Disproving hypothesis clears path for research for new treatment options for schizophrenia

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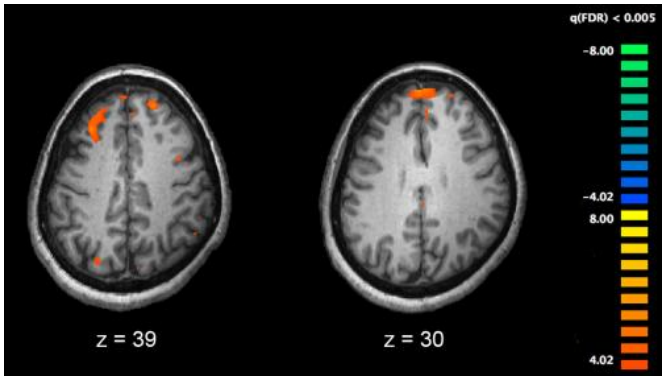

Functional magnetic resonance imaging (fMRI) and other brain imaging technologies allow for the study of differences in brain activity in people diagnosed with schizophrenia. The image shows two levels of the brain, with areas that were more active in healthy controls than in schizophrenia patients shown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

Researchers reported results from the first repeated-dose study of a dopamine-1 receptor (D1R) agonist for treating the cognitive and negative symptoms of schizophrenia today in the *Journal of Psychopharmacology*.

Cognitive and negative symptoms, such as problems with social interactions, affect and responsiveness, slowed movement and speech, and memory problems, are central features of schizophrenia and cause major limitations in functional capacity for patients. These symptoms can begin even before psychotic symptoms of the disorder manifest. Currently, there are no effective treatments for these symptoms.

Based on preclinical research published in 2000, which suggested that reduced signaling through the D1R might contribute to cognitive and negative symptoms, scientists speculated that administering ultra-low doses of D1R agonists might help counteract these symptoms in patients with schizophrenia. For over a decade, researchers have sought to reproduce comparable results in clinical studies, with mixed findings and no definitive answers.

In this study, the researchers randomized 49 participants to receive low intermittent doses of a D1R agonist or placebo over three weeks. Functional magnetic resonance imaging was used to evaluate the effects of the drug on brain activity during a working memory task. No treatment effects were observed.

"This study does not support the hypothesis that ultra-low amounts of D1R stimulation would be beneficial in treating cognitive or negative symptoms in schizophrenia." said Jeffrey A. Lieberman, MD, the Lawrence C. Kolb professor and chair of psychiatry at Columbia University Medical Center (CUMC), director of the New York State Psychiatric Institute (NYSPI), and the senior author of the study. "However, our findings do not preclude the possibility that a D1R agonist administered at higher doses might be therapeutic."

"Resources should be directed to seeking novel drugs that stimulate the D1R at higher levels, and with longer durations of action and exposure," noted lead author Ragy Girgis, MD, assistant professor of clinical psychiatry at CUMC and director of the COPE Clinic at NYSPI. "The challenge to develop better paradigms that test the efficacy of higher dose treatments without causing unacceptable side effects is the focus of the next stage of our research."