Optogenetics Pioneer Karl Deisseroth Meets his Latest Challenge: Writing a Book

By Grace Huckins

The recent history of neuroscience might reasonably be divided into two epochs: before optogenetics, and after optogenetics. By cleverly leveraging a protein typically found in algae, optogenetics techniques allow researchers to stimulate particular groups of neurons simply by shining a light on them. They've allowed neuroscientists to trigger specific memories in mice, manipulate relationships among prairie voles, and make mice perceive scents that don't actually exist, among thousands of other scientific achievements. And though it took the efforts of countless scientists, spanning over a century, to make the approach a reality, there's one name everyone associated with it: Karl Deisseroth.

Deisseroth is a professor of bioengineering and psychiatry at Stanford, where he helms an enormous laboratory that continues to push the boundaries of what optogenetics can do. He recently won a Horwitz Prize and a Lasker Prize—seen as bellwethers for the Nobel—for his central role in the development of optogenetics. And somehow he still finds time to work as a practicing psychiatrist, specializing in autism and mood disorders. Microscopic proteins and human minds might seem quite disparate foci around which to center one's work. But Deisseroth doesn't see himself as pursuing two separate careers. He attacks the problem of psychiatric illness from two sides, working to understand the biological roots of mental illness as he contends with its effects on the lives of his patients.

Lately, Deisseroth has put on a third hat, besides those of the researcher and the psychiatrist: that of the writer. In 2021 he published *Projections: A Story of Human Emotions*, a work of literary non-fiction described as an "enthralling masterpiece" by Nobel Laureate Robert Lefkowitz. In the book, which is aimed at the general public, Deisseroth weaves together the threads of genetics, neuroscience, and mental health and draws heavily on his career and personal history. As accomplished as Deisseroth is, he faces this new venture with some trepidation. "I felt very vulnerable last year when it was coming out," Deisseroth said, in conversation with Angela McIntyre at Stanford's eWear Symposium in September. "So actually, it's a relief every time somebody says it wasn't a total disaster."

The book functions, in some sense, as an argument for Deisseroth's bifurcated career—in each of its chapters, he knits together optogenetics research and clinical anecdotes to tell the story of a particular dimension of human emotional life. This integrative thesis is present even in the book's title, which Deisseroth described at the symposium as a "sort of triple entendre."

Projections can refer to the psychological phenomenon of projection, in which someone attributes their own emotions to someone else, but the title also references the axonal projections through which regions of the brain communicate with each other. And the title implicates genetics and evolution as well, Deisseroth said, because the development of those brain projections is choreographed by genes, an influence that projects across the history of humanity. (The downside of this clever titling, Deisseroth said, is that it made translation extremely difficult.)

The relevance of brain projections to psychology was clear when Deisseroth discussed his research on anxiety. By cleverly deploying optogenetic techniques, Deisseroth and his colleagues had demonstrated that three separate projections from the same brain region—the bed nucleus of the stria terminalis—independently control three different components of anxiety. One pathway increases your breathing rate, another makes you act more conservatively, and a third makes you feel bad. In *Projections*, Deisseroth illustrates this astonishing separability with the case of "Mateo," a patient of his who had recently lost his wife but could not manage to cry. Crying, too, Deisseroth suggests, is importantly separated in the brain from feelings of sadness. At some point in our long history, through a small change in the brain's pathways, crying became a common part of the experience of grief. But it's not universal, and it's not intrinsic—it all comes down to the brain's projections.

After discussing his anxiety research, Deisseroth spoke in more detail about a patient of his, "Charles," who is autistic and struggles with anxiety. Through months of treatment, Deisseroth was able to help Charles resolve much of his anxiety, but as he did so he noticed something unexpected: As much as Charles's condition had improved, he was still unable to look Deisseroth in the eye for any significant period of time. "I was stunned by this disparity," Deisseroth said. When he asked Charles about this, he learned that Charles wasn't avoiding eye contact out of anxiety; rather, he found it too difficult to process Deisseroth's changing facial expressions while also maintaining a conversation.

This observation, too, seemed to Deisseroth to be rooted in neuroscience. Some neurons are excitatory—they make other neurons more likely to fire—and some are inhibitory, and all brains need to maintain a balance between this excitation and inhibition. In autistic people, Deisseroth said, that balance may work a bit differently, which might make it difficult for them to process incoming information quickly. On the other hand, he noted, that imbalance may confer some cognitive advantages. Deisseroth is interested broadly in the ways in which psychiatric states can be advantageous—in the symposium, he related a story from his undergraduate years in which, after a mugging, he experienced a temporary state of increased energy. While in that state, he said, his mood was elevated, and he needed less sleep. He drew

a connection to mania. “It made me think, is there a hidden logic to some of these states?” he said.

That logic could explain why some conditions are so common across the human population. Deisseroth connected psychiatric states like mania to sickle cell anemia, a disease caused by having two copies of a mutation that, when present only once, protects against malaria. Similarly, he suggested, the advantages of occasional manic states could have evolutionarily favored some genes that can also lead to conditions like bipolar disorder.

As a clinician, Deisseroth doesn’t just seek to resolve these puzzles about neurobiology and evolution and mental illness—he also aspires to contribute to novel treatments. For him, developing better treatments for mental illness will require bridging the scales of neurons and entire brains, as he has worked to do in much of his career and in the pages of *Projections*. “We don’t really understand those big questions yet,” he said. “But once we understand those, that opens the door to treatment.”


Prof. Karl Deisseroth, Stanford U.

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