# Researchers identify new target in brain for treating schizophrenia

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Research from the University of Pittsburgh could expand the options for controlling schizophrenia by identifying a brain region that responds to more than one type of antipsychotic drug. The findings illustrate for the first time that the orbitofrontal cortex could be a promising target for developing future antipsychotic drugs—even those that have very different mechanisms of action. The study will be published during the week of Nov. 3 in the online edition of the journal *Proceedings of National Academy of Sciences*, with a print version to follow.

Bita Moghaddam, a professor in the Department of Neuroscience in Pitt's School of Arts and Sciences and the paper's lead author, found that schizophrenia-like activity in the orbitofrontal cortex—a brain region responsible for cognitive activity such as decision making—could be triggered by the two different neurotransmitters linked to schizophrenia: dopamine and glutamate. Brain activity was then normalized both by established antipsychotic medications that regulate only dopamine and by experimental treatments that specifically target glutamate.

"The orbitofrontal cortex is an area that's been somewhat neglected in schizophrenia research. This study should encourage researchers to focus on this brain region in imaging and other human studies, and also to use as a model for developing antipsychotic drugs," Moghaddam said. "Schizophrenia appears to be caused by very diverse and sometimes rare genetic mutations. Diverse mutations can end up causing the same disease if they disrupt the function of a common group of neurons or networks of neurons. We think that the key to understanding the

pathophysiology of schizophrenia and finding better treatments is to identify these networks. This data suggests that the orbitofrontal cortex may be a critical component in networks affected by schizophrenia."

Working with UPMC neurology resident Houman Homayoun, Moghaddam first established that dopamine and glutamate could, separately, produce schizophrenia-like symptoms in the orbitofrontal cortex. They first simulated symptoms brought on by irregular neural receptors of glutamate. Studies within the last few years—including work by Moghaddam at Yale University—have shown that under-functioning glutamate receptors known as NMDA receptors can produce schizophrenia-like symptoms. Moghaddam and Homayoun found that stunting the NMDA receptors resulted in schizophrenia-like effects in the orbitofrontal cortex. The team also used a dose of amphetamine to simulate dopamine-related schizophrenia symptoms in the orbitofrontal cortex; schizophrenia is often linked to an excess of dopamine in the brain.

Moghaddam and Homayoun then tested the currently prescribed medication—a treatment developed more than 50 years ago that targets neural receptors of dopamine—and new experimental drugs that work on the glutamate system. They found that both medications normalized brain activity.

Source: University of Pittsburgh

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