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Scientists induce, relieve depression symptoms in mice with light

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Among those who suffer from depression, the dual inabilities to experience enjoyment in things once pleasurable and to physically motivate oneself—to meet challenges, or even to get out of bed in the morning—have been documented for decades, though it has been mysterious why these very different kinds of symptoms show up together, and also disappear together when depression is successfully treated. It has been suspected that the brain chemical dopamine could be a key player in the illness. And yet, in the long history of the study of depression, no one has been able to clearly tie these key concepts together, until now.

Researchers at Stanford University have successfully induced and relieved depression-like deficiencies in both pleasure and motivation in mice by controlling just a single area of the brain known as the ventral tegmental area. It is the first time that well-defined types of neurons within a specific brain region have been directly tied to the control of myriad symptoms of major depressive illness.

In the paper to be published in *Nature* on Dec. 12, Stanford bioengineer Karl Deisseroth, MD, PhD, and a team including postdoctoral scholars Kay Tye, PhD, and Melissa Warden, PhD, and research assistant Julie Mirzabekov have used a technique known as optogenetics to pinpoint a specific brain location that produces multiple depression-like symptoms. The region in question is the ventral tegmental area, or VTA, a source of dopamine and a central player in the brain's internal motivation and reward systems.

"We have for the first time directly tied dopamine neurons in the VTA to controlling and relieving these very different and diverse symptoms," said Deisseroth, the study's senior author and a professor of bioengineering and of psychiatry and behavioral sciences. "While depression is a complex disease with still many unknowns, this knowledge may help launch new kinds of investigation into the pathways of depression in the brain, and develop concepts to help people suffering from depression."

Deisseroth's team was able to both induce and relieve multiple depression-like symptoms in laboratory mice by genetically modifying the dopamine neurons in the VTA to be sensitive to light. Using fiber optic cables inserted in rodents' brains, they could then instantaneously produce and inhibit the depression-like symptoms by turning the light on and off. This research technique, developed by Deisseroth at Stanford in 2005, is known as optogenetics.

The team examined mice in a depressed-like, low-motivation state induced by mild stressors whose VTA neurons had been optogenetically modified. "When given light stimulation to the VTA dopamine neurons, these mice showed a robust increase in escape-related behavior. They immediately tried harder to get out of challenging situations—reversing back to normal levels of effort from the depressed-like state they were in," explained Deisseroth.

Similarly, he said, when offered the choice of sugar water over plain, the mice that had been in a depressed-like state chose the sugar water with much greater frequency when their VTA dopamine neurons were stimulated by illumination. They opted to experience pleasure—back to normal levels. Finally, and remarkably, Deisseroth noted, optogenetically inhibiting the VTA dopamine neurons instead of stimulating them caused, rather than corrected, both kinds of depression symptoms—instantaneously and reversibly.

"These results directly implicated a single class of neuron in a single brain region—ventral tegmental dopamine neurons—in both producing and relieving very different depression-related symptoms, addressing a mystery in disease pathophysiology," said Deisseroth.

And yet, another key question still remained: What are the VTA dopamine neurons doing to downstream circuits? In other words, how are the depression-related control signals read out? To answer these questions, the researchers next took the work a step further by mapping the effects of dopamine neuron activity in the VTA on the nucleus accumbens, a brain center thought to influence diverse functions of pleasure, and likely the site of action for addictive drugs as well as natural rewards. Seeing a change in the nucleus accumbens would provide information on the mechanism for how VTA dopamine neuron effects are manifested in the brain.

"Indeed, we established that electrophysiological representation of action in the nucleus accumbens is in fact fundamentally altered by VTA dopamine neuron activation. If we activate the VTA dopamine neurons, it influences the nucleus accumbens' encoding of physical, motivated action," emphasized Deisseroth. Together, these results represented a long-sought circuit-level insight into the causes and nature of depression-related behavior.

While the results are significant, Deisseroth, who is also a practicing psychiatrist, cautioned that depression and other mental illnesses are complex, multidimensional and vary from patient to patient. The symptoms of depression are certainly influenced by many neural circuits, he said.

"Nonetheless, the VTA dopamine circuitry we studied is very similar in both rodents and humans. And we have shown that the neurons in this circuit specifically cause, correct and encode diverse symptoms of

depression. This is a significant advance in our understanding of the biological underpinnings of depression and related behaviors, with promising implications for future research," said Deisseroth.

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