Researchers tie social behavior to activity in specific brain circuit

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Credit: Rice University

A team of Stanford University investigators has linked a particular brain circuit to mammals' tendency to interact socially. Stimulating this circuit—one among millions in the brain—instantly increases a mouse's appetite for getting to know a strange mouse, while inhibiting it shuts down its drive to socialize with the stranger.

The new findings, to be published June 19 in *Cell*, may throw light on psychiatric disorders marked by impaired social interaction such as autism, social anxiety, schizophrenia and depression, said the study's senior author, Karl Deisseroth, MD, PhD, a professor of bioengineering and of psychiatry and behavioral sciences. The findings are also significant in that they highlight not merely the role of one or another brain chemical, as pharmacological studies tend to do, but rather the specific components of brain circuits involved in a complex behavior. A combination of cutting-edge techniques developed in Deisseroth's laboratory permitted unprecedented analysis of how brain activity controls behavior.

Deisseroth, the D.H. Chen Professor and a member of the interdisciplinary Stanford Bio-X institute, is a practicing psychiatrist who sees patients with severe social deficits. "People with autism, for example, often have an outright aversion to social interaction," he said. They can find socializing—even mere eye contact—painful.

Deisseroth pioneered a brain-exploration technique, optogenetics, that involves selectively introducing light-receptor molecules to the surfaces of particular nerve cells in a living animal's brain and then carefully positioning, near the circuit in question, the tip of a lengthy, ultra-thin optical fiber (connected to a laser diode at the other end) so that the photosensitive cells and the circuits they compose can be remotely stimulated or inhibited at the turn of a light switch while the animal remains free to move around in its cage.

Using optogenetics and other methods he and his associates have invented, Deisseroth and his associates were able to both manipulate and monitor activity in specific nerve-cell clusters, and the fiber tracts connecting them, in mice's brains in real time while the animals were exposed to either murine newcomers or inanimate objects in various laboratory environments. The mice's behavioral responses were captured by video and compared with simultaneously recorded brain-circuit activity.

In some cases, the researchers observed activity in various brain centers and nerve-fiber tracts connecting them as the mice variously examined or ignored one another. Other experiments involved stimulating or inhibiting impulses within those circuits to see how these manipulations affected the mice's social behavior.

To avoid confusing simple social interactions with mating- and aggression-related behaviors, the researchers restricted their experiments to female mouse pairs.

The scientists first examined the relationship between the mice's social interactions and a region in the brain stem called the ventral tegmental area. The VTA is a key node in the brain's reward circuitry, which produces sensations of pleasure in response to success in such survival-improving activities as eating, mating or finding a warm shelter in a cold environment.

The VTA transmits signals to other centers throughout the brain via tracts of fibers that secrete chemicals, including one called dopamine, at contact points abutting nerve cells within these faraway centers. When dopamine lands on receptors on those nerve cells, it can set off signaling activity within them.

Abnormal activity in the VTA has been linked to drug abuse and

depression, for example. But much less is known about this brain center's role in social behavior, and it had not previously been possible to observe or control activity along its connections during social behavior.

Deisseroth and his colleagues used mice whose dopamine-secreting, or dopaminergic, VTA nerve cells had been bioengineered to express optogenetic control proteins that could set off or inhibit signaling in the cells in response to light. They observed that enhancing activity in these cells increased a mouse's penchant for social interaction. When a newcomer was introduced into its cage, it came, it saw, it sniffed. Inhibiting the dopaminergic VTA cells had the opposite effect: The host lost much of its interest in the guest.

On the other hand, such manipulations of the VTA's dopaminergic cells had no effect on the mice's penchant for exploring novel objects (a golf ball, for example) placed in their cages. Nor did it change their overall propensity to move around. The effect appeared to be specific for social interaction.

Finding out exactly which dopaminergic projections from the VTA, traveling to which remote brain structures, were carrying the signals that generate exploratory social behavior required designing a new monitoring methodology. The signals traveling along such projections are extremely weak and confounded by background noise, especially when located deep within the brains of ambulatory animals. Deisseroth's group overcame this by developing a highly sensitive technology capable of plucking these tiny signals out of the surrounding noise. The new technique, called fiber photometry, is a sophisticated way of measuring calcium flux, which invariably accompanies signaling activity along the fibers projecting from nerve cells.

Using a combination of optogenetics and fiber photometry, the investigators were able to demonstrate that a particular tract projecting

from the VTA to a mid-brain structure called the nucleus accumbens (also strongly implicated in the reward system) was the relevant conduit carrying the impetus to social interaction in the mice.

A third technological trick helped determine which recipient nerve cells within the nucleus accumbens were involved in the social-behavior circuitry. That structure's two types of dopamine-responsive cells are differentiated by the types of dopamine receptors, referred to as D1 and D2, on their surfaces. The team performed experiments in animals bioengineered so that the normally D1-containing cells instead expressed a modified, light-inducible version of that receptor. These experiments, along with complementary experiments blocking the D1 receptors with specific drug antagonists, showed that the D1 nucleus-accumbens nerve cells were mediating the changes in social behavior. Tripping off those receptors, either by optogenetically inducing incoming tracts to deliver dopamine to these receptors, or by directly stimulating light-activated forms of these receptors on the target cells, enhanced mice's social exploration.

"Every behavior presumably arises from a pattern of activity in the brain, and every behavioral malfunction arises from malfunctioning circuitry," said Deisseroth, who is also co-director of Stanford's Cracking the Neural Code Program. "The ability, for the first time, to pinpoint a particular nerve-cell projection involved in the social behavior of a living, moving animal will greatly enhance our ability to understand how social behavior operates, and how it can go wrong."

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