

BEYOND THE BENCH

Beyond the bench: A conversation with Ofer Yizhar

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Ofer Yizhar photographed war zones before he ever imaged a mouse brain.

Today, the former documentary photographer in the Israeli army is professor of neurobiology at the Weizmann Institute of Science in Rehovot, Israel, where he builds tools — such as engineered proteins and neural probes — to **manipulate and monitor neural circuits** using pulses of light.

Yizhar works at the forefront of a type of neurotechnology called **two-photon optogenetics** that enables researchers to stimulate and monitor neural circuits at the same time, **including in moving mice**. He uses this technology to study the neural circuits underlying autism and other complex conditions.

Yizhar became fascinated with neural engineering as a doctoral student at Tel Aviv University after reading a paper that discussed how to **manipulate neurons in a fly** using chemicals and light. By 2008, he was creating optogenetics tools to do the same in the mammalian brain during a post-doctoral fellowship in **Karl Deisseroth**'s lab at Stanford University in California.

Yizhar spoke with *Spectrum* about the books that kickstarted his interest in neuroscience, his long runs through the desert and how he outlines scientific papers to tell a story.

***Spectrum*: What did you do before you became a scientist?**

Ofer Yizhar: I was sure that I was going to be a professional musician when I was in high school. I was a music major and played piano for many years — still do, but much less than I want to. Things changed for me, though. I went to the army for three years, because Israel has mandatory service, and I was less certain that music was right for me after that. Instead, I became a documentary

military photographer in the army.

After leaving the army, I kept working as a photographer for some time and was certain that I'd be a professional photographer for the rest of my life. But then I got fed up with that, too. My interest in neuroscience began after I read two books, and a friend mentioned that there was a new kind of undergraduate program at the Hebrew University of Jerusalem for combining psychology and biology. That's how I got into neurobiology when I was about 23 years old.

S: What were the two books?

OY: One is “The Man Who Mistook His Wife for a Hat,” by Oliver Sacks. That really caught my imagination — how the brain perceives the world, and how changes in the brain's networks can lead to behavioral changes. The other book is by an Israeli scientist, **Peretz Lavie**. It's called “The Enchanted World of Sleep.”

S: What ‘big question’ drives your research?

OY: For the past 15 years, I've been interested in optogenetics. Part of my group works on creating new tools for manipulating neural circuits. Specifically, we are improving techniques for manipulating the brain using light and genetic engineering, and we aim to use these techniques to address unmet needs for neuroscientists.

Another part of my group is using these optogenetics tools, along with behavioral analysis and brain activity recordings, to understand the mechanisms that govern complex behaviors such as social behavior, learning and decision making, and to try to understand the circuits that mediate these behaviors. We've been focusing a lot on the **prefrontal cortex**, which is involved in **learning** and **social behaviors**, because we understand few details regarding how these processes are achieved. What kinds of neuron populations drive what kinds of behaviors? How do changes in the **connectivity of these neuron populations**, or changes in their dynamics, lead to changes that are associated with psychiatric and developmental conditions such as autism?

S: Whose work do you admire?

OY: The earliest experiment that really inspired me to build tools for manipulating neural activity was by **Gero Miesenböck** at Oxford University in the United Kingdom. He published a paper in 2005 in which he engineered an elaborate system to **modify neural activity in flies**. It was kind of like optogenetics but required that substances be injected into the brain. He injected flies with molecules that, when combined with a receptor, could be used to modify the activity of an ‘escape’ neural circuit in the fly. So when he flashed light on these flies, they would flap their wings because this ‘escape’ circuit was being triggered by the light. That paper blew my mind and ignited my interest in doing neural engineering. I want to advance the technology to a point where we can easily influence or modify the activity of circuits in the brain so that we can 'reverse

engineer' its circuits and understand them better.

Miesenböck's technology didn't really work for mammals, though. But **Karl Deisseroth**'s lab published a paper about **channelrhodopsin** proteins that could be engineered into cells, stimulated with light and used to activate neurons. That kickstarted optogenetics, and it was clear to me that this would be a more feasible approach for manipulating the mammalian brain. That's what pushed me to contact Karl and ask to do a postdoctoral fellowship with him. Karl is definitely one of the scientists I admire, and that's one of the reasons I joined his lab in 2008.

I also really admire the work of **Bernardo Sabatini** of Harvard University, who studies how neural circuits form and change over time, and **Leslie Vosshall** of Rockefeller University in New York City, who works on mosquitoes. They're both doing amazing, brilliant work. I'm always inspired by people who are very multidisciplinary, who step out of their comfort zone and create new methods to ask new kinds of questions.

S: Do you have hobbies that help you think through work problems?

OY: My hobbies mainly make me not think, or think less, about work. I especially enjoy running. Over the past decade, I've been running a lot, and training for marathons and ultramarathons. I run a little bit almost every day, typically in the mornings because in Israel, in the summer, you have to get out early to escape the heat. I used to play the piano more than I do now. In the past year, because the house was always full with my kids, who were stuck at home due to COVID-19, it's been hard to find the quiet time for music, but I also find myself more engaged by the simplicity of running.

S: Where do you like to run?

OY: My favorite area, in general, is the desert. It's amazing. If you are there at the right time, there are really incredible places to see. It's completely quiet. You can run for hours without seeing anybody. That's a major plus in such a dense and crowded country. For my weekday runs, I usually stay around my city and go for 10 to 15 kilometers (6 to 9 miles). On the weekends, I usually meet up with a friend or two and we run in the mountains near Jerusalem.

S: What does a typical day look like for you?

OY: In the summer, which pretty much runs from about May to November in Israel, I get up at 4:30 or 5:00 a.m. and go out for a run by 5:30. I finish by 7:30, take a quick shower, send the kids to school and sit down at the computer to do 'deep work.' It's this concept, based on a book with the same name, that talks about how the modern world prevents us from taking time to deeply reflect and focus on tasks. The book explains how to avoid interruptions and manage your time, basically.

So, I use this 'deep work' time to write papers or grants, or to think more intensely about problems that I'm facing. I shut down my email, my messaging, my phone. After 11:00 a.m., the world starts banging on the door. In the afternoons, I talk to people, meet with students and go to all kinds of meetings. Typically, I head home by 6:00 or 7:00 p.m., hang out with my family and go to sleep early.

S: What's on the whiteboard behind you?

OY: We use the whiteboard to storyline papers. I like to think visually, so we print out all the figures or figure panels in a study, hang them up on the whiteboard with tape and plan out the structure of papers.

S: Are there any jokes from the lab that you can share?

OY: I had two people named Mathias (Mahn) and Matthias (Prigge) in the lab. They were both German, both fantastic and both very tall. My lab manager, who's a bit shorter, would ask them for help reaching things on the higher shelves. After Mathias and Matthias left the group, we bought a lab stool so that the lab manager could reach everything. We named the stool Ma(t)thias.

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