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Control Desk for the Neural Switchboard

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Treating anxiety no longer requires years of pills or psychotherapy. At least, not for a certain set of bioengineered mice.

In a study recently published in the journal Nature, a team of neuroscientists turned these high-strung prey into bold explorers with the flip of a switch.

The group, led by Dr. Karl Deisseroth, a psychiatrist and researcher at Stanford, employed an emerging technology called optogenetics to control electrical activity in a few carefully selected neurons.

First they engineered these neurons to be sensitive to light. Then, using implanted optical fibers, they flashed blue light on a specific neural pathway in the amygdala, a brain region involved in processing emotions.

And the mice, which had been keeping to the sides of their enclosure, scampered freely across an open space.

While such tools are very far from being used or even tested in humans, scientists say optogenetics research is exciting because it gives them extraordinary control over specific brain circuits — and with it, new insights into an array of disorders, among them anxiety and Parkinson's disease.

Mice are very different from humans, as Dr. Deisseroth (pronounced DICE-er-roth) acknowledged. But he added that because "the mammalian brain has striking commonalities across species," the findings might lead to a better understanding of the neural mechanisms of human anxiety.

David Barlow, founder of the Center for Anxiety and Related Disorders at Boston University, cautions against pushing the analogy too far: "I am sure the investigators would

agree that these complex syndromes can't be reduced to the firing of a single small neural circuit without considering other important brain circuits, including those involved in thinking and appraisal."

But a deeper insight is suggested by a follow-up experiment in which Dr. Deisseroth's team directed their light beam just a little more broadly, activating more pathways in the amygdala. This erased the effect entirely, leaving the mouse as skittish as ever.

This implies that current drug treatments, which are far less specific and often cause side effects, could also in part be working against themselves.

David Anderson, a professor of biology at the California Institute of Technology who also does research using optogenetics, compares the drugs' effects to a sloppy oil change. If you dump a gallon of oil over your car's engine, some of it will dribble into the right place, but a lot of it will end up doing more harm than good.

"Psychiatric disorders are probably not due only to chemical imbalances in the brain," Dr. Anderson said. "It's more than just a giant bag of serotonin or dopamine whose concentrations sometimes are too low or too high. Rather, they likely involve disorders of specific circuits within specific brain regions."

So optogenetics, which can focus on individual circuits with exceptional precision, may hold promise for psychiatric treatment. But Dr. Deisseroth and others caution that it will be years before these tools are used on humans, if ever.

For one, the procedure involves bioengineering that most people would think twice about. First, biologists identify an "opsin," a protein found in photosensitive organisms like pond scum that allows them to detect light. Next, they fish out the opsin's gene and insert it into a neuron within the brain, using viruses that have been engineered to be harmless —"disposable molecular syringes," as Dr. Anderson calls them.

There, the opsin DNA becomes part of the cell's genetic material, and the resulting opsin proteins conduct electric currents — the language of the brain — when they are exposed to light. (Some opsins, like channelrhodopsin, which responds to blue light, activate neurons; others, like halorhodopsin, activated by yellow light, silence them.)

Finally, researchers delicately thread thin optical fibers down through layers of nervous tissue and deliver light to just the right spot.

Thanks to optogenetics, neuroscientists can go beyond observing correlations between the activity of neurons and an animal's behavior; by turning particular neurons on or off at will, they can prove that those neurons actually govern the behavior.

"Sometimes before I give talks, people will ask me about my 'imaging' tools," said Dr. Deisseroth, 39, a practicing psychiatrist whose dissatisfaction with current treatments led him to form a research laboratory in 2004 to develop and apply optogenetic technology.

"I say: 'Interestingly, it's the complete opposite of imaging, which is observational. We're not using light to observe events. We're sending light in to cause events.' "

In early experiments, scientists showed that they could make worms stop wiggling and drive mice around in manic circles as if by remote control.

Now that the technique has earned its stripes, laboratories around the world are using it to better understand how the nervous system works, and to study problems including chronic pain, Parkinson's disease and retinal degeneration.

Some of the insights gained from these experiments in the lab are already inching their way to the clinic.

Dr. Amit Etkin, a Stanford psychiatrist and researcher who collaborates with Dr. Deisseroth, is trying to translate the findings about anxiety in rodents to improve human therapy with existing tools. Using transcranial magnetic stimulation, a technique that is far less specific than optogenetics but has the advantage of being noninvasive, Dr. Etkin seeks to activate the human analog of the amygdala circuitry that reduced anxiety in Dr. Deisseroth's mice.

Dr. Jaimie Henderson, their colleague in the neurosurgery department, has treated more than 600 Parkinson's patients using a standard procedure called deep brain stimulation. The treatment, which requires implanting metal electrodes in a brain region called the subthalamic nucleus, improves coordination and fine motor control. But it also causes side effects, like involuntary muscle contractions and dizziness, perhaps because turning on electrodes deep inside the brain also activates extraneous circuits.

"If we could find a way to just activate the circuits that provide therapeutic benefit without the ones that cause side effects, that would obviously be very helpful," Dr. Henderson said.

Moreover, as with any invasive brain surgery, implanting electrodes carries the risk of infection and life-threatening hemorrhage. What if you could stimulate the brain's surface

instead? A new theory of how deep brain stimulation affects Parkinson's symptoms, based on optogenetics work in rodents, suggests that this might succeed.

Dr. Henderson has recently begun clinical tests in human patients, and hopes that this approach may also treat other problems associated with Parkinson's, like speech disorders.

In the building next door, Krishna V. Shenoy, a neuroscience researcher, is bringing optogenetics to work on primates. Extending the success of a similar effort by an M.I.T. group led by Robert Desimone and Edward S. Boyden, he recently inserted opsins into the brains of rhesus monkeys. They experienced no ill effects from the viruses or the optical fibers, and the team was able to control selected neurons using light.

Dr. Shenoy, who is part of an international effort financed by the Defense Advanced Research Projects Agency, says optogenetics has promise for new devices that could eventually help treat traumatic brain injury and equip wounded veterans with neural prostheses.

"Current systems can move a prosthetic arm to a cup, but without an artificial sense of touch it's very difficult to pick it up without either dropping or crushing it," he said. "By feeding information from sensors on the prosthetic fingertips directly back into the brain using optogenetics, one could in principle provide a high-fidelity artificial sense of touch."

Some researchers are already imagining how optogenetics-based treatments could be used directly on people if the biomedical challenge of safely delivering novel genes to patients can be overcome.

Dr. Boyden, who participated in the early development of optogenetics, runs a laboratory dedicated to creating and disseminating ever more powerful tools. He pointed out that light, unlike drugs and electrodes, can switch neurons off — or as he put it, "shut an entire circuit down." And shutting down overexcitable circuits is just what you'd want to do to an epileptic brain.

"If you want to turn off a brain circuit and the alternative is surgical removal of a brain region, optical fiber implants might seem preferable," Dr. Boyden said. Several labs are working on the problem, even if actual applications still seem far off.

For Dr. Deisseroth, who treats patients with autism and depression, optogenetics offers a more immediate promise: easing the stigma faced by people with mental illness, whose appearance of physical health can cause incomprehension from family members, friends

and doctors.

“Just understanding for us, as a society, that someone who has anxiety has a known or knowable circuitry difference is incredibly valuable,” he said.