The ‘storm in their minds’: How the gap between laboratory insights and clinical analysis is narrowing

When someone close to you develops signs of mental illness, you spring into detective mode. You ask questions, but the answers seem vague and incomplete. You scour your memory for any years-old signs, any warnings that might have seemed innocuous in the moment but raise red flags in retrospect.

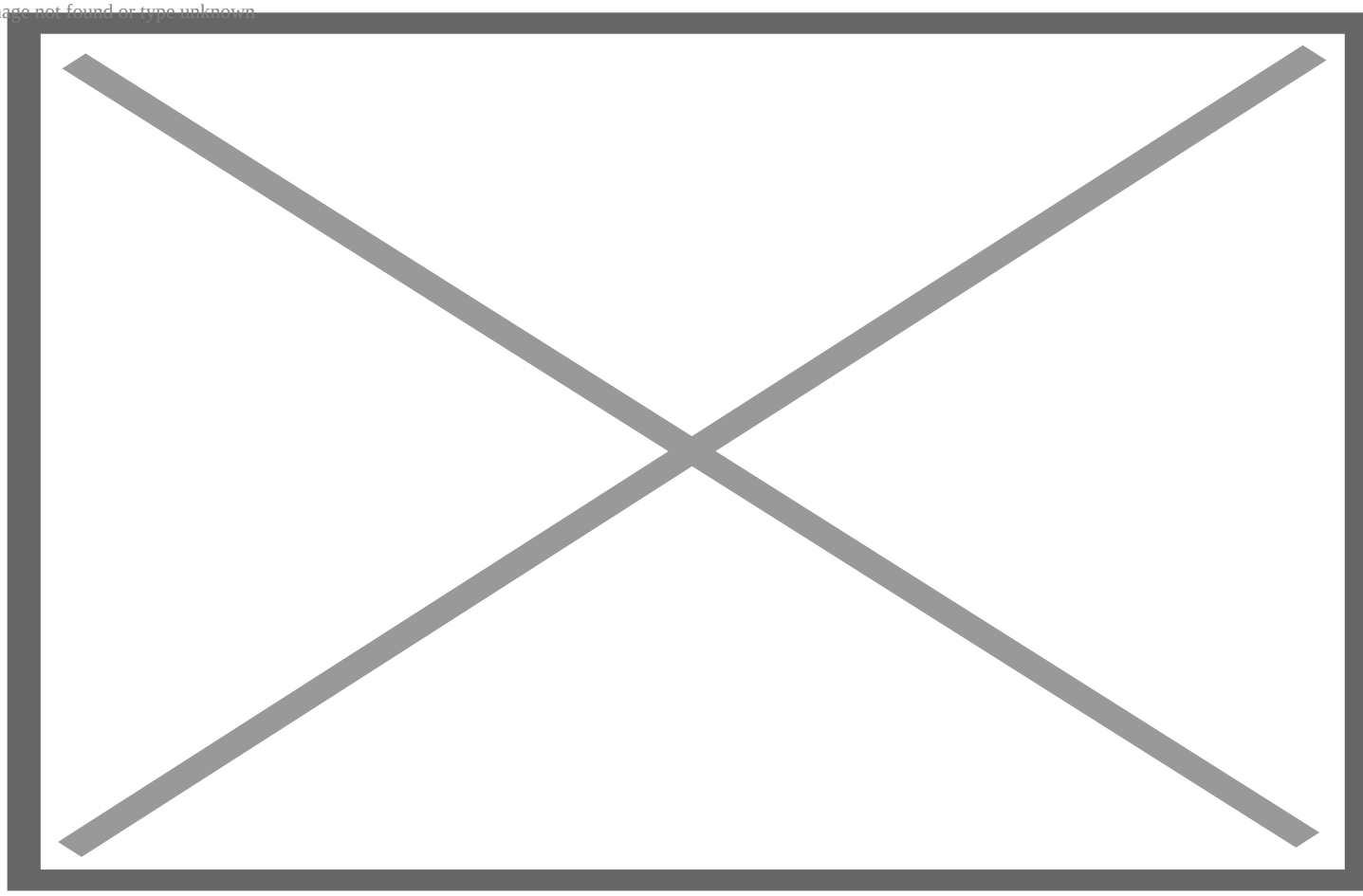
You wonder: If anyone had noticed then, would things be different now? And if they refuse to seek treatment, you think, it doesn’t have to be this way — if only you could figure out how to break through.

If this sounds familiar, you might be interested in “Projections: A Story of Human Emotions” by Karl Deisseroth and “A Sense of Self: Memory, the Brain, and Who We Are” by Veronica O’Keane, two recent entrants in the vast arena of nonfiction books that explore both the biology of mental illness and how the brain works in general. Both authors use patient stories as conduits to talk about advancements in neuroscience, illuminating the brain’s various structures and the connections between them.

Patient narratives across both books show that not all who receive psychiatric treatment survive the storm in their minds, while others regain a sense of themselves that was lost. And though scientists may be inconceivably far away from revealing how a 3-pound fatty organ in the skull gives rise to all the complexities of mental life, at least the questions “can be well posed,” as Deisseroth puts it.

Deisseroth, a professor at Stanford University, is best known for developing new and influential technologies for studying the brain. But in this book he draws from his work as an emergency psychiatrist at a hospital in Silicon Valley, and explores how confronting people in crisis influenced the way he investigates the brain in both humans and animals, potentially laying the groundwork for future clinical treatments. It “is enthralling to consider: the experiences of suffering human beings, and thoughts about mouse and fish brains, are informing each other,” he writes.

Image not found or type unknown

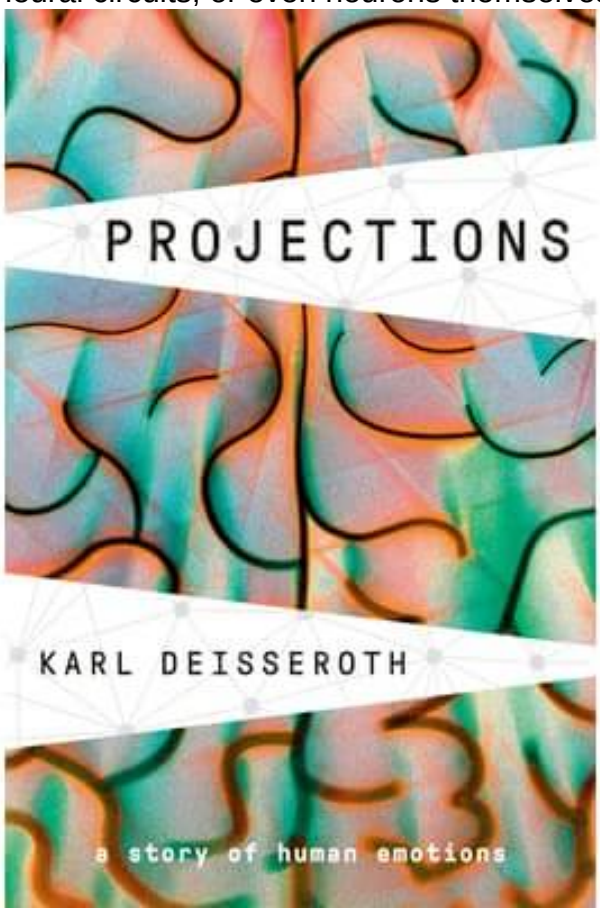


Karl Deisseroth. Credit: Stanford

Presenting a cast of characters encountered in the cramped, windowless Room Eight of the hospital, Deisseroth reflects on a broad swath of his psychiatry experiences, from his residency in the early 2000s to his more recent patient work. His book resembles a series of connected short stories interwoven with recent findings from research on the neural circuits that give rise to mental illness. At times it may feel like reading fiction because it partly is — Deisseroth freely uses his imagination in his portrayal of patients and their inner lives. But he pulls these threads together with his own memoir-ish voice, revealing the struggles, frustrations, and triumphs of someone driven to understand both the cold science of the brain and the hot mess of the mind.

A man loses his pregnant wife in a car accident and doesn't know why he can't cry. A patent lawyer believes her neighbor has installed a satellite dish to channel her thoughts. After a breakup, a 19-year-old begins cutting his arms. Deisseroth ends up in a dramatic chase when a patient slips out of the exam room, only to find she'd gone to binge-eat and vomit. Unlike Psychology 101 disease prototypes, thesefeel like real people. And while they're actually "projections," filtered through the lens of a doctor who fictionalizes details to protect patients' privacy, they are vivid reminders that mental health can be afragile, elusive thing.

But psychotherapy and imagination aren't the only ways Deisseroth peers into the brain. Seeking answers to tough questions that have confounded psychiatrists for decades, Deisseroth helped pioneer a technology called optogenetics. Once patients leave the hospital, Deisseroth has no control over their behavior, let alone their brains. But with optogenetics, he and other researchers can turn on and off individual neural circuits, or even neurons themselves — at least, in laboratory animals.



In optogenetics, researchers hijack genes called microbial opsins from bacteria and algae and encode them in the brain cells of lab animals — mostly mice, rats, and fish. These exotic genes lead to the

creation of proteins with a special power to convert light to electrical current. Normally, most neurons don't turn on in the presence of light (although a 2019 study questions that assumption). But as a result of this feat of genetic engineering, scientists can activate individual brain cells by delivering light to them. With unprecedented precision, they can then investigate how different parts of the brain participate in both typical behaviors and symptoms of mental illness.

The impact of optogenetics has been far-reaching in revealing the brain's inner workings, at least in animal models. And after more than 15 years of laboratory study, its potential is moving into the human realm. In May 2021, too recent to make it into this book, scientists reported in Nature Medicine that a blind patient regained partial vision as a result of optogenetic therapy.

But in terms of innovations in psychiatric patient care, what are the lessons from optogenetics? A lot of this work is still in its infancy. Deisseroth says his laboratory research informs the psychiatric patient care that he continues to give, yet many of the landmark studies are about causations and chemical pathways in genetically modified mice, not humans. Scientists can model eating disorders in rodents, but no one is talking about removing the skull flaps of people with anorexia, genetically modifying particular brain cells and zapping them with light to restart the drive to eat normally. Nor might it be that simple. Yet there is some hope that by understanding the fundamental mechanisms at work, new treatments could one day be developed.

One of the most direct feedback loops between Deisseroth's hospital and lab work is a patient named Charles, who changed Deisseroth's thinking about autism. Charles comes to Deisseroth as a young information technology specialist who, among other social impairments, consistently avoids eye contact. One morning, Deisseroth asks him what makes him look away. Charles tells him, "It overloads the rest of me."

This introspection is so profound to Deisseroth that he says it justifies his entire career progression: "All the extra years of both MD and Ph.D. training, all the pain and personal challenges of internship, all the call nights as a single father, worrying about my lonely son. This alone was enough."

While in, which stimulate other neurons, compared to inhibitory cells, which do the opposite. In 2011, Deisseroth's team used optogenetics to increase the activity of excitatory cells in the prefrontal cortex of mice, which appeared to cause them to be less social with other mice. This part of the book is a bit technical, but the bottom line is that an imbalance in cellular activity could play a role in the asocial behaviors associated with autism.

Tantalizingly, it appears that this imbalance might be corrected. In 2017, Deisseroth's team reversed social impairment in mice carrying genetic mutations associated with autism through opposite methods in the prefrontal cortex — making inhibitory cells fire more, or lowering the activity in excitatory cells. In fact, such experiments suggest that social avoidance can be turned on or off in adult mice, a revelation that may generate new hope for future interventions in adult humans.

encounters with patients in vulnerable, distressing circumstances. Veronica O'Keane, on the other hand, describes longer-term relationships with her patients in "A Sense of Self: Memory, the Brain, and Who We Are" — although patient stories take more of a backseat to science in this book. She is a professor of psychiatry at Trinity College Dublin, and has been practicing for more than 30 years. "Like all psychiatrists, as a patient once said to me, I am like a detective," she writes.

O'Keane draws from her clinical experiences to offer a comprehensive tour of the current state of knowledge about how memory operates in the brain. "Individuals with psychiatric illnesses have a great deal to tell neuroscience, and the larger world, about the processes involved in the organization of memory," she writes.

"A Sense of Self" at times reads like a textbook, complete with a few diagrams. Anyone who has read a neuroscience book previously will recognize H.M., who was famously unable to form new memories after undergoing brain surgery, as well as Phineas Gage, who was impaled with an iron rod — and how the tragic circumstances of their impairments taught the fledging field of neuroscience a lot about what does what in the brain.

But what makes O'Keane's book engaging is how she incorporates references to literature and folklore, putting a different spin on familiar stories — like Lewis Carroll's "Through the Looking- Glass," in which Alice's adventures closely mimic feelings of psychosis.

Another is Charlotte Perkins Gilman's 1892 short story "The Yellow Wallpaper," about a woman trapped in the wall of her bedroom. It's often portrayed as a tale of the oppression of women at that time, but O'Keane has a different take: It's a perfect description of experience of what we now call postpartum psychosis, she writes.

Postpartum psychosis, a condition seldom spoken about, can make otherwise healthy new mothers lose sight of what is real and what is not. Perkins Gilman herself experienced postpartum psychosis, and years later, after her cancer treatments failed, ended her own life in 1935.

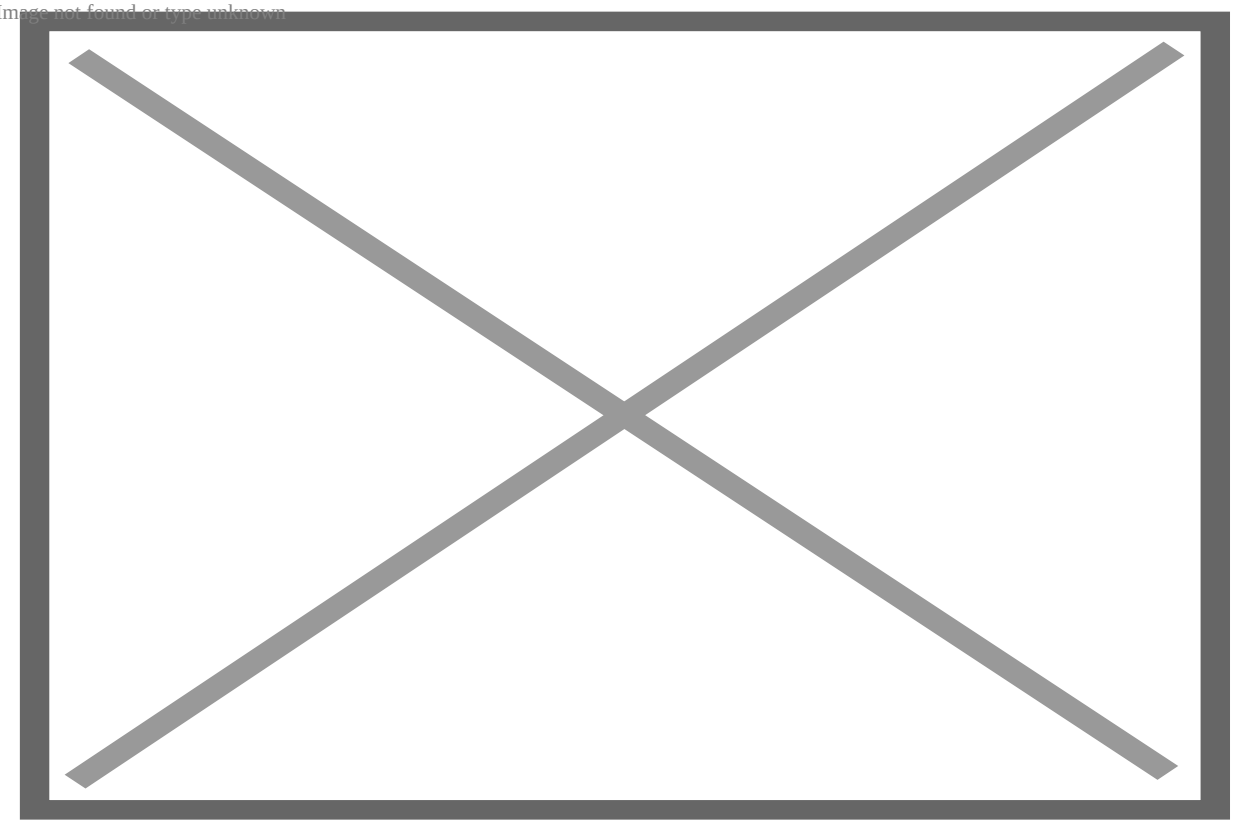
O'Keane describes a patient, Edith, who developed delusions about her baby being an imposter, as well as her own husband. With the help of antipsychotic medications, Edith heals and comes back to reality. Yet she still feels terror when she sees the gravestone that she had believed to be the site of her baby's burial — "the memories are real," she tells the author. This distinction "set me on a long-term pathway of inquiry about the nature of the matter of memory," O'Keane writes.

Some who suffer psychosis are so accustomed to the voices in their heads and other delusions that they decline medicine to make them go away. They feel scared to let go of their inner lives and participate in the same reality that others share.

Like much of life, mental health can be seen as a matter of achieving some kind of equilibrium. Everyone, psychotic or not, operates by balancing one's inner world full of thoughts, feelings, and memories with the external world and all of the stuff of society. "If there is anything that I have learned from my work with mentally ill patients it is that the achievement of an easy equilibrium between oneself and the world is

what determines one’s happiness,” O’Keane writes.

Image not found or type unknown



Veronica O’Keane. Credit: Colm Mahady/Fennells

As it happens, O’Keane also briefly touches on innovations in optogenetics. She focuses on an experiment by Susumu Tonegawa using optogenetics to implant false memories in mice, which I covered as a CNN reporter in 2013. By genetically altering neurons and shining blue light on them, scientists made mice believe they had been shocked in one chamber, even though they were shocked in a different chamber. The mice eventually froze up in fear even when the researchers were not activating the memory in their brains.

O’Keane’s take on this research is that artificial modification of memory is “fascinating,” but that in some sense the mouse memories aren’t “false” because “the neural matter of the experience is formed” regardless. Just as Edith regarded her hallucinations about her baby’s death as real memories, these mice have real memories of something that never occurred. “Edith brought home to me how memory is, in essence, neurally coded experience,” O’Keane writes.

As we go about our lives, according to O'Keane, we tag experiences with emotions, which are then triggered later as we are reminded of them, but we never re-live them in quite the same way. "Is thereever a boundaried memory untouched by the present, like a walled cement garden?" she writes. Theanswer in her view is decidedly no, for each time we recall a moment, it is colored by who we havebecome since it happened.

O'Keane's book will be useful for anyone looking for a deep dive into how memory works, but it is not as much of a page-turner as "Projections." Still, I was moved by both authors' concerns for their patients and acknowledgement that science has only scratched the surface of learning how psychiatric illness works at a fundamental level in the brain. The double-edged sword here is that you are not alone, but also, no one really understands.

Yet, there is hope. The stories in both works reveal a range of humanity that is barely understood by people who devote their lives to the study of mental illness and is often stigmatized by those who do not. They are in some sense thank-you notes to the patients who have taught the authors about the nature of the brain and given them more to investigate in the future.

And while a person battling with delusions of paranoia may seem far removed from academic papers on genetically engineered mice, both authors argue that the gap between laboratory insights and clinical practice is narrowing. "As this science develops, psychiatric illness will become a major target of investigation, and I believe this will be the beginning of the ending of the stigmatization of psychiatric illness," O'Keane writes.

"An important caveat here," she adds, "is that most of my patients do not feel similarly optimistic."

Elizabeth Landau is a science journalist and communicator living in Washington, D.C. She has contributed to The New York Times, The Washington Post, Quanta Magazine, Smithsonian, and Wired, among other publications. Find her on Twitter at @lizlandau

A version of this article was originally posted at Undark and is reposted here with permission. Undark can be found on Twitter @undarkmag