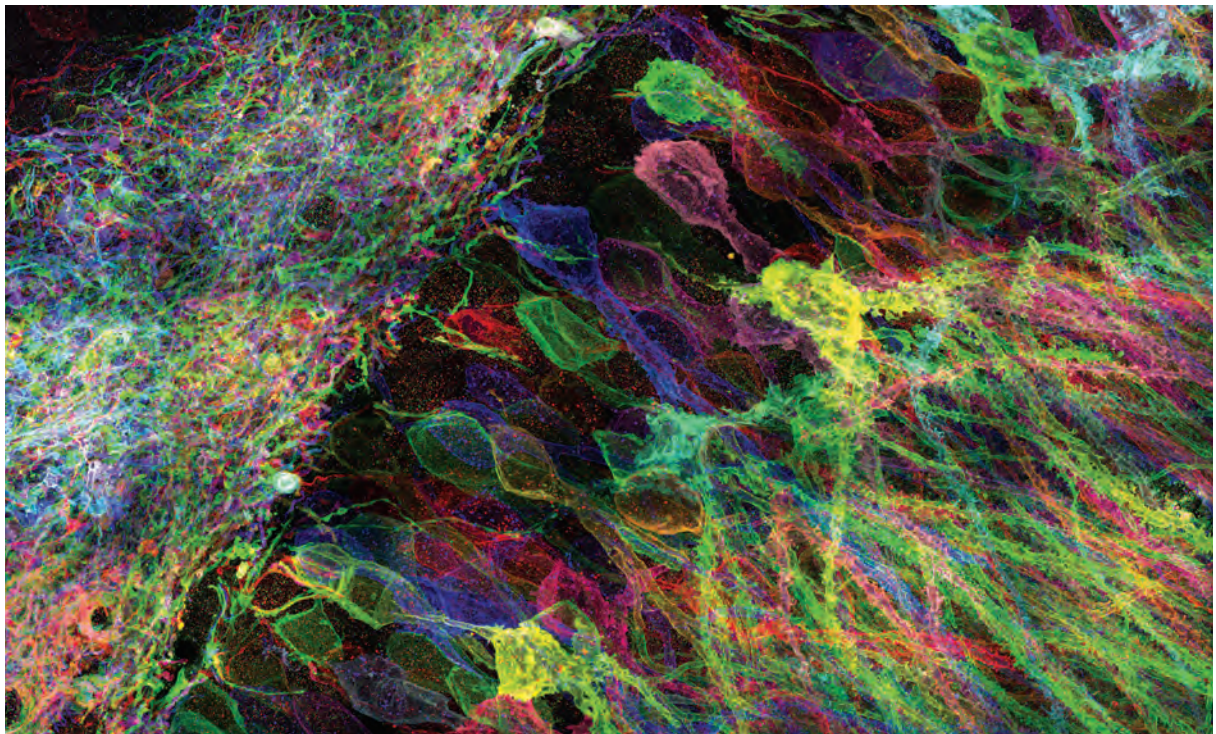


Shedding light on the mind

Ed Boyden has pioneered three transformative technologies for studying the brain. He tells **Clare Wilson** how these will help us to discover what thoughts and feelings are really made of



FEI CHEN, DANWEN CAI, ED BOYDEN, MIT

THE brain is a complex network of some 86 billion neurons. To find out how they operate, we need to be able to record the activity of these cells. That is why the methods developed by neuroscientist Ed Boyden are so crucial. His breakthrough came in 2004 when, as a graduate student, he flashed a blue light at a nerve cell to see how it would react. Instantly, it fired. This was the birth of optogenetics, a technology that has revolutionised the study of brains and behaviour. We caught up with him to find out more.

What is the ultimate goal of your brain studies?

I have a deep desire to understand what it means to be human – the meaning of our

thoughts and feelings. That is really what motivates me to get out of bed in the morning. This is something I have been obsessing about for many years, ever since I was a kid.

That is pretty ambitious. How will optogenetics help get us there?

Optogenetics involves putting new genes into brain cells to let us turn them on and off with light. Light has the unique advantage that you can really focus it down, even to individual cells. In 2017, along with Valentina Emiliani's group at the Vision Institute in Paris, we activated individual cells with 1-millisecond precision in an intact circuit in a slice of living brain tissue.

What else are you working on?

A technology that is the opposite of optogenetics in a way. Instead of sending light into the brain to trigger neurons to activate, or fire, we make neurons glow when they fire. This is called voltage imaging. It lets us watch the brain as it computes, with the precision of looking at individual brain cells.

Another of your technologies, expansion microscopy, is really different. It makes brain tissue physically bigger so you can see it better. What made you think of that?

I was brainstorming with one of my postdocs about the fact that in a neuron, all the molecules are jam-packed together. What if

Expanded brains

Brain circuitry can be visualised in unprecedented detail by using a swellable gel and fluorescent tags – techniques developed by Ed Boyden

you could separate them and make enough room to label them with visible molecules?

Almost as a joke, we started thinking maybe we should blow the brain up. Later, together with two fantastic graduate students in the lab, we started reading lots of papers on “swellable” polymers. We figured out a chemistry that worked.

We use basically the same kinds of polymers that you find in diapers, which absorb a lot of water. The idea is you inset the subunits of the polymer into the cells. Once in there, they form links and turn back into the diaper polymer. Then, when you add water, the polymer, and thus the brain, expands.

What have you discovered with the technique?

In 2019, we combined this technique with a kind of microscopy that takes advantage of the fact that when you expand something, you fill it with water and it becomes transparent. That means you can take a series of 2D pictures at different depths, blazingly fast, to create a 3D scan. This microscope is called the lattice light-sheet microscope.

How do these brain analysing technologies connect with each other?

These are all part of a 50-year plan that I have long been thinking about, to actually solve the brain. The idea is, we use expansion

microscopy to make a map of the brain, use voltage imaging to see activity throughout the brain and use the optogenetic tools to perturb the brain activity.

Then, we combine these three data sets to make biologically accurate models of how brains compute. I hope we can understand what thoughts and feelings really are.

Could you use this to investigate the nature of consciousness?

We still don't have a way of measuring consciousness. We are just at the beginning of this multi-decade quest. I'd argue that if you could understand the processes in the brain that occur during or before the generation of a conscious state, that would at least tell us something about how consciousness arises.

Does it tell you what consciousness is? I think we would have to do the science and understand what the process of generating consciousness is like before declaring victory. Even if we could measure the neural correlates, that is not the same as quantifying an actual conscious experience.

Can the expansion technique be used to investigate neurological disorders too?

Yes. In collaboration with Eric Betzig's group at the Howard Hughes Medical Institute – who invented the lattice light-sheet microscope – we mapped out how myelin varies in different cell types. Myelin is really important for nerve conduction and it goes wrong in diseases like multiple sclerosis.

“Almost as a joke, we started thinking maybe we should blow the brain up”

We were also able to look at the shapes of all the cells of a single type, dopamine-releasing cells, in a fly's brain. Dopamine is important for learning and memory, reward and addiction, and also in Parkinson's disease.

Another group has used expansion microscopy to look at human epilepsy brain specimens, removed during surgery. They were expanded to analyse the changes in the brain that occur in people who have seizures. We are also investigating other brain disorders



Ed Boyden is a neuroscientist at the Massachusetts Institute of Technology who pioneered optogenetics, a technique to switch brain cells on and off using light

like Alzheimer's and brain cancer. Such images might yield better treatments by helping us understand the disease better.

What else can you use it for apart from blowing up brains?

Another application is in early disease diagnosis. Early detection is hard to do for many diseases, because the changes are so subtle. But by expanding a biopsy, our hope is to bring the invisible early signs of disease into the large-scale visible realm. In 2017, we showed this could be helpful with breast cancer and kidney disease. I co-founded a company to explore this area.

Have you made any progress in treating disease yet?

Li-Huei Tsai at the Massachusetts Institute of Technology has been using our optogenetic tools to discover patterns of brain activity that can help clean up Alzheimer's-like symptoms in a mouse. If you can stimulate brainwaves at the right frequency, it boosts the activity of cells that clear away toxic proteins such as amyloid.

Her team, with our help, went on to find that if you play lights and sounds in the right pattern, you could stimulate these same brainwaves, which actually halt the degenerative process of Alzheimer's, in mice.

Li-Huei and I co-founded a company that is running human trials of lights and sounds delivered at this frequency, to see if we can treat Alzheimer's disease. It is too early to reach any conclusions yet, but our hope is that we can do something that is very efficacious, but also very accessible. What could be cheaper than a movie? ■

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