Illuminating the Brain

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Shortly after starting his lab at Stanford in 2004, Karl Deisseroth began work on a technique that would revolutionize brain science. With graduate students Feng Zhang and Edward Boyden, over the next several years his lab developed optogenetics, in which light-sensitive proteins from algae are inserted into neurons, allowing researchers to precisely control neural activity with light. His next groundbreaking technique began as an effort with lab members Viviana Gradinaru and Charu Ramakrishnan to build polymers and hydrogels within brains, and was developed with postdoctoral fellow Kwanghun Chung into a method for rendering brains transparent but leaving neural structures intact. Called CLARITY, this technique offers researchers an unprecedented view of brain networks.

A member of the National Academy of Sciences and the National Academy of Medicine, Deisseroth is the recipient of numerous awards, including the Lurie Prize in Biomedical Sciences, the Keio Prize, the Dickson Prize, and the Breakthrough Prize in Life Sciences.

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Birth of a neuroscientist

When I went to college, I was pretty serious about exploring my creative side. In my first semester at Harvard I took a creative writing course. But at the same time, I became enthralled by biological science, particularly the linkages between computation and biology. I became extremely interested in biochemical computations—how the networks of signaling molecules work inside cells.

That interest broadened to neuroscience when I learned in an engineering class how the field of computational information processing and storage had influenced neuroscience in a bidirectional way. I was exposed to computational means by which you can use neuron-like programs—basically computational neural networks—to store information. At that moment there was no turning back.

The best-laid plan

Having decided that I wanted to understand aspects of how neural systems work, I thought, Well, I've got to study the most complicated one. That was the human brain. I decided to become a neurosurgeon because they had the best access to the brain. That meant I had to go to medical school.

In the third and fourth years of medical school, you do rotations and get exposed to different types of medicine. I was so sure I was going to do neurosurgery that that was the very first rotation I did, and I loved it. I enjoyed the operating room. I loved the impact you could make on patients' lives.

I also had to do some required rotations, including one in psychiatry. I was not looking forward to it. There were not many things I was sure I wouldn't do, but that was one of them. Then the time came when I had to do it, and it was transformative. It was fascinating to me that these patients' brains could work so differently but without a clear focus of something that you could point to that showed why: a lab test, a measurement, an image. The nature of the pathology is completely hidden. Right away I thought, This is it. This is where I should be.

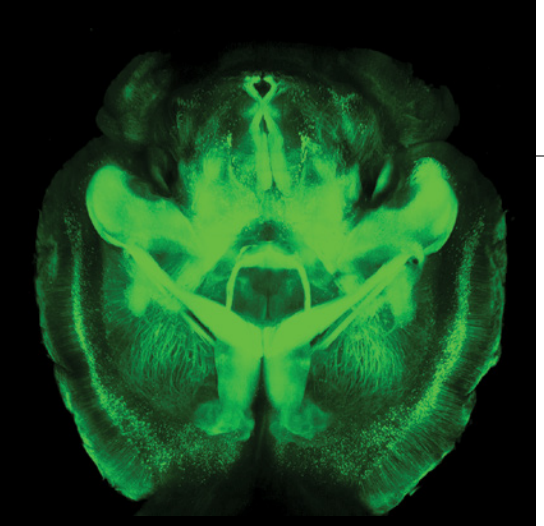
Beyond imagination

The human brain has a blood supply, ion channels, and metabolic needs, and all the things that make a complex tissue work. What really makes it special is how it creates emotions, perception, action; how it resolves dilemmas, stores information, and creates a unitary percept out of immensely complicated information streams.

There are so many incredible tasks that the brain has to do and problems that it solves, yet not only do we not *know* how they are done, we can't *imagine* how they are done. We cannot replicate those effects—that creation of emotion or affect, the high rates of information processing with fragile and low-power biological devices—in a computer. It is just amazing how the brain achieves these extremely complex cognitions and emotions and reality constructions from cells.

Shedding light on neural circuits

How do you understand the causal significance of what a cell or a group of cells is doing? That is really the heart of understanding how the brain works. You can look at brain imaging, and you can image blood flow during behavior with MRI, and you can put electrodes in to hear the action potentials that neurons use to communicate. But you don't



A mouse brain rendered transparent by CLARITY

really know what is actually causing anything to happen.

Even though neurons are electrical, there are no effective ways to selectively stimulate one cell type but not another cell type with an electrode. That had held back basic neuroscience, and psychiatry, too. So what I and many other people around the world had hoped to do was to find a way to get specific control of specific cells. This would help us understand how neural circuits give rise to behavior.

After launching my independent lab at Stanford, I carried out a very humble experiment. On July 1, 2004, I inserted a gene for a light-sensitive protein borrowed from an algae into neurons in a dish. I then found that when those neurons were stimulated with light, they responded with a marker of neuronal activation. That finding got people excited and triggered more experiments over the next few years, as my lab engaged in building and testing all the components of what became known as optogenetics.

Neural frontiers

It was really rewarding to launch that effort because not only has it helped us answer some of the questions that got me into neuroscience in the first place, but so many thousands of labs have now used these methods. I have been able to send these tools to people all over the world, and they are doing experiments that I never could have dreamed of.

In my own lab, we have found ways in which the brain is able to turn off fear or anxiety responses. We found a pathway that had not been known to exist but that appears to be a very powerful means by which the brain can regulate (by turning down) fear and anxiety behaviors. For me as a psychiatrist, that was extremely interesting because we know that some of the most effective therapies for fear- and anxiety-related diseases—PTSD and others—are not medications but cognitive therapies, ways in which you teach patients to use their thoughts to turn down fear and anxiety responses. Using optogenetics and other methods, we have found what may be the physical pathways by which those high-level cognitions are able to exert their influences on the very subcortical—or deep—fear- and anxiety-generating circuits.

From clinic to lab and back again

I still do inpatient and outpatient work as a psychiatrist. It is very valuable for me to be able to share with students what the patients are really like: This is what really matters to a fearful, anxious patient. This is what really matters to a depressed patient. This is what an autistic patient's social dysfunction is like; this is how it looks and feels. That directly helps us guide our work.

That flow of information between the clinic and lab is very powerful. People are already successfully using optogenetically derived ideas to help patients. Last December there was a finding on how to potentially treat cocaine addiction using ideas that came from optogenetics. It was an early-stage pilot study using a non-invasive brain stimulation treatment called transcranial magnetic stimulation, or TMS. The researchers guided the TMS delivery based on optogenetic findings on the neural circuits that regulate cocaine-seeking behavior in rodents. People are also using optogenetic concepts to decide how to best place deep-brain stimulation electrodes. I think we are going to see more and more of that as time goes on.

Growth in all directions

When I was young I certainly had some difficulty thinking about all the things I was interested in and all the things I felt I was good at. Picking a direction seemed to mean sacrificing something. I would encourage kids to keep growing all these different parts of themselves, all the capabilities of their brains. Don't get too focused too soon. Keep growing in all the ways you want to grow.

These interests are eventually going to come together; they will help each other in the future in ways you can't imagine now. You won't have to give up something you don't want to give up. In fact, you will find that things may fuse in interesting and exciting ways. ■

Learn more about **Karl Deisseroth** and his research at these sites:

- http://web.stanford.edu/group/dlab
- www.optogenetics.org
- clarityresourcecenter.org
- www.nytimes.com/2013/04/11/science/brains-as-clear-as-jell-o-for-scientists-to-explore.html
- www.newyorker.com/magazine/2015/05/18/lighting-the-brain
- www.youtube.com/watch?v=L3bSx4TBs6M
- www.youtube.com/watch?v=c-NMfp13Uug