Brain's cerebellum found to influence addictive and social behavior

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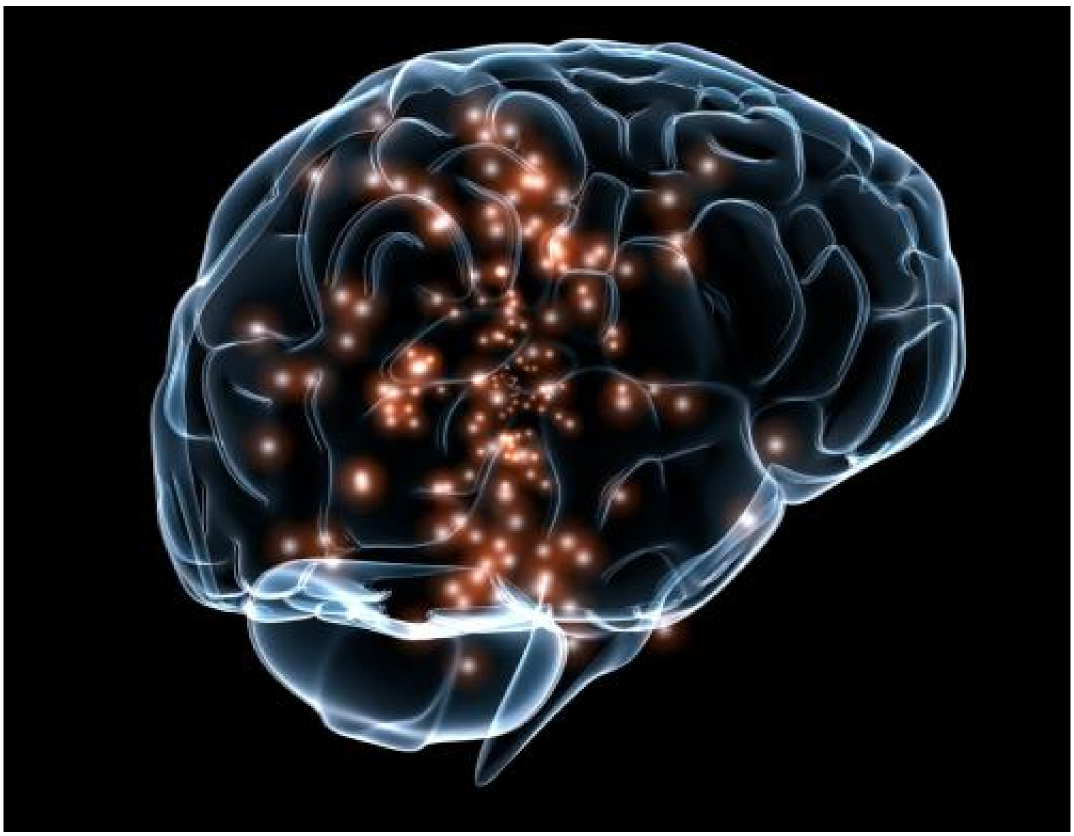

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In a study published online today in the journal *Science*, researchers at Albert Einstein College of Medicine, part of Montefiore, prove for the first time that the brain's cerebellum—long thought to be mainly involved in coordinating movement—helps control the brain's reward circuitry. The surprising finding indicates that the cerebellum plays a major role in reward processing and social behaviors and could potentially lead to new strategies for treating addiction.

Previous studies had hinted that the talents of the cerebellum—a fist-sized structure located just above the brainstem—were under-appreciated. For example, several functional MRI studies (which measure blood-flow changes that occur with brain activity) assessed the brain activity of people recovering from addiction who were shown images associated with their addiction, such as a syringe. Unexpectedly, the cerebella of these individuals glowed on MRI scans, indicating heightened activity; in addition, the intensity of the glow correlated with a person's risk of relapse. This and other evidence suggested that the cerebellum is somehow involved in triggering release of the feel-good neurotransmitter dopamine in brain areas that receive rewarding stimuli.

"The notion that the cerebellum did much beyond controlling movement was met with a lot of skepticism—and no one had any real clues as to how the cerebellum might affect dopamine release," said study leader Kamran Khodakhah, Ph.D., professor and chair of the Dominick P. Purpura Department of Neuroscience and the Florence and Irving Rubinstein Chair in Neuroscience. Ilaria Carta, a Ph.D. student at Einstein, and Christopher Chen, Ph.D., are co-first authors on the study.

Dr. Khodakhah, who is also professor of psychiatry and behavioral sciences and professor in the Saul R. Korey Department of Neurology, suspected that the cerebellum directly connected with and activated the ventral tegmental area (VTA), a nearby structure known to play a role in addiction. (VTA neurons synthesize and release dopamine into the mesolimbic pathway, which mediates pleasure and reward.) In studies designed to test this hypothesis, his lab showed that stimulating cerebellar neurons activates the VTA and leads to "addictive" behaviors in mice.

Opting for Optogenetics

To conduct these studies, Dr. Khodakhah used optogenetics, which involves inserting genes that produce light-sensitive proteins into select neurons. The researchers are then able to selectively activate or inactivate the treated neurons by exposing them to light.

In an initial experiment, Dr. Khodakhah's team inserted the genes into cerebellar neurons, some of which connected with the VTA via long fibers called axons. When the cerebellar axons extending into the VTA were selectively stimulated with light, about one third of the VTA neurons increased their firing. Since only the cerebellar axons contained the light-sensitive proteins and could be activated by the light, this experiment proved for the first time that cerebellar neurons form working synapses (connections) with VTA neurons.

Triggering the Reward Center

Do those connections have any influence on behavior? To answer that question, Dr. Khodakhah conducted a so-called open-field chamber test, in which mice were free to explore any corner of a square enclosure. Each time a mouse reached a particular corner (randomly chosen for each mouse), cerebellar neurons linked to the VTA were optogenetically stimulated. If the mice found this stimulation pleasurable, they'd be expected to preferentially return to this corner (to get another rewarding flash of light) instead of to the other corners—and they did, much more often than occurred with control animals.

Could stimulating cerebellar projections to the VTA trigger "addiction" in mice? To find out, Dr. Khodakhah and colleagues put mice in a chamber that was half dark and half brightly lit. Since mice prefer dark areas—the better to avoid becoming a predator's next meal—they spent more time exploring the dark part of the chamber. The researchers then repeated the experiment—except this time, every other day for six days, mice were confined to the bright side for 30 minutes while cerebellar axons with connections to the VTA were optogenetically stimulated. After that initial conditioning period, the mice were allowed to freely explore the entire chamber.

"Even though mice normally shun bright areas, now they preferentially ran toward the light, because that's where they remembered getting a reward," said Dr. Khodakhah. "This suggests that the cerebellum plays a role in addictive behaviors." He notes that the results were "very similar" to findings in other studies in which mice confined to the bright part of chambers received addictive drugs such as cocaine instead of cerebellar stimulation.

A Role in Social Behavior

Cerebellum abnormalities have been implicated in autism spectrum disorder (ASD), although how the cerebellum contributes to ASD isn't clear. Because the VTA is required for social behavior, Dr. Khodakhah and colleagues tested whether the cerebellum-VTA pathway may be involved. They placed mice in a three-chambered box in which they were free to travel to an inanimate object, another mouse or an empty chamber. The activity of cerebellar axons within their VTA was monitored.

The mice being studied typically spent most of their time socializing with another mouse—and when they did, cerebellar axons in their VTA were most active, consistent with the idea that the cerebellum relays information relevant to social behavior to the VTA. Intriguingly, when the researchers optogenetically silenced cerebellar axons projecting into the VTA, the mice no longer preferred interacting with other mice. This finding suggests that social behavior requires a functioning cerebellum-

VTA pathway and that interference with this pathway may be a glitch through which cerebellar dysfunction contributes to ASD.

Next Steps

In future studies, Dr. Khodakhah will test whether the cerebellum-VTA pathway can be manipulated, using drugs or optogenetics, to treat addiction and prevent relapse after treatment. He will also investigate whether cerebellar neurons affect the prefrontal cortex and the nucleus accumbens, two other brain regions that are targeted by the VTA and are intimately associated with addictive behavior and mental disorders. "Cerebellar abnormalities are also linked to a number of other mental disorders such as schizophrenia," said Dr. Khodakhah, "so we want to find out whether this pathway also plays a role in those disorders."

More information: I. Carta el al., "Cerebellar modulation of the reward circuitry and social behavior," *Science* (2019). science.sciencemag.org/cgi/doi … 1126/science.aav0581

"The cerebellum gets social," *Science* (2019). science.sciencemag.org/cgi/doi … 1126/science.aaw2571

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