Researchers discover a mechanism that impairs synaptic plasticity in the brains of schizophrenia patients

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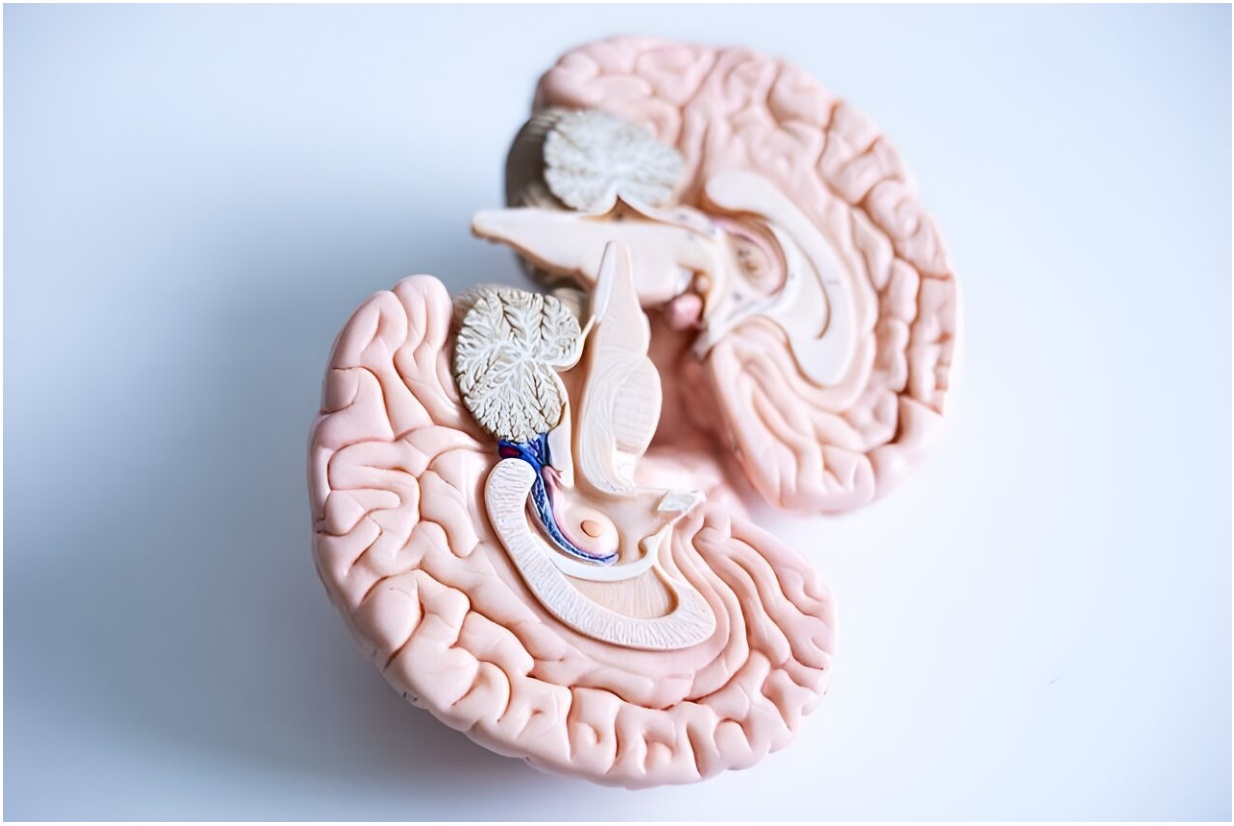

A recent study demonstrates that specific alterations in the expression of genes associated with schizophrenia result in impairments in synaptic plasticity. Credit: Jonne Renvall

A study led by researchers at Tampere University has mapped genes linked to schizophrenia and uncovered a mechanism that disrupts synaptic plasticity in affected individuals. The researchers showed the role of three proteins in mediating the impairments of plasticity in schizophrenia. The findings may hold promise for the development of new treatments.

The research paper titled "Genetic mechanisms for impaired synaptic plasticity in schizophrenia revealed by computational modeling" was published in the *Proceedings of the National Academy of Sciences* on 14 August.

Although significant progress has been made in understanding the association of genes and genetic variants with schizophrenia, the genetic mechanisms underlying this mental disorder remain elusive. This is partly because it has been impossible to test how the variants of each gene or their altered expression influence the symptoms or phenotypes of schizophrenia, which are the observable characteristics of the condition in individual patients.

Advances in computational neuroscience now enable researchers to study psychiatric disorders using computational simulations. In a recent study, researchers at Tampere University collaborated with partners in Norway and the U.S. to develop a computational model for testing the effects of genetic and molecular alterations on synaptic plasticity.

Synaptic plasticity—a cellular mechanism whereby the strength of synaptic connections between neurons strengthens or weakens over time—is crucial for learning and memory. Disruptions in this process are believed to contribute to the development of schizophrenia.

"Our computational model demonstrates that specific alterations in the expression of genes associated with schizophrenia result in impairments

in synaptic plasticity. This conclusion is supported by our subsequent analysis, where we adjusted polygenic risk scores from genome-wide association studies to measure the exclusive contribution of plasticity-related genes to the risk of developing schizophrenia," says Academy Research Fellow Tuomo Mäki-Marttunen, the lead author of the research paper.

Genome-wide association studies (GWAS) are conducted to identify statistical associations between different regions of the genome and a particular phenotype. These studies are particularly useful for investigating polygenic conditions, such as schizophrenia, which result from the interplay of hundreds or thousands of genetic variants.

"The adjusted polygenic risk factors were found to correlate with an impaired response to visual stimuli detected by the electroencephalograms (EEGs) performed by our collaborators. This demonstrates that certain genetic variants among plasticity-related genes can predict an impaired EEG response. Our computational model was therefore shown to accurately, or at least more reliably, predict a disruption of plasticity in schizophrenia," Mäki-Marttunen says.

The next step is to consider the impact of environmental factors

According to Mäki-Marttunen, the findings mark an important step forward in understanding the mechanisms underlying schizophrenia, as they provide a mechanistic polygenic model for examining the single-cell level pathology associated with the condition. Few computational models currently account for the contributions of multiple genes.

Studies on animals have revealed the effects of individual radical genetic mutations at the cellular and behavioral levels. On the other hand, new in

vitro techniques have shed light on how the phenotypes of schizophrenia are affected by switching the whole genome between schizophrenia patients and healthy controls. However, experimentally measuring how the interplay of multiple genes contributes to the phenotypes of the condition and identifying which genetic variants among thousands are responsible for the observed changes remains challenging.

"Our computational modeling approach addresses this gap. We can assess each gene individually to determine how different alterations in gene expression levels impact the phenotype of schizophrenia. In addition, we can easily investigate the combined effects of alterations in the expression of multiple genes," explains Mäki-Marttunen.

The findings highlight three plasticity-related proteins that may significantly contribute to the schizophrenia-associated plasticity deficits. Mäki-Marttunen hopes that the findings will inspire new animal and cell culture studies to further elucidate the role of these proteins in the condition. This could pave the way for new treatments.

"Our study does not yet explain how the observed alterations in gene expression and the resulting changes in synaptic plasticity affect the symptoms of schizophrenia. To address this, we need new computational models to explore the phenomena associated with schizophrenia symptoms, such as working memory. In addition, our computational model should be expanded, so we could study the impact of not only hereditary but also environmental factors on the symptoms and phenotypes of schizophrenia," Mäki-Marttunen says.

The study is a part of the Neural model building for psychiatric diseases—From genes to networks (ModelPsych) project, which runs from 2020 to 2025.

More information: Tuomo Mäki-Marttunen et al, Genetic

mechanisms for impaired synaptic plasticity in schizophrenia revealed by computational modeling, *Proceedings of the National Academy of Sciences* (2024). DOI: 10.1073/pnas.2312511121