Deficiency in certain brain proteins shown to promote compulsive behavior

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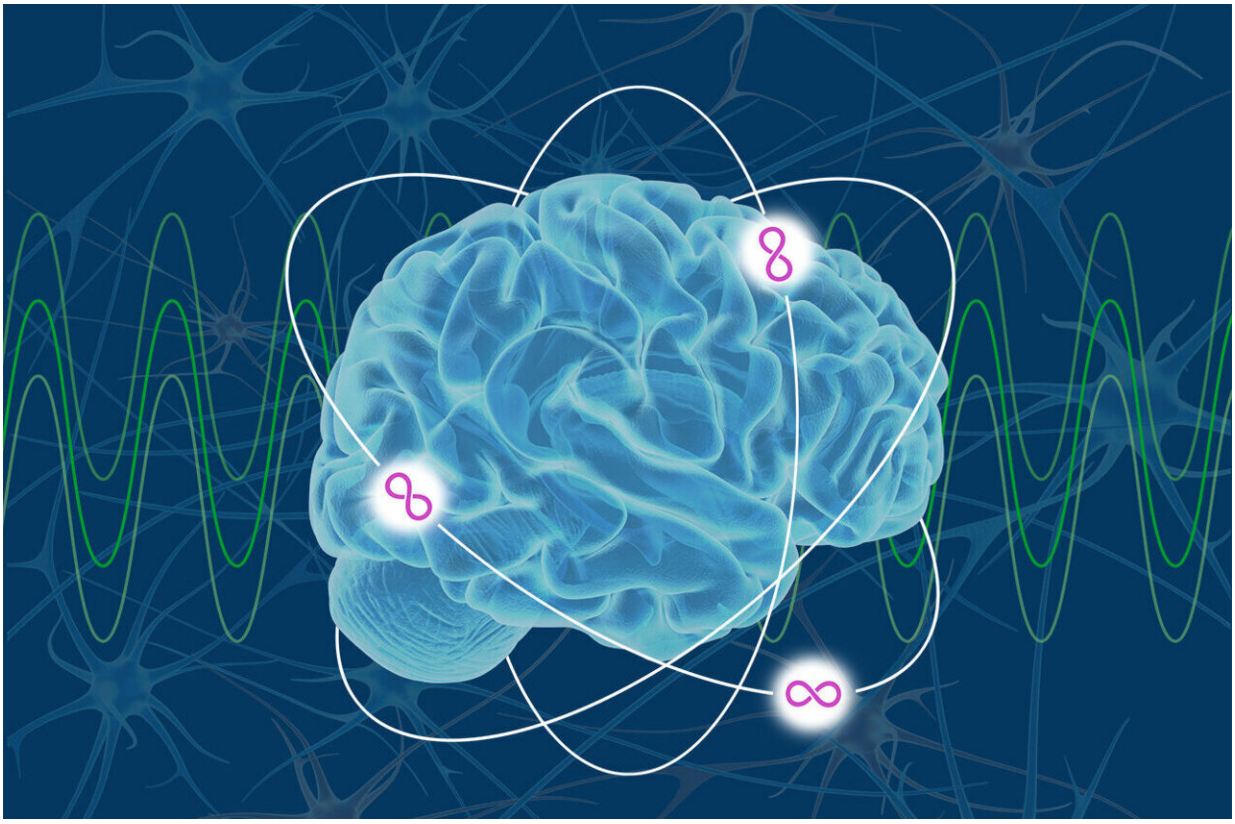

Credit: Claudia Knorr/FMP

Our behavior is controlled through neural circuits in the brain. Molecular disturbances can lead to stereotypical behavior, as seen in neuropsychiatric disorders such as obsessive-compulsive and autism

spectrum disorders.

A research team has now demonstrated that the absence of two proteins, Intersectin1 and Intersectin2, in mice leads to disrupted neural signaling and compulsive repetitive behavior, which is also observed in patients with Intersectin 1 mutations. This supports the idea that such defects can cause neuropsychiatric diseases. The study is published in *Proceedings of the National Academy of Sciences*.

Our brain is essentially our body's computer. Through a complex interplay of various nerve cells in different areas, it controls and regulates all vital functions, such as breathing, how we move and speak, and how we respond to environmental stimuli with specific behavioral patterns. The so-called cortico-striatal circuit, which connects the cortex and striatum, two parts of the cerebrum, plays a key role in guiding goal-directed behavior.

"We already know that human behavioral disorders, in which a specific behavior is compulsively repeated, are associated with this circuit or network," says Professor Dr. Tanja Maritzen, who studies nanophysiology at the University of Kaiserslautern-Landau (RPTU). However, much of what happens in this part of the brain at the molecular level remains a mystery to science.

In the current study, the team around Tanja Maritzen closely collaborated with the laboratory of Prof. Dr. Volker Haucke from Leibniz-Forschungsinstitut für Molekulare Pharmakologie (FMP), Charité Universitätsmedizin Berlin and Freie Universität Berlin. The researchers focused on two specific proteins that play a crucial role in this circuit.

"Intersectin 1 and Intersectin 2 are large scaffold proteins that have many interaction sites," says Professor Haucke. "Previous research has

shown that their mutation in humans correlates with behavioral abnormalities."

To explore their exact role, the team inhibited the production of these proteins in mice. The results showed that the Intersectin proteins are vital for the organism, as some of the mice died early. A different subset displayed behavioral abnormalities: they stood on their hind legs in the corner and repeatedly jumped up and down.

"Such symptoms, where a particular, essentially pointless behavior is compulsively repeated, are also known in neuropsychiatric diseases," Professor Maritzen notes, citing autism spectrum disorders and obsessive-compulsive disorders as examples.

But what goes wrong at the molecular level? The team specifically looked at the NMDA receptor. "We observed that the absence of the two proteins results in fewer of these receptors at the ends of nerve cells, the synapses," explains Professor Haucke. This is crucial for the transmission of signals from one nerve cell to another. Neurotransmitters, chemical messengers, carry the excitation between cells by binding to receptors. "The Intersectin proteins, as scaffold proteins, are important to stabilize the NMDA receptor at the synapse."

The deficiency of these proteins isn't solely responsible for the onset of behavioral abnormalities. It is rather one component in a complex molecular system. This study has helped us to understand a part of it better, reinforcing the notion that mutations in Intersectin can lead to neurological symptoms. Moreover, the study suggests that the NMDA receptor is a potential candidate for developing drug therapies for neuropsychiatric disorders.

More information: Dennis Vollweiter et al, Intersectin deficiency impairs cortico-striatal neurotransmission and causes

obsessive–compulsive behaviors in mice, *Proceedings of the National Academy of Sciences* (2023). DOI: 10.1073/pnas.2304323120