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Social deficits associated with autism, schizophrenia induced in mice with new technology

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Researchers at Stanford University School of Medicine have been able to switch on, and then switch off, social-behavior deficits in mice that resemble those seen in people with autism and schizophrenia, thanks to a technology that allows scientists to precisely manipulate nerve activity in the brain. In synchrony with this experimentally induced socially aberrant behavior, the mice exhibited a brain-wave pattern called gamma oscillation that has been associated with autism and schizophrenia in humans, the researchers say.

The findings, to be published online in *Nature* on July 27, lend credence to a hypothesis that has been long floated but hard to test, until now. They mark the first demonstration, the researchers said, that elevating the brain's susceptibility to stimulation can produce social deficits resembling those of autism and schizophrenia, and that then restoring the balance eases those symptoms.

Autism spectrum disorder and schizophrenia each affect nearly 1 percent of all people. At present, there are no good drugs for mitigating the social-behavioral deficits of either disorder. While they differ in many ways, each syndrome is extremely complex, involving diverse deficits including social dysfunction. Mice are social animals, and there are many well-established tests of sociability in these animals.

Social behavior can't be ascribed to a single brain region, said Karl

Deisseroth, MD, PhD, associate professor of psychiatry and behavioral sciences and of bioengineering and the study's senior author. "To form a coherent pattern of another individual, you need to quickly integrate all kinds of sensations. And that's just the tip of the iceberg," said Deisseroth, a practicing psychiatrist who routinely sees autistic-spectrum patients. "It's all changing, millisecond by millisecond, as both you and the other individual act and react. You have to constantly alter your own predictions about what's coming next. This kind of interaction is immensely more uncertain than, for example, predator/prey activity. It seems that it has to involve the whole brain, not just one or another part of it."

One intriguing hypothesis holds that social dysfunctions characteristic of autism and schizophrenia may stem from an altered balance in the propensity of excitatory versus inhibitory nerve cells in the brain to fire, resulting in an overall hyper-responsiveness to stimulation. Evidence for this hypothesis includes the higher seizure rate among patients with autism, and the fact that many autistic children's brains exhibit elevated levels of a high-frequency brain-wave pattern — known as "gamma oscillation" — that can be picked up by an electroencephalogram. Many schizophrenics also exhibit social deficits as well as higher levels of this anomalous brain-wave pattern, even at rest.

In addition, said Deisseroth, "autistic kids seem to be over-responding to environmental stimuli." For instance, they find eye contact overwhelming, or may cover their ears if there are too many people talking at once.

There has been no direct way to test the "excitation/inhibition-balance" hypothesis, Deisseroth said. It's been impossible to experimentally shift the balance between excitation and inhibition in the brain by selectively raising the firing propensities of one class of nerve cells but not the opposing class, because there have been no drugs or electrophysiological

methods that act only on excitatory cells of the brain, or only on inhibitory cells.

But Deisseroth's team has a way of doing that, with a new technology, pioneered in his laboratory and called optogenetics: selectively bioengineering specific types of nerve cells so that they respond to light. These cells can be bioengineered to be either more or less likely — depending on the researchers' intent — to relay an impulse to the next nerve cell in a circuit. So with the flick of a switch, the scientists can activate a nerve circuit in the brain or inhibit it. Nerve cells can also be rendered responsive, in various ways, to different frequencies of light, allowing several circuits to be manipulated at once. (The optogenetic technique cannot be used in humans at this time as it requires still-experimental genetic modifications to brain cells.)

For the experiments in this study, the investigators targeted excitatory and inhibitory nerve cells in the medial prefrontal cortex, the most advanced part of the mouse brain, Deisseroth said. This region is very well-connected to everyplace else in the brain and is involved in processes such as planning, execution, personality and social behavior, he said.

"We didn't want to precisely direct the firing patterns of excitatory or inhibitory cells," Deisseroth said. "We wouldn't know where to start, because we don't know the neural codes of behavior. We just wanted to bias excitability."

Instead, the researchers bioengineered the nerve cells to respond to specific wavelength bands of light by becoming, for extended periods of time, either more or less likely to fire. "Nerve cells have an all-or-nothing tipping point," Deisseroth said. "Up to that point, they won't do much. But at a certain threshold, they fire."

The study's two first co-authors, postdoctoral researcher Ofer Yizhar, PhD, (now at Weizmann Institute of Science in Rehovot, Israel), and Lief Fenno, a graduate student in the medical school's MD/PhD program, devised ways of activating or inhibiting brain circuits by a light pulse for up to a half-hour, variously increasing or decreasing the firing propensity of nerve cells in those circuits. This time period was long enough to let the animals engage in various tests of social behavior.

The researchers subjected the mice they'd bioengineered to standard assays of rodent behavior, and compared the results to outcomes using normal mice.

The experimental mice exhibited no difference from the normal mice in tests of their anxiety levels, their tendency to move around or their curiosity about new objects. But, the team observed, the animals in whose medial prefrontal cortex excitability had been optogenetically stimulated lost virtually all interest in engaging with other mice to whom they were exposed. (The normal mice were much more curious about one another.)

"Boosting their excitatory nerve cells largely abolished their social behavior," Deisseroth said. In addition, these mice's brains showed the same gamma-oscillation pattern that is observed among many autistic and schizophrenic patients. "When you raise the firing likelihood of excitatory cells in the medial prefrontal cortex, you see an increased gamma oscillation right away, just as one would predict it would if this change in the excitatory/inhibitory balance were in fact relevant."

And when the scientists restored that balance by revving up inhibitory nerve-cell firing in the medial prefrontal cortex, they saw a moderate but significant recovery of social function.

"The behavioral results and the correspondence of gamma-oscillation

changes to alterations in the animals' excitatory/inhibitory balance suggest that that what we're observing in animals could be relevant to people," said Deisseroth.

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