High levels of glutamate in brain may kick-start schizophrenia

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An excess of the brain neurotransmitter glutamate may cause a transition to psychosis in people who are at risk for schizophrenia, reports a study from investigators at Columbia University Medical Center (CUMC) published in the current issue of *Neuron*.

The findings suggest 1) a potential diagnostic tool for identifying those at risk for schizophrenia and 2) a possible glutamate-limiting treatment strategy to prevent or slow progression of schizophrenia and related psychotic disorders.

"Previous studies of schizophrenia have shown that hypermetabolism and atrophy of the hippocampus are among the most prominent changes in the patient's brain," said senior author Scott Small, MD, Boris and Rose Katz Professor of Neurology at CUMC. "The most recent findings had suggested that these changes occur very early in the disease, which may point to a brain process that could be detected even before the disease begins."

To locate that process, the Columbia researchers used neuroimaging tools in both patients and a mouse model. First they followed a group of 25 young people at risk for schizophrenia to determine what happens to the brain as patients develop the disorder. In patients who progressed to schizophrenia, they found the following pattern: First, glutamate activity increased in the hippocampus, then hippocampus metabolism increased, and then the hippocampus began to atrophy.

To see if the increase in glutamate led to the other hippocampus changes, the researchers turned to a mouse model of schizophrenia. When the researchers increased glutamate activity in the mouse, they saw the same pattern as in the patients: The hippocampus became hypermetabolic and, if glutamate was raised repeatedly, the hippocampus began to atrophy.

Theoretically, this dysregulation of glutamate and hypermetabolism could be identified through imaging individuals who are either at risk for or in the early stage of disease. For these patients, treatment to control glutamate release might protect the hippocampus and prevent or slow the progression of psychosis.

Strategies to treat schizophrenia by reducing glutamate have been tried before, but with patients in whom the disease is more advanced. "Targeting glutamate may be more useful in high-risk people or in those with early signs of the disorder," said Jeffrey A. Lieberman, MD, a renowned expert in the field of schizophrenia, Chair of the Department of Psychiatry at CUMC, and president-elect of the American Psychiatric Association. "Early intervention may prevent the debilitating effects of schizophrenia, increasing recovery in one of humankind's most costly mental disorders."

In an accompanying commentary, Bita Moghaddam, professor of neuroscience and of psychiatry, University of Pittsburgh, suggests that if excess glutamate is driving schizophrenia in high-risk individuals, it may also explain why a patient's first psychotic episodes are often caused by periods of stress, since stress increases glutamate levels in the brain.

More information: "Imaging Patients with Psychosis and a Mouse Model Establishes a Spreading Pattern of Hippocampal Dysfunction and Implicates Glutamate as a Driver" *Neuron*, 2013.