UNIVERSITÉ DE GENÈVE

PRESS RELEASE

Geneva | Month XXth, 20XX

Hôpitaux Universitaires Genève

WARNING: embargoed until Month XXth, 20XX, XX:XX GMT

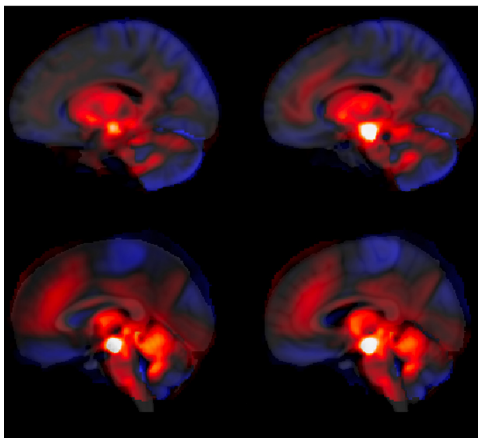
Schizophrenia: The cerebellum's unexpected role

A UNIGE and HUG team has, for the first time, described the interaction between the cerebellum and the brain's reward system in people with schizophrenia.

Apathy, social withdrawal, and loss of motivation — the so-called "negative" symptoms of schizophrenia — are among the most disabling and hardest to treat. A team from the University of Geneva (UNIGE) has now uncovered the unexpected role of the cerebellum in the emergence of these symptoms, through its ability to modulate the brain's reward system. This mechanism, which has remained largely unexplored until now, opens the door to new targeted and non-invasive therapeutic approaches. The study is published in *Biological Psychiatry*.

Schizophrenia is a neuropsychiatric disorder that affects around 1% of the population and is best known for its hallucinatory and delusional symptoms. However, it is also marked by profound apathy, a reduced ability to experience pleasure, and progressive social withdrawal. These so-called "negative" symptoms — for which no effective treatment currently exists — are particularly disabling.

Several studies have shown that abnormalities in the brain's reward system — particularly in the dopamine-producing ventral tegmental area (VTA) — are associated with these symptoms. In people with schizophrenia, the VTA is believed to be overactive, leading to a blunted perception of salience, where "everything feels the same," and resulting in a lack of motivation.



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Illustrative image of the connectivity between the cerebellum and the VTA.

The cerebellum, a hidden regulator

In an innovative study, a team from the University of Geneva (UNIGE) and the Geneva University Hospitals (HUG) has shown that the cerebellum plays a key role in regulating — or dysregulating — this mechanism via the VTA. "What is sometimes called our 'little brain' actually contains 50% of all our neurons. Although it was long considered to have a purely motor function, we are now discovering that it also plays important emotional and cognitive roles," explains Indrit Bègue, Assistant Professor in the Laboratory of Neuroimaging and Translational Psychiatry in the Department of Psychiatry at the UNIGE Faculty of Medicine, researcher at the Synapsy Centre for Neuroscience Research in Mental Health, and University hospital physician in the Department of Adult Psychiatry at HUG, who led the study.

High resolution pictures

By following 146 patients over a period of 3 to 9 months, and by analysing an independent validation cohort, the team was able to observe and describe for the first time the functional connection between the cerebellum and the VTA in the context of schizophrenia.

"We show that stronger cerebellar regulation of the reward system is associated with a reduction in negative symptoms — and conversely, weaker regulation with an increase in symptoms. This newly identified mechanism opens up promising avenues for targeted therapeutic interventions," explains Jade Awada, a doctoral student in Indrit Bègue's team at the Laboratory of Neuroimaging and Translational Psychiatry in the Department of Psychiatry at the UNIGE Faculty of Medicine, researcher at the Synapsy Centre for Neuroscience Research in Mental Health, and first author of the study. The analyses were carried out by Jade Awada and Farnaz Delavari, co-first author of the study and a researcher in Professor Stephan Eliez's laboratory.

A more accessible therapeutic target?

Unlike the VTA, which lies deep within the brain, the cerebellum is located on the surface, at the back of the skull. This makes it far more accessible — and a promising target for non-invasive interventions such as transcranial magnetic stimulation (TMS). "This technique involves generating magnetic fields near the targeted brain area — in this case, the cerebellum — in order to stimulate and strengthen its activity. We are currently evaluating the potential of this approach to 'treat' the circuit between the cerebellum and the VTA that we identified in our study," explains Indrit Bègue. A randomized controlled trial, funded by the Leenaards Foundation (2023 Science Prize) and the Fondation Privée des HUG, is already under way with a cohort of patients at Campus Biotech. Results are expected in 2028.

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DOI: 10.1016/j.biopsych.2025.06.009

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