Researchers eye potential schizophrenia 'switch'

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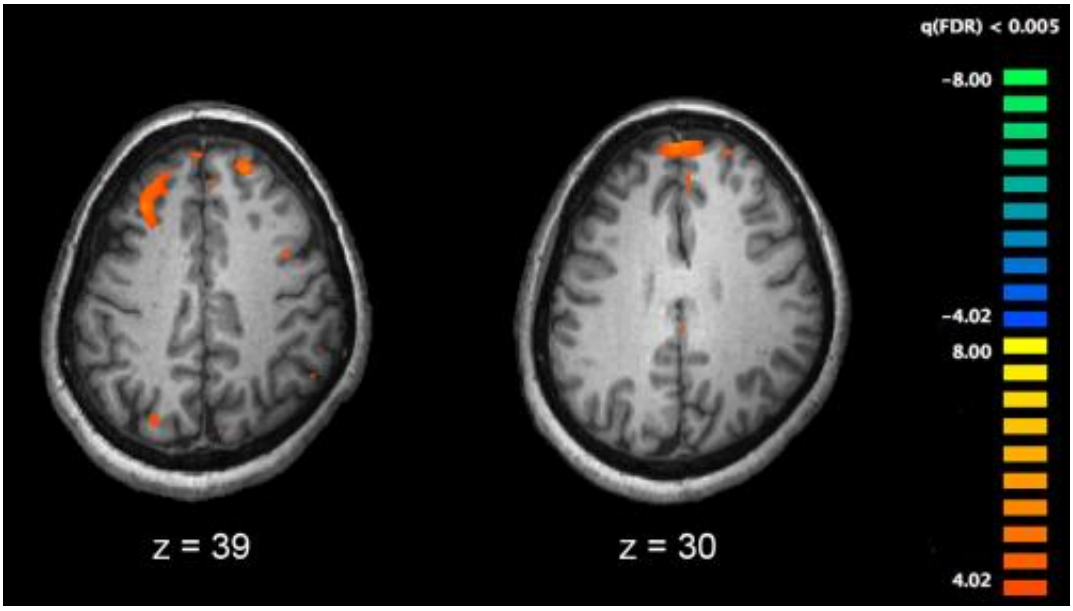

Functional magnetic resonance imaging (fMRI) and other brain imaging technologies allow for the study of differences in brain activity in people diagnosed with schizophrenia. The image shows two levels of the brain, with areas that were more active in healthy controls than in schizophrenia patients shown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

Researchers at Vanderbilt University Medical Center have discovered a key mechanism that explains how compounds they're developing can suppress schizophrenia-like symptoms in mice without side effects.

On the basis of this discovery, reported this month in the journal *Neuron*, "we now have much stronger understanding of the therapeutic potential and mechanism of action of compounds that are advancing to clinical development," said P. Jeffrey Conn, Ph.D., director of the Vanderbilt Center for Neuroscience Drug Discovery.

An estimated 3 million Americans have schizophrenia, which is associated with excessive amounts of the neurotransmitter dopamine in a part of the forebrain called the striatum.

Current medications reduce hallucinations and delusions, the hallmark of schizophrenia, by blocking dopamine receptors. But because they also block dopamine receptors in the cerebral cortex, they can worsen cognitive difficulties.

That's why a new treatment approach is urgently needed, said Conn, the Lee E. Limbird Professor of Pharmacology at Vanderbilt University School of Medicine.

Several years ago, a drug being tested in humans for treatment of Alzheimer's disease was shown to have "robust" effects in reducing psychotic symptoms in both Alzheimer's and schizophrenia patients. The drug activated "muscarinic" receptors in the brain that bind the neurotransmitter acetylcholine.

While the drug didn't make it to market, Conn and his colleagues seized on the possibility that activating muscarinic receptors could be a new way to treat schizophrenia.

For several years, they have been developing positive allosteric modulators, or PAMs, drug-like compounds that can "tune up" the activity of receptors in specific areas of the brain.

They identified a particular muscarinic receptor, M4, and developed compounds—PAMs—that increase its activity. As expected, switching on the M4 "amplifier" in animals produced anti-psychotic-like effects similar to those observed in the clinical trial. A big unanswered question was how M4 activation mediated this antipsychotic activity.

The current study showed that the M4 PAMs didn't block dopamine receptors, but prevented dopamine from being released in the first place.

To find out how, Daniel Foster, Ph.D., research instructor in Pharmacology and first author of the paper, used genetically-modified mice in which the gene for the M4 receptor was selectively deleted from different neuron populations.

In this way, he traced the primary source of M4 receptors to "spiny projection neurons," which receive signals from dopamine neurons, but which were not previously known to send signals back. This suggested to the researchers that spiny projection neurons must release a signaling molecule that can affect dopamine release.

They looked for compounds released by the neurons and identified an endocannabinoid called 2-arachidonoylglycerol, which binds to the cannabinoid CB2 receptor on dopamine neurons. Endocannabinoids are natural signaling molecules that activate cannabinoid receptors in the brain.

While the CB1 receptor is associated with reward and binds THC, the active compound in marijuana, the CB2 receptor previously had been linked primarily to immune function.

The Vanderbilt study defines a new role for CB2—modulating dopamine signaling in the striatum, Conn said. This provides a mechanism by which the M4 PAM can relieve psychotic symptoms without causing

adverse cognitive effects in other parts of the brain, he said.

More information: Daniel J. Foster et al. Antipsychotic-like Effects of M4 Positive Allosteric Modulators Are Mediated by CB2 Receptor-Dependent Inhibition of Dopamine Release, *Neuron* (2016). DOI: 10.1016/j.neuron.2016.08.017

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