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Interview with Edward S. Boyden

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Dr Ed Boyden is Associate Professor at the MIT Media Lab, where he leads the Synthetic Neurobiology Group. He also holds joint appointments in the Department of Biological Engineering, the Department of Brain and Cognitive Sciences, and the McGovern Institute at MIT. He holds Bachelor and Master's degrees in physics, electrical engineering, and computer science from MIT and a PhD degree in neuroscience from Stanford. Dr Boyden, collaborating with Karl Deisseroth and colleagues, reported on utilization of the light-gated cation channel channelrhodopsin-2 to make neurons controllable by light in 2005, which opened new doors for experimentation in neuroscience. Since then, Dr Boyden and his laboratory have continued to research and refine optogenetic tools and to develop other technologies for analyzing and engineering brain circuits. He has received numerous awards and honors, including the inaugural A.F. Harvey Prize (2011) and the Perl/UNC Prize (2011).

You have a broad background in the sciences, including three degrees in physics and electrical engineering. How did you become interested in neuroscience?

I have always been a philosopher at heart, wondering about the nature of thought, how the universe came to be, how consciousness arises. Some of my first research experiences were in chemistry, working in Paul Braterman's laboratory at the University of North Texas on experiments probing the origins of life. We were trying to see if the building blocks of DNA could emerge from inorganic materials intercalated in layers of clays that might have existed in the early ocean. Of course, we did not create life, but I learned a lot about chemistry and also acquired a taste for high-risk, high-payoff research. Later I trained in physics and electrical engineering at MIT; I loved physics for the intuition it yielded about the nature of the universe, and electrical engineering for the ability to build devices and analyze signals. Around the time I was completing my Master's degree in electrical engineering, working on autonomous robot submarines, quantum computers, and other projects at MIT, I got interested in the development of tools for neuroscience. I spent time at Bell Labs, then arguably one of the capitals of technology development for brain analysis, and where lots of physicists worked on such problems; it was great! There was so much need in neuroscience and so much opportunity to invent technologies to help solve the mysteries of the brain.

Optogenetic tools are revolutionizing the questions that can now be addressed experimentally, not just in the neurosciences but also in other areas of biology. Did you foresee the potential of this technology at the time you started developing it in collaboration with Karl Deisseroth at Stanford and Georg Nagel at the Max Planck Institute for Biophysics?

When Karl and I started the collaboration with Georg – who co-discovered the channel nature of the channelrhodopsin-2 (ChR2) protein, along with Ernst Bamberg and Peter Hegemann – in early 2004, it was clear that it could be used to control many things. In the original study published by Georg, Ernst, and Peter (*PNAS*, 2003) that reported the discovery of ChR2, they had already expressed it in human cell lines and showed that they could control the voltage of mammalian cells, remarking on its potential as a tool for biologists. Karl and I had brainstormed about applying opsins to neurons back in 2000, and we even started collecting opsins back then, when we were both students. It was clear that if we could insert ChR2 into specific neurons embedded within a complex network, and if the protein was expressed and functioned with the right speed and magnitude of photocurrent, then we could turn those neurons on with light. We brainstormed about the things you could do with it – two-photon neural activation, control of the heart, control of hormone release – and a lot of those ideas ended up in the series of patent applications that Karl and I filed at Stanford on various uses for ChR2. Karl and I tried out the gene in the summer of 2004, and it worked on the first try, resulting in light-driven action potentials in cultured mammalian neurons. I was a graduate student in the laboratories of Dick Tsien and Jennifer Raymond at the time we started collaborating, so we obtained the first light-activated spikes on my old rig in Dick's laboratory.

Can the technology be adapted for clinical use? If so, what disorders do you think it would be most beneficial for treating?

There is a lot of excitement about potentially using optogenetic technologies for fixing the neural circuit changes associated with intractable brain disorders. Over a billion people suffer from a brain disorder and many cannot be treated, and most of the treatments that do exist are partial and have side effects. Therefore, one appealing idea regarding optogenetics is that you could activate or silence exactly the set of cells that would repair a brain disorder, leaving nearby cells unaffected. Of course, for this to work, you have to have some circuit rationale, deep scientific knowledge of which cells to go for. In addition, there should not be competitive approaches using more traditional means, because optogenetic therapy would be

a gene therapy and thus has more hurdles to overcome from a safety and regulatory standpoint than other kinds of treatment. For disorders such as photoreceptor loss blindness, in which the cellular and circuit nature of the disorder is well defined and for which there are few alternatives, there is a lot of excitement. Many blind patients have lost photoreceptors, but the rest of the retina is relatively intact. By making specific spared cells within the retina sensitive to light, in animal blindness models you can restore vision to some extent. We are collaborating with several groups seeking to develop such treatments.

You have recently been awarded the inaugural A. F. Harvey Engineering Research Prize. Have you had a chance to consider how you will use the research funding (£300,000) associated with this prize? Will your laboratory continue to develop novel optogenetic tools or are you excited about heading in a new direction?

We are continuing to pursue more powerful optogenetic tools, as well as optogenetic tools that exhibit novel scientific capabilities (e.g., different-colored activator molecules, non-invasive neural silencers, and other new kinds of optogenetic tool). My group is also entering new areas, such as the creation of new electrode technologies for reading out large-scale neural activity with great precision in an automated fashion. For example, we recently published a paper in collaboration with the laboratory of Craig Forest at Georgia Tech on the automation of one of the most precise and informative techniques in neuroscience, whole-cell patch clamp recording of neurons in live mouse brain (*Nat. Methods*, 2012). With our robot, it is possible to record synaptic events even in sets of neurons in the living brain, allowing new insights into how circuits work. We are also working on closed-loop 3D light delivery systems with Clif Fonstad's microfabrication group at MIT, which might allow testing of theories of neural coding, and might also support ultraprecise neural prosthetics for entering information into the brain.

Besides optogenetics, are there other recent technological developments that have stood out to you as being particularly significant for neuroscience?

It seems that new technologies to confront neural circuits fall into two categories: ways to observe and perturb the millisecond-timescale dynamics, and ways to observe and engineer the wiring and structure. In the first category, genetically encoded sensors for reading out cellular calcium and voltage with light are certainly opening up new frontiers in neural recording. Recently, in collaboration with Konrad Kording, George Church, and Keith Tyo, we published a brief study (*PLoS ONE*, 2012) that explored whether this could be extended to the direct recording of calcium signals into strands of DNA, enabling neural activity to be analyzed via biochemical means. In the second category, tools for large-scale determination of neural circuit wiring, such as tools for serial-section electron microscopy that are starting to yield connectomic data, will help to reveal how circuits are wired up. Arguably, one of the areas that needs innovation is how to connect these two lines of inquiry, to enable researchers to observe and control the real-time neural dynamics of the brain, and then to extract the circuitry and wiring that generated those dynamical patterns. That is going to be a very interesting area in the coming years.

You have launched a series of classes at MIT that teach principles of neuroengineering, including the basics of how to control and observe neural functions, as well as strategies for launching companies founded on neurotechnology. Is there a particular lesson that you have learnt from these classes, either from the students or the teaching process?

One thing that I have learned is that revolutionary ideas for neurotechnology can come from almost any discipline, so bringing new disciplines into neuroscience needs to be a constant endeavor. Of all the engineering disciplines that humans have created – resulting in new materials, devices, molecules, chemicals – most have not been applied to neuroscience. Thus, a collaborative network willing to work together to create new technologies and utilize them is essential. You might call neuroengineering an omnidisciplinary field of endeavor.

What advice would you give to someone who is just starting their independent scientific career?

I would make two suggestions. First, never make assumptions. In science you often hear of Occam's razor, the idea that the simplest explanation is most likely correct. This might be true for physics. But in the brain, I think we have something different going on. I like to call it Occam's sledgehammer: for the brain, the most complex and messy hypothesis is probably true, at least in some circuit in the brain of some species.

Second, learn how to learn new things rapidly and to be able to synthesize new ideas rapidly. I was lucky to have trained in chemistry, then physics and electrical engineering, and then neuroscience; having those multiple perspectives is very helpful, because they help me work across boundaries. In the post-internet age, having the ability to synthesize new ideas out of multiple solution spaces towards solving a problem is essential.

Do you have a scientific hero?

I think a lot about the physicists who, launching from the concrete and comfortable safety of equations and atoms, turned to the ambiguity and messiness of biology in the first half of the 20th century, and then bravely plowed in. The book *Time, Love, Memory* by Jonathan Weiner describes a lot of these people and how they tried to extract the principles of life. They obtained the structure of DNA, the architecture of the gene, the triplet genetic code, and so forth. It is inspiring to think about how we might soon be able to do such things for the brain, empowered by new technologies and perspectives.

Disclaimer statement

E.S.B. is the co-founder of Eos Neuroscience, a company working on developing a treatment for blindness using optogenetic approaches.

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