Computer modeling provides insight into cellular-level effects of schizophrenia risk genes

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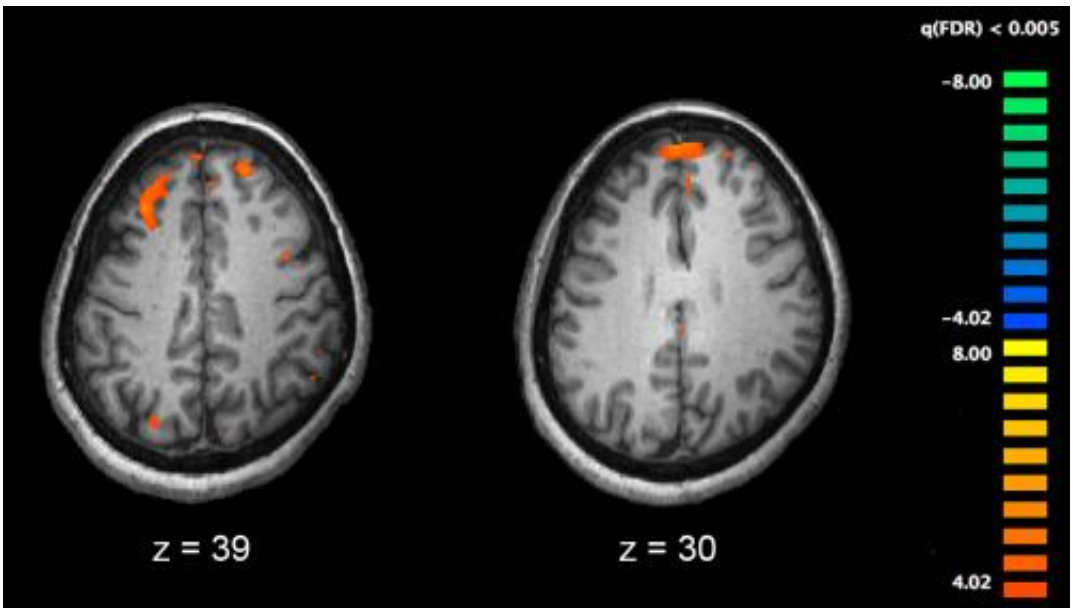

Functional magnetic resonance imaging (fMRI) and other brain imaging technologies allow for the study of differences in brain activity in people diagnosed with schizophrenia. The image shows two levels of the brain, with areas that were more active in healthy controls than in schizophrenia patients shown in orange, during an fMRI study of working memory. Credit: Kim J, Matthews NL, Park S./PLoS One.

Numerous genetic variants associated with risk for schizophrenia have been identified. However, little is known about how these genes have

their effects in the brain.

A proof-of-concept study published in the inaugural issue of the journal *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* proposes a computer model for measuring the cumulative impact of multiple genetic variations on the function of individual neurons.

Authors of the study focused on schizophrenia-linked gene variations that are known to influence cellular structures such as ion channels and calcium transporters. Any changes to these structures would have an impact on the excitability of individual neurons. Using computational analysis, the investigators were able to predict how alterations in these structures would change the behavior of neuronal cells.

"Our computational simulations suggest that mutations in many of the schizophrenia-linked genes affect specific aspects of neuronal excitability and synaptic integration at the single-cell level," explained Dr. Anders Dale, corresponding author of the study and Professor of Neurosciences and Radiology at University of California, San Diego. "The results may provide important clues about basic physiological mechanisms underlying schizophrenia, which could be targeted with pharmaceutical interventions, and also lead to more targeted biomarkers for assessing therapeutic effects."

The published results suggest that most of the studied gene variants could have significant effects on a neuron's behavior. These neuronal changes could be a fundamental contributor to schizophrenia and other psychiatric disorders.

In addition to schizophrenia, this new computational model could be applied to other conditions including bipolar disorder, autism, attention-deficit/hyperactivity disorder, and substance use and addiction, as risk genes related to neuronal excitability in those conditions are identified.

"This novel approach integrates biological and mathematical modeling in the brain to help us understand the link between genetic risk and altered brain function," said Dr. Cameron Carter, Professor of Psychiatry and Behavioral Sciences at University of California, Davis and Editor of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*. "Understanding the effect that disease-related genetic variation has on cells could unlock new insights into how to diagnose and treat these disorders."

More information: Tuomo Mäki-Marttunen et al. Functional Effects of Schizophrenia-Linked Genetic Variants on Intrinsic Single-Neuron Excitability: A Modeling Study, *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* (2016). DOI: 10.1016/j.bpsc.2015.09.002

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