By rendering individual neurons photosensitive, Deisseroth's technique brings a once unthinkable level of precision and control to

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PROFILES

LIGHTING THE BRAIN

Karl Deisseroth and the optogenetics breakthrough.

BY JOHN COLAPINTO

experiments designed to determine how the brain processes information and drives behavior.

On a recent Friday morning, a gray-haired woman whom I will call Sally arrived for an appointment with Karl Deisseroth, a psychiatrist and a neuroscientist in the bioengineering department at Stanford University. Sally, now in her sixties, had suffered since childhood from major depression, and had tried the standard treatments: counselling, medication, even electroconvulsive therapy. Nothing helped. She had spent much of her adult life in bed, and had twice attempted suicide. Seven years ago, she was referred to Deisseroth, who uses a combination of unusual medications and brain stimulation to treat autism and severe depression. He accepts only patients for whom all other treatments have failed.

On Deisseroth's advice, a surgeon implanted beneath Sally's left collarbone a small, battery-powered device that regularly sends bursts of electricity into the vagus nerve, which carries the signal into a deep-brain structure that doctors think regulates mood. Originally developed for epilepsy, vagus-nerve stimulation (VNS) has been approved by the Food and Drug Administration for use in the kind of treatment-resistant depression from which Sally suffers, but the exact reason for its effectiveness is not understood. Sally says that VNS has transformed her life, and that, apart from one period of "going pancake," she has experienced just a few "dips."

She seemed to be in one of those dips when she took a seat facing Deisseroth. "There's just so much going on," she said. She had recently suffered a blackout, which her physician thought might be related to a drop in blood pressure, and she had decided, reluctantly, to stop driving until she understood why it had happened. Walking was hard, too; she was scheduled to have knee surgery soon, but it frightened her.

"Well, that's a lot to think about," Deisseroth said. He spoke quietly but with a positive lilt, countering the downward tug of Sally's mood. "Not super-low blood pressure," he said, scanning her chart. "So that's actually not as concerning as I thought." Of her decision to suspend driving, he said, "That is smart while it's

being figured out." He added, "You're still socializing, I see—which is very important."

She was not mollified. "Mood's been down," she said. "Just spiralling down." She mentioned insomnia, bad dreams, low appetite.

"No suicidal thoughts?" he asked.

"Mmm, no," she said. With sudden urgency, she asked to have the VNS current increased: "Can we *please* go up to 1.5?" She had been receiving 1.2 milliamps every five minutes for thirty seconds, but was no longer able to feel the effects.

"You're tolerating the device very well," Deisseroth said, after some discussion. "I think we can go up a little."

He handed her a programming wand, which looked a little like a Wii remote. She placed the broad, flat end against her left collarbone, over the implant. Deisseroth took from his desk what appeared to be a smartphone—a controller for the wand—and thumbed the screen as if tapping out a text. The wand emitted a trilling tone. "I can feel it," she said.

"But you're not coughing," he said. "That's good."

Problems with the throat are not the only side effects of VNS. Cells outside the targeted treatment area can be roused, affecting cognition. After increasing the voltage, Deisseroth asked Sally that day's date and the counties she'd travelled through to get to his office, and to count backward from a hundred by sevens. She performed all the tasks. "Good," he said. "Flawless cognition."

In the course of the next few minutes, Sally underwent a remarkable change. Her frown disappeared, and she became cheerful, describing the pleasure she'd had during the past Christmas holiday and recounting how she had recently watched some YouTube videos of Deisseroth. ("The N.I.H. in June—your demeanor behind the podium is, like, *Wow!* Very strong.") She was still smiling and talking when the session ended and Deisseroth walked her out to the reception area.

Later, Deisseroth told me that Sally's response to the treatment was good evidence for the efficacy of VNS. But it also provided valuable insight for Deisseroth in his work as a neuroscientist. "When I'm sitting in front of a patient and hearing what they're feeling, it concentrates the mind wonderfully," he says. "It's a source of hypothesis, a source of ideas."

For much of the history of brain research, it has been nearly impossible to accurately test ideas about how the brain works. "When we have the complexity of any biological system—but particularly the brain—where do you start?" Deisseroth says. Among scientists, he is best known for his development of optogenetics, a technology that renders individual, highly specific brain cells photosensitive and then activates those cells using flashes of light delivered through a fibre-optic wire. Optogenetics has given researchers unprecedented access to the workings of the brain, allowing them not only to observe its precise neural circuitry in lab animals but to control behavior through the direct manipulation of specific cells. Deisseroth, one of the rare neuroscientists who are also practicing psychiatrists, has made mental illness a major focus of his optogenetic research. Other scientists around the world are using the method to investigate some of the most stubborn riddles of neuroscience, including the fundamental question of how the physical brain—the nearly hundred billion neurons and their multitudinous connections—gives rise to the mind: thought, mood, behavior, emotion.

In the late seventeen-hundreds, the Italian physician Luigi Galvani noticed that static electricity could induce a dead frog's leg to move. For the first time, scientists understood that the nervous system operates under the influence of electrical activity. But it was not until the nineteen-twenties that a Swiss researcher, Walter R. Hess, using implanted wires to stimulate the brains of cats, showed that emotion and behavior also arise from electrical impulses in the brain. By stimulating various brain regions, Hess induced different reactions: for example, a cat could be made to show the defensiveness it might otherwise display when confronted by a dog.

In the nineteen-fifties, a Spanish physiologist at Yale, José Manuel Rodriguez Delgado, conducted experiments with electrodes implanted in the brains of human subjects, using a device he had invented, called a "stimoceiver," a half-dollar-size electrode operated by remote control. Delgado used the stimoceiver in some twenty-five patients, most of them epileptics and schizophrenics in a Rhode Island mental hospital, and reported that it was "possible to induce a large variety of responses, from motor effects to emotional reactions and intellectual manifestations." The experiments sparked outrage when they were made public, and Delgado returned to Spain.

The ethical concerns inherent in implanting electrodes in human brains gave way, in the early nineteen-nineties, to the adoption of a wholly noninvasive brain-imaging technology: functional magnetic resonance imaging, or fMRI. It was instrumental in bolstering the theory that the brain is divided into discrete regions responsible for different aspects of behavior. The technology uses powerful magnets to detect changes in blood flow in the brain in subjects who are exposed to various stimuli—images, sounds, thoughts. Activated regions can be presented on a screen as luminous blobs of color. But fMRI has severe limitations. There is a time lag, and different neuronal events that happen a second or more apart can blur together when the excited area appears onscreen—a liability in studying an organ that works at millisecond speed. Nor can fMRI reveal what brain cells are actually doing. The technique registers activity only at the scale of hundreds of thousands of neurons, and a lit-up area might represent any number of neural processes. Given this lack of precision, even some of fMRI's defenders offer faint praise. Nancy Kanwisher, of M.I.T., who has done groundbreaking work to isolate a brain region implicated in face recognition, says, "The real miracle of fMRI is that we ever see anything at all."

To analyze the role of small groups of neurons, scientists have relied on a method not unlike the one that Hess used with his cats: stimulating targeted brain areas, in experimental animals, with thin electrodes. Because electrodes spread current through brain

tissue, stimulating activity in unwanted areas, researchers use a drug to suppress neural activity. But the method is cumbersome and time-consuming.

In 2005, Deisseroth published his first paper on what came to be known as optogenetics. Because the technology permits researchers not only to trigger the activity of cells at the speed that the brain actually works but also to target cells in regions, like the amygdala, where there are mixed populations of hundreds of kinds of cells, optogenetics offers a previously unthinkable level of experimental precision. At present, optogenetics can be used only on animals like mice and rats, whose brain functions associated with elemental emotions, like fear and anxiety and reward, are similar to those in humans. But Deisseroth's work with patients like Sally, whose VNS implant allows him to control emotions and behavior, hints at what may one day be possible.

Christof Koch, the chief scientific officer of the Allen Institute for Brain Science, in Seattle, calls optogenetics one of the most momentous developments in neuroscience in the past hundred and sixty years—from the original dye-staining of cell types, in the late nineteenth century, through the use of electrodes, in the fifties and sixties, to the advent of fMRI. "Optogenetics is the fourth wave," Koch told me. "I can now begin to intervene in the network of the brain in a very delicate, deliberate, and specific way." Experiments have shed light on many brain functions, including learning, memory, metabolism, hunger, sleep, reward, motivation, fear, smell, and touch.

Optogenetics was a major spur to the Obama Administration's announcement, in 2013, of the BRAIN Initiative, a three-hundred-million-dollar program for developing technologies to treat such neurological ailments as Alzheimer's disease, autism, schizophrenia, and traumatic brain injury. Deisseroth was part of the working group that created the Initiative and has vetted grant applications for it.

"First time, long time."

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Deisseroth, who is forty-three, has dark hair that falls into droopy eyes. His voice rarely rises above a murmur, and he comes across as unusually easygoing for someone who developed a transformative neuroscience technology before he was forty. The Stanford neuroscientist Rob Malenka, who oversaw Deisseroth's postdoctoral work, told me that in some ways he underestimated his trainee. "I knew he was really smart. I didn't appreciate that underneath that laid-back, almost surfer-dude kind of persona is this intense creative and intellectual drive, this intense passion for discovery. He almost hides it by his presentation."

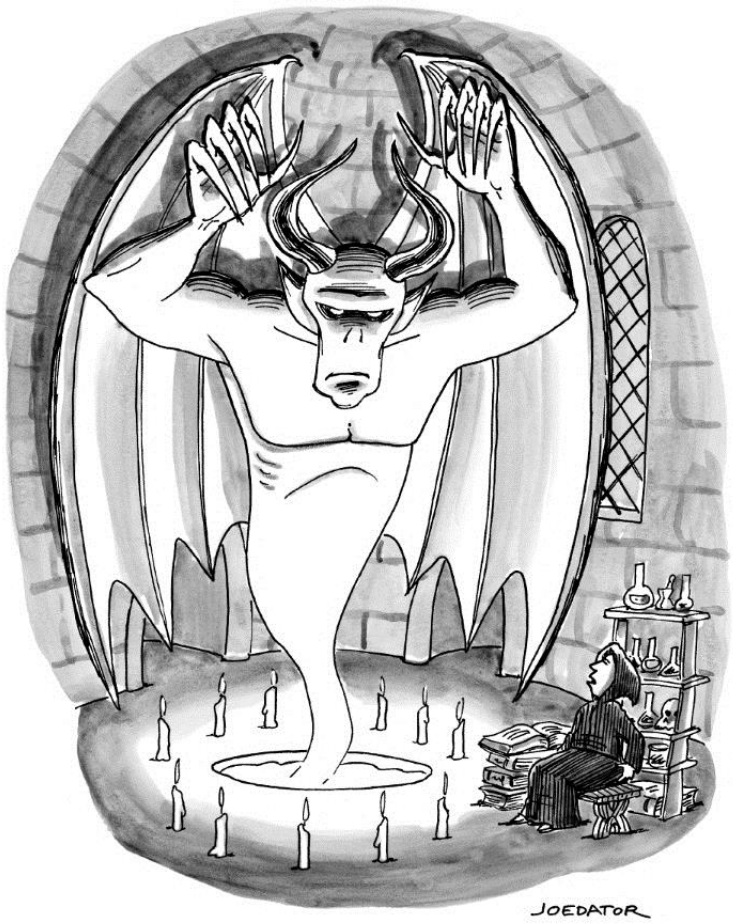
Dressed in his usual T-shirt, jeans, and scuffed leather jacket, driving around campus in a dented gray Chevy pickup, Deisseroth could be mistaken for a slightly shambolic creative-writing professor. His initial dream, in fact, was to write. He took writing courses as an undergraduate, and when he was a graduate student in both medicine and neuroscience at Stanford he took a fiction-writing class that met two nights a week at a junior college nearby. He remains an avid reader of fiction and poetry, and he is polishing a book of short stories and essays loosely inspired by Primo Levi's "The Periodic Table." Deisseroth says that he perceives a connection between scientific inquiry and creative writing: "In writing, it's seeing the truth—trying to get to the heart of things with words and images and ideas. And sometimes you have to try to find unusual ways of getting to it." His fiction bears little resemblance to the technical prose of his neuroscience papers. In a short story describing his first encounter with a schizoaffective patient as a medical intern, Deisseroth wrote that the man's disordered speech was "Finnegans Wake on the psych ward," a "soliloquy of suffering" that evoked "science and art together, not in parallel but as actually the same idea, fused, as if I were hearing a Gerard Manley Hopkins poem on neurobiology."

One morning, when I was scheduled to meet Deisseroth in Palo Alto, I found him standing at the curb with an elderly motorist who had just added a fresh dent to the back of Deisseroth's truck. The man was agitated. After unhurriedly talking him into a state of calm, then exchanging phone numbers, Deisseroth climbed into the driver's seat, nudged aside some teething rings (he has three children under the age of six, along with an eighteen-year-old son from an earlier marriage), and asked if I'd slept well. He seemed

to have put the accident entirely behind him—even though it had made him late for an important meeting. Many people, I said, would still be discombobulated. "Like those poker players who have a bad hand at the beginning of the night and can't get back on track?" he said, with a smile. "They call it being 'on tilt.'"

Deisseroth seems never to be on tilt. He attributes this partly to his psychiatric training: "Those nights on call where there are five emergencies, you've got a patient in restraints in the E.R., where they need you immediately, patients up on the psychiatry floor, where someone punched a nurse—you develop a little bit of a 'just get through it one thing at a time.'" His unusual calm has allowed him to compartmentalize competing demands (fatherhood, marriage, neuroscience, literary endeavors, clinical psychiatry, speaking appearances at dozens of conferences a year), so that he can think through complex problems. He told me that, while many people find that walking or jogging shakes ideas loose from the subconscious, he needs to quell all physical activity. "Otherwise, I get this disruption from the motor cortex," he said. "I have to be totally still." Ideas come floating up "like a bubble in liquid." At that point, he goes into an excitable motor state, pacing or scribbling down ideas.

His wife, Michelle Monje—a neuroscientist who specializes in pediatric brain cancer—has seen the process in action often. "He had this idea of controlling specific brain cells years before actually being able to accomplish it," she says. "It was so out there. Like, 'Yeah, that would be great—if it *worked*.'"



"Oh, sorry—I think I just butt-summoned you."

Deisseroth was born in Boston, but he grew up all around the country as his father, a hematologist-oncologist, followed a series of postings from Boston to Potomac, Houston, and Marin County. His mother taught high-school physics and chemistry; the elder of his two sisters is an orthopedic surgeon, the younger a clinical psychologist. Deisseroth loved reading—he recalls riding his bike with a book open on the handlebars, and crashing into parked cars—but he was also a classic science kid. "I stopped and looked at bugs and thought about how they were making their decisions," he says. "And I inspected roadkill with great intensity."

He was in the third grade when he learned that his own brain functioned in an unusual way. A teacher asked the class to choose a poem to recite from memory. Deisseroth opened his reader, looked at a page containing "The Road Not Taken," and put his hand up. When the teacher explained that he needed to memorize the poem first, he said that he already had, and recited it. The teacher, disbelieving, spent the rest of the class calling on him to quickly glance at a poem and then recite it. "It kind of turned into a circus act," Deisseroth says.

He remains a preternaturally fast and retentive reader. At a recent conference, he attended a talk by David and Nic Sheff, the father-and-son authors of the addiction memoirs "Beautiful Boy" and "Tweak." In the course of an hour, while listening to the two men, Deisseroth read both books in their entirety. He does not use the standard techniques of speed-reading but, instead, sees printed pages "in blocks," he says, and instantly "fills in gaps." Colleagues suggest that this ability helped Deisseroth to acquire the wide-ranging knowledge necessary for the development of optogenetics, which required a working familiarity with virology, optics, animal behavior, genetics, 3-D imaging, microbiology, materials science, and chemistry.

Deisseroth graduated from high school at sixteen and won a scholarship to Harvard, where he planned to major in creative writing. Instead, he ended up getting a degree in biochemistry, and was admitted, at the age of twenty, to Stanford's combined M.D. and Ph.D. program. Motivated by a desire to better understand human nature, he decided to pursue his Ph.D. in neuroscience. "I didn't come in by asking, 'How many bits per second can flow through a pathway?'" he says. "I came in—maybe from the literature exposure—wanting to know where feeling came from. How you could be uplifted by words. How imagination worked."

For his Ph.D., he studied how activity at the synapses of neurons affects the nucleus and influences gene expression, a highly specialized subject but one that is central to an important aspect of being human: memory. "There was all this evidence coming out that changes in gene expression were important for things like long-term-memory storage," Rob Malenka says. "Karl—in what I now understand was his typical way—was asking, 'What's a big question, a big topic that hasn't been adequately addressed?'" Deisseroth's dissertation, which he completed in 1998, spawned papers in the journals *Neuron* and *Nature*.

Deisseroth had initially planned to become a neurosurgeon, but he changed his mind after doing a mandatory four-week rotation in psychiatry, where his first patient was the schizoaffective man whose speech he compared, in his short story, to "Finnegans Wake." Deisseroth prescribed strong antipsychotic and mood-stabilizing medications, but the man remained too overcome by the disorder to leave the psych ward. Deisseroth was both disappointed and fascinated. "It was the unknown that grabbed me," he says. "I knew how far we were from a glimmer of understanding."

During his residency, he struggled to reconcile his lab research with the ailing people he talked with on the ward. Malenka recalls, "He'd spend all day seeing patients, then rush over to my lab and spend four or five hours running experiments." He was frustrated that psychiatry's view of the most intractable disorders—severe depression, schizophrenia, autism—was limited by a fundamental lack of understanding of how the brain works. "A cardiologist can explain a damaged heart muscle to a patient," Deisseroth told me. "With depression, you cannot say what it really is. People can give drugs of different kinds, put electrodes in and stimulate different parts of the brain and see changed behavior—but there is no tissue-level understanding." He added, "That problem has framed everything. How do we build the tools to keep the tissue intact but let us see and control what's going on?"

In 1979, Francis Crick, the co-discoverer of the double helix, published an article in *Scientific American* in which he laid out his hopes for the future of brain science. Neuroscientists were already routinely using electrodes to stimulate the brain, but Crick, noting the method's imprecision, called for a tool that would allow researchers to turn specific neurons on and off, while leaving other cell types untouched. In a later paper, he suggested a way to achieve it: "This seems rather far-fetched, but it is conceivable that molecular biologists could engineer a particular cell type to be sensitive to light."

It turned out that the key to engineering such a cell had already been discovered, in the early seventies, when a German biochemist named Dieter Oesterhelt described the first microbial opsin. Opsins are light-sensitive proteins found in the photoreceptors of the eye, among other places in nature. Oesterhelt's opsin was from a single-celled bacteria that lives in highly saline lakes in Egypt and Kenya, and survives its harsh environment by converting light into energy. Oesterhelt's discovery prompted a wave of research in labs around the world, but no one supposed that genes from a single-celled bacteria could be transported across billions of years of evolution to function in a mammalian brain. "There is so much that is different about microbial cells and our cells," Deisseroth says. "Their whole inner workings are different—how they shuttle proteins from one spot to another, how they store things, package them, send them to the surface of the cell."

In 2002, Gero Miesenböck, at Memorial Sloan Kettering Cancer Center, in New York, became the first researcher to use an opsin to render a brain cell light-sensitive. He used an opsin taken from the retina of a fruit fly. Miesenböck is considered one of the fathers of optogenetics, and in 2013 he shared a major award, the Brain Prize, with Deisseroth and several others. The fruit-fly opsin required three proteins acting together to get the treated cell to fire. To adapt the experiment to a living animal's brain would mean importing the genetic code for each of the signalling proteins—an unwieldy task.

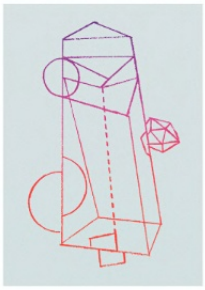
In 2003, a group of German researchers announced the discovery of a new microbial opsin, derived from a green algae that grows in ponds. When introduced into human embryonic kidney cells, the opsin made the cells respond to flashes of blue light. Deisseroth recognized the discovery as being potentially revolutionary. Unlike the fruit-fly opsin, the new opsin—channelrhodopsin-2, or ChR2—converted light into electricity in a single step, at virtually the speed of electrical impulses in the brain.

For a few years, Deisseroth had been thinking about using opsins to make neurons in a living animal sensitive to light, but he stresses that he was not the only person who had that idea; he brainstormed with others at Stanford, including a graduate student named Ed Boyden. There was every likelihood that it would be impossible in brain cells, which are far more complex and fragile than the kidney cells that the German team used. "For many scientists, the risk of wasting time and money was too great," Deisseroth says.

In the summer of 2004, Deisseroth opened his own lab at Stanford, and hired a brilliant Ph.D. student named Feng Zhang, who in his teens had worked in a gene-therapy lab. Zhang seemed like the ideal person to do the delicate work of introducing the pond-scum opsin into a brain cell. The opsin would have to be smuggled into the cell using a virus, but at a concentration that would not kill

the neuron. Deisseroth told Zhang that the experiments could be transformative. "He even mentioned something like 'This is one of those things that only come around every five or ten years,'" Zhang recalls.

Deisseroth's lab isolated a rat neuron in a petri dish, and Zhang chose a benign lentivirus to introduce the opsin into the cell. Deisseroth enlisted Ed Boyden to run tests on the treated cell. When Boyden flashed blue light on the culture, the cell produced strong action potentials—the spikes in electrical activity that neurons use to communicate. After a year of experiments, the team had created the world's first reliable technology for generating light-sensitive neurons that signalled at the speed of the brain.



But Deisseroth's excitement was tempered. He says, "It wasn't clear that this would work for what I really cared about—not just a toy experiment in a dish but actually controlling behavior in a living animal in a way that could teach us about what the brain is really doing." Indeed, when the team submitted a paper announcing its results to *Science* and to *Nature*, both journals praised the experiment's ingenuity but saw no practical application, and rejected it. When the paper was eventually published, in *Nature Neuroscience*, in August, 2005, the scientific community was uncertain that the technique could ever be made to work in a living animal.

The doubts only motivated Deisseroth. "I felt a sort of personal need to see what was possible," he says. Malenka told me that this understates the case considerably: "There's this drive of, like, 'You think I'm wrong about this, motherfucker? I'm going to show you I was right.'" Deisseroth began working furiously. "He was getting up at 4 or 5 A.M. and going to bed at one or two," Monje says. He kept up this schedule for five years, until optogenetic experiments began working smoothly. "There are people who don't need as much sleep," Monje says. "Karl is not one of those people. He's just that driven."

Deisseroth and his colleagues faced a series of challenges. They struggled to target the opsins to specific brain cells—those associated with, say, sleep or memory or anxiety. Finally, they devised a means for attaching small bits of DNA to the opsins, which acted like a password, insuring that they would be produced only in the correct cells. Then they had to figure out a way to deliver flashes of light to regions deep inside the brain, and settled on a fibre-optic wire attached to a laser diode. In late 2005, they began preliminary tests to see if they could control behavior in mice. In the first experiments, on cells in the hypothalamus—a region involved in sleep—they coaxed the animals to sleep in a dark room, then flashed blue light deep inside their brains. The mice woke—sort of. "It was a very subtle change," Zhang says. "The animal would twitch, then fall back to sleep." This was hardly the dramatic response they had hoped for.

Deisseroth's next scientific advance was the result of a publicity stunt. As word of what was going on in his lab spread, a *Times* reporter requested a visit in the summer of 2007. "Karl asked if I could come up with something interesting to show the reporter," Zhang told me. "I said, 'Maybe I can stimulate the motor cortex and cause the mouse to shake, or something.'" Deisseroth showed me a video that re-created the experiment. A mouse—apparently normal, except for a small tube emerging from the top of its head, where the fibre-optic wire is implanted—is filmed from above, standing on its hind legs and sniffing at the side of its enclosure. The instant that a blue glow appears, the mouse begins to run in wide circles to the left. (The fibre-optic wire was shining light on the motor neurons on the right side of the brain, which control movement on the left side of the body.) The instant the light is shut off, the mouse stops running and resumes its sniffing. It's clear that the behavior was not a pain response, since the brain has no pain receptors. By stimulating the motor cortex with light, Deisseroth had turned a freely moving animal into something close to a video-game avatar controlled with a joystick. "That's really the moment we knew that it could drive very, very robust behavior," Zhang says. "I went to grab Karl, and he said, 'This is what we should show the reporter.'"

The reporter was impressed enough to feature the experiment in her article. But it was another two years before Deisseroth and other researchers demonstrated that optogenetics could be more than what the *Times* had called a "science-fiction version of stupid pet tricks." In the spring of 2009, Deisseroth's graduate student Viviana Gradinaru published a paper about using optogenetic manipulation in rodents to define precise neural connections in Parkinson's disease. Shortly after that, Zhang co-authored an article in *Science* that examined the role that highly specific dopamine neurons play in feelings of reward—results that had special significance for drug addiction. Two papers in *Nature* showed the role of cells in brain activity related to schizophrenia and autism. The papers appeared in quick succession. "That was all people needed," Deisseroth told me. "The world ran with it."

Scientists wrote to request clones of the opsins to use in their own experiments, and, in the years since, bioengineering subspecialties in the design and development of new opsins have sprung up. Ed Boyden, who left Stanford to launch his own lab, at M.I.T., had already shown that, under flashes of yellow light, the photosensitive protein in the original bacteria that Oesterhelt found in Africa could produce an electrical current that turns off neuronal activity. By using it in concert with the blue-light opsin, researchers can play neural circuitry like an organ, turning brain activity on and off at the actual speed with which neurons communicate with one another—a process, Deisseroth says, that has brought extraordinary control to experiments designed to determine how the brain processes information and drives behavior. By dye-staining cells with proteins that glow fluorescent when neurons fire, researchers

can not only "play in" behaviors, by stimulating optogenetically treated brain cells with the fibre-optic light flashes, but also "read out" the circuit activity triggered when a lab animal is put through certain tasks.

Gary Lynch, a professor of psychiatry and human behavior at the University of California, Irvine, and an expert on memory, says that optogenetics has become an indispensable tool in neuroscience. "The tremendous power is that it lets you take specific populations of neurons that are mixed up with other kinds of neurons and stimulate the type you want to stimulate"—as in some parts of the amygdala, where neurons relevant to emotion, memory, and sociability intermingle. The problem with previous experiments on the amygdala, Lynch says, is that "when you stimulated it with electrodes and you got effects, you didn't know if it was because of this population or that population of neurons."

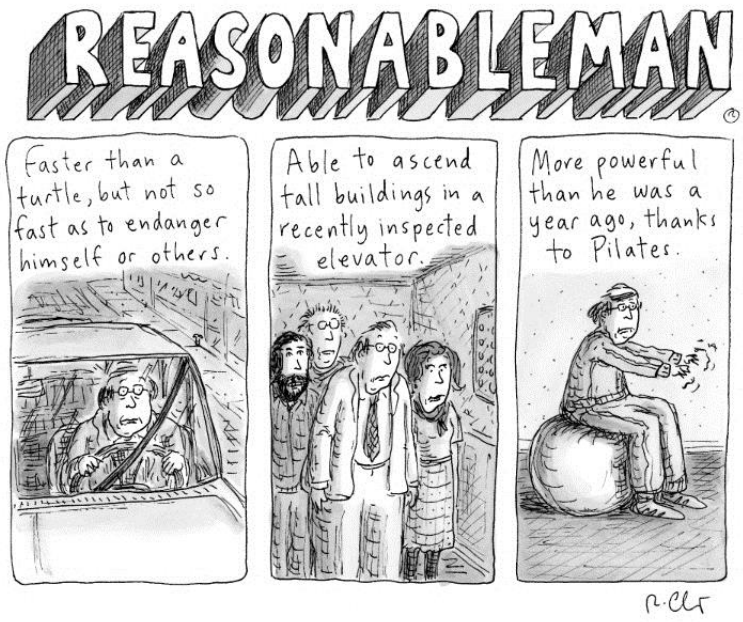
Lynch says that he recently began optogenetic experiments on the hippocampus, a deep-brain structure, crucial to narrative memory, that was especially difficult to study with the old methods, because of the myriad neurochemical "inputs" from other parts of the brain. "For years, I and others have been trying to understand what these different inputs do to the hippocampus—what are they adding?" he says. "Short of using drugs and electrical stimulation and painfully teasing it out, we find it very, very difficult to get a good answer." Optogenetics, however, offers an ideal way to pinpoint the neurons in those inputs, turn them on and off, and note the effect that doing so has on memory. The research, he says, could have implications for the tailoring of drugs used to alleviate Alzheimer's.

Deisseroth estimates that optogenetics is now being used in more than a thousand laboratories worldwide, and he takes twenty minutes every Monday morning to sift through written requests for the opsins. It was not until Monje joined her husband at a recent neuroscience conference in Washington, D.C., that she understood the fame that optogenetics had brought him. "People were stopping us at the airport asking to take a picture with him, asking for autographs," she said. "He can't walk through the conference hall—there's a mob. It's like Beatlemania. I realized, I'm married to a Beatle. The *nerdy* Beatle."

Stanford is known for the scarcity of its lab space, but in 2012, as Deisseroth was wooed by rival institutions, the university offered him a dedicated research facility in the hills above Palo Alto. A sleek white structure that he calls the Cracking the Neural Code Building, it once housed a biotech company. The lobby is dominated by a twisting central staircase, like a strand of DNA, linking two floors filled with laboratories, animal surgeries, and offices, where thirty-five students work under Deisseroth's direction.

In one recent experiment, he investigated a major symptom of depression: the inability to take pleasure in formerly enjoyable activities. Mice strongly prefer sugar water to regular water, but after a few weeks of what Deisseroth calls "mild, non-painful stress" they no longer cared whether the water had sugar in it. By examining brain pathways of mice that have been subjected to the stress, Deisseroth traced the specific neural connections that relate to their apathy, isolating the relevant cells and connections. Because we share with rodents many of the protein markers that define those pathways, it is hoped that drugs tailored to those circuits will eliminate the symptoms with an exactitude not previously possible. "That's the direction that clinical psychiatry is going anyway—to more of a symptom-focussed treatment,"

"Yes, I was asleep. But it was a vigilant sleep."



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Deisseroth told me. Many psychiatrists expect that drugs aimed at alleviating the blanket disease of depression—like Prozac—will increasingly give way to drugs that target precise symptoms, such as anxiety, that occur in multiple disorders. "It matters less which exact disease category someone falls into," he added. "What matters more is, What are the symptoms and what are the medications that help with those symptoms?"

It's possible that optogenetics could be used as a therapeutic tool in humans, and Deisseroth has been given grants aimed at that outcome. With those grants, he has performed experiments to control the differentiation of embryonic stem cells, with the idea of one day developing optogenetics for the treatment of organic brain disorders. He published several papers on the subject in 2010. "A lot of people have followed that up," he told me, but he has moved on, and is currently focussed on the basic science of the brain, where "the opportunities dwarf everything else in terms of impact." Some scientists have imagined treatments evocative of Delgado's stimoceiver: implanted L.E.D.s that flash light deep into the brain to quiet anxiety symptoms or, in schizophrenics, hallucinations. Deisseroth warns that such therapies face considerable hurdles, owing to the unknown effects of injecting viruses into the brains of living patients. But, he told me, some clinicians are already looking at possible treatments in the peripheral nervous system—the nerves that go to the arms and legs. "If you could turn down the pain fibres without affecting movement or the normal sensations, then we'd have a big impact," he said.

Botond Roska, a neuroscientist in Basel, and Jose-Alain Sahel, an ophthalmologist in Paris, are working with optogenetics to restore sight in the blind. Early tests have been successful in mice and primates. "We also did it in human retinas that had been kept alive from organ donors," Roska says. "It's another way we know that our vectors will probably work in human subjects." They hope to run the first human trials in the next year or two.

Deisseroth, meanwhile, also adapts knowledge gained from his optogenetic experiments to use on the patients in his clinical practice. At a recent therapy session, he met with a tall, courtly man in his seventies, who suffers from severe depression associated with Parkinson's disease. I will call him Henry. As Deisseroth worked with Henry, he thought about his studies in mice, which showed a correlation between depression-like states and a dearth of dopamine-producing neurons. A year earlier, he had prescribed for Henry a pill that acts on the dopamine system. "Agents that act just on the dopamine system are very rarely given in depression," he told me. "But it has been really good for him." In the session, Henry described a significant improvement in his outlook. Before beginning the drug regimen, he had been unable to summon the will to walk across the room; lately, he had been stretching every morning. He told Deisseroth, "I'm not looking backward at things, so I'm shaded to the positive."

At the end of the session, Henry described the worst depths of his depression, saying that everything could fill him with hopelessness and dread. "It could be an object," he said, pointing at the desk. "Like that piece of paper. It bothers me in some unimaginable fashion."

Deisseroth, who had been typing notes on his laptop, looked up. "That's a great phrase," he said. "Just looking at an object and it making you feel bad. I've never heard any patient say that. That's a great, crystalline description of how it just touches everything: perception, action, and feeling."

Later, when we were driving back to the lab, I asked Deisseroth about his excited reaction. Did Henry's phrase interest him as a writer, or was it useful to him as a scientist? "That's very usable," Deisseroth said. "I can think about doing experiments in animals now with that. For example, by using optogenetics to turn down the dopamine neurons, can I make an animal feel aversive toward a formerly neutral object?" He pulled up in front of the building. "I could go in right now and tell a student, 'Hey, do that experiment.'"

One day in early 2010, Deisseroth was in his office, enjoying a few minutes of peace. Optogenetics was finally working as he'd hoped. His phone was on mute. He was getting no disruption from his motor cortex.

He had been thinking about one of the most vexing problems in neuroscience: how to create a detailed image of all the brain's neurons and their interconnections. X-rays and other techniques that use light to penetrate the tissues don't work, because of the brain's high volume of fats and water, which cause light to disperse. For years, neuroscientists had resorted to slicing cadaver brains into razor-thin sheets, scanning them, then putting the sections back together, trying to realign the nerve fibres, many of which had been damaged by being cut into layers. "You basically can't do it," Deisseroth says. "You can only do very local, small-scale anatomy." Removing the fats and the water was considered impossible, since they make up the "aspic" that holds the delicate network of neurons and axons in place.

Monje recalls her first hint that her husband was working on a new project, which came while they were changing a diaper together. Deisseroth said something about how great it would be if one could render a brain completely transparent. By then, she knew enough not to dismiss such a notion. "I thought, He'll probably figure out how to do it," she said. In his office, Deisseroth wondered if he could displace the fats and the water with a scaffold that would support the wiring but allow light to penetrate—perhaps a hydrogel, a water-based polymer used to support cells in human-tissue repair. He opened a spiral-bound notebook and began to fill pages with words and sketches, ideas for what he called an "endoskeleton" that would "digest away" the fats and the water. "The resulting structure can be studied in unprecedented detail," he wrote. The idea became CLARITY, an acronym for "Clear Lipid-exchanged Anatomically Rigid Imaging/immunostaining-compatible Tissue hYdrogel." CLARITY is Deisseroth's second great contribution to neuroscience—a method for rendering cadaver brains completely transparent, save for the perfectly intact cells and nerve fibres.

Unlike optogenetics, the idea progressed rapidly to practical use. Deisseroth hired a chemical engineer named Kwanghun Chung, and within a few months they were experimenting with a hydrogel called acrylamide. They injected the acrylamide as a liquid into the tissues, then soaked the brain in warm water, which caused the liquid to turn into a gel. By running a gentle electrical current through the tissues, they drove the fats out, leaving the neural circuitry suspended in the clear hydrogel, and rendering the brain "transparent."

In April, 2013, Deisseroth announced the new technology in *Nature;* the journal's Web site posted videos of a clarified mouse brain, showing a tangle of fantastically fine cells and nerve fibres, which glowed green against a black background. Thomas Insel, the director of the National Institute of Mental Health, called it "probably one of the most important advances for doing neuroanatomy in decades." It has since become a standard tool for scientists and clinicians around the world. Recently published studies using CLARITY have provided fresh insight into the buildup of deposits in the brains of people with Alzheimer's. Monje uses CLARITY to study tumors from the particularly invidious form of pediatric brain cancer that she specializes in. The technology has been adopted as a critical tool for a project, endorsed by the BRAIN Initiative, to make a complete map of a mouse's brain and, perhaps eventually, the human brain—an enormous undertaking, on the scale of the Human Genome Project, in which researchers will plot and categorize the nearly hundred billion neurons and the hundred trillion connections among them.

On the day I visited Deisseroth's research building, he walked me through labs where mouse brains were being clarified. Small test tubes, wrapped in foil, stood in racks on motorized, lightly heated platforms that rocked them continuously in a circular motion. He took one of the tubes and peeled away the foil. At the bottom was a small, pinkish, semi-transparent lump floating in cloudy liquid. A fully clarified brain would be nearly invisible to the naked eye.

For decades, researchers have imagined the brain as a soup of neurochemicals whose normal functioning depends on those chemicals remaining in proper balance. Mental illnesses were believed to result from a "chemical imbalance"—the wrong amount of this or that neurotransmitter in certain synapses. Limitations to that approach were becoming obvious even before the advent of optogenetics and CLARITY. "If you say, 'There's some such thing as a serotonin deficiency in depression,' then anything you do that specifically increased serotonin would be an antidepressant," Deisseroth told me. "But it's not true. So you can't explain things at that level. Likewise for psychosis, or schizophrenia. Some things fit chemical patterns, others don't."

Increasingly, neuroscientists believe that the key to understanding how the brain works lies in its over-all neural circuitry, and the way that widely separated brain regions communicate through the long-range projection of nerve fibres. In this view, mental disorders result from the shorting-out or disruption of the larger circuit wiring of the brain—and it is in defining and describing those circuit connections that Deisseroth's innovations promise to be especially helpful.

Christof Koch, at the Allen Institute, likens Deisseroth to Galileo, whose early improvements of the telescope afforded a huge advance in our understanding of the cosmos. Even so, like Galileo's telescope, which opened up the immensity of space, Deisseroth's technologies have helped reveal how little we know about the brain—what Koch calls "by far the most complex piece of organized matter in the known universe."

Koch says, "Over the past four hundred years, since the discovery of the telescope, each successive generation of astrophysicists has realized that the universe is still bigger than the previous generation thought. So it is with the brain. Each generation of neuroscientists turns up more complexity, more hidden layers."

Deisseroth told me that he is no closer to understanding the greater mystery of the mind: how a poem or a piece of music can elicit emotions from a mass of neurons and circuits suspended in fats and water. "Those are all incredibly important questions," he said. "It's just too early to ask them." ♦