. (Mood-altering surgery) feels like fundamentally modifying who a person is."

Matthews, herself a medical doctor and geneticist, says that application of this technology will be difficult, practically as well as ethically. "It's hard enough to translate what a drug is doing in a mouse to what it's doing in a human. This could be orders of magnitude harder."

Yet this is the very task of the Deisseroth lab, located deep in a basement at Stanford, down a perfectly white hall inexplicably streaked with jagged red neon. The lab itself is a jumble of metal bookshelves, crammed with weighty psychology and physics texts, as well as a place to display some whimsically personal touches: Pinned up against the end cap of one desk is a Sigmund Freud action figure, still in its box. Down the hall is the animal experimentation area, a quiet room filled with glass tanks and partitioned with black cloths hanging from the ceiling.

While Deisseroth studies the organ of the mind, he also seeks to strengthen it to resist its pathologies and moments of inadequacy.

"How surprising (it is), clearly we did not evolve to do calculus. Nothing in our evolution involved calculus and yet we can do it. Why is that? It just shows the fundamental versatility of our brain. That it's set up to do unanticipated things gives me hope," he says.

Deisseroth started as a regular engineering undergrad at Harvard. But his path took a twist when he took a class on neural networks. He was enchanted, decided he wanted to spend his life focused on the real neural network, and became a psychiatrist. Eventually, frustrated with the paucity of tools for working directly with the brain, he started building his own.

Deisseroth still spends one day a week seeing patients. In his practice he treats depression. Talking about their hopelessness darkens his otherwise ebullient demeanor. "I see the lack of (hope) in my patients.... I want to understand the biological underpinnings of (it)," he says. His clinical time gives his research a sense of human immediacy rare in academia.

However odd or uncomfortable the idea of engineering the human brain might seem, if yours is broken enough, the philosophical arguments cease to hold any water: You just want it fixed. Nowhere is this more true than for someone suffering from depression. For the most serious sufferers the condition transforms the natural dread of death into something like their only hope for peace, undermining the basic urge to survive. It's as confusing to understand clinically as it is to experience.

"Depression ... is where the brain substrate is all there but the mind is not coming through," says Deisseroth. "The neurons are ready to go, but the mind is not driving them right."

Antidepressants are commonly used for treating depression, but they're incredibly crude tools. Instead of precision engineering, these drugs are the equivalent of trying to build a bridge by piling up a lot of rocks. They go everywhere in the body and interact with everything. In order to get past the blood-brain barrier, psychoactive drugs often must be delivered in much higher concentrations into the blood, often causing unpleasant and dangerous side effects. When a drug does get to the brain, its effects are felt in all parts of the brain, including our mental faculties, our senses, even how we move -- not just the broken bits.

These problems severely limit what drugs are ever likely to accomplish, despite the hopes of the pharmaceutical industry. Worse, recent studies have shown [strong evidence](#) that anti-depressants [probably aren't even working](#) much of the time. That our drugs seem very advanced and specialized is only in comparison to the horror stories of the thiazine shuffle and *One Flew Over The Cuckoo's Nest*. Not only that, the drugs' side effects are so strange and inconsistent that they point to our bodies being far more individual than medicine is equipped to handle, and to our minds being far more complicated.

Deisseroth is blunt. "Not only do we not have a model for how our brains do complex tasks, we can't even imagine one."

Metaphorically, the neuroengineering approach brings the study of the brain into the Age of Enlightenment. By isolating, then testing and altering individual parts of the neural system, we can, for the first time, truly understand what those components do. Ultimately, we can enhance an individual function while leaving the rest of the system untouched. It's the same transition that let us move from alchemy to atomic physics. Boyden is trying to get his optical switch precise enough to fire a single neuron, the atomic unit of the mind. This is what makes the possibilities of neuroengineering so staggering. Its pioneers are bringing science and technology into a system basically unchanged since we climbed down from the trees.

Tomorrow: Dialing in happiness





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