

New study pinpoints genetic mechanism linking dopamine to schizophrenia

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Ball-and-stick model of the dopamine molecule, a neurotransmitter that affects the brain's reward and pleasure centers. Credit: Jynto/Wikipedia

Researchers at the Lieber Institute for Brain Development (LIBD) believe they have solved a riddle that has challenged scientists for more

than 70 years: how the brain chemical dopamine relates to schizophrenia, the often-devastating brain disorder characterized by delusional thinking, hallucinations and other forms of psychosis.

Through their exploration of the expression of genes in the caudate nucleus—a region of the [brain](#) linked to emotional decision-making—the researchers found [physical evidence](#) that [neuronal cells](#) are unable to precisely control levels of dopamine, and they also identified the [genetic mechanism](#) that controls the dopamine flow. Their findings were published today in the journal *Nature Neuroscience*.

"Until now, scientists have been unable to decipher whether the dopamine link was a causative factor or solely a way to treat schizophrenia," said Daniel R. Weinberger, M.D., chief executive and director of the Lieber Institute and a co-author of the study. "We have the first evidence that dopamine is a causative factor in schizophrenia."

Dopamine, a type of neurotransmitter, acts as a chemical messenger that sends signals between neurons—nerve cells in the brain—to change their activity and behavior. Dopamine is the reward neurotransmitter that enables people to feel pleasure.

According to the National Institute of Mental Health, schizophrenia is 1 of the top 15 leading causes of disability worldwide, with [psychotic symptoms](#) such as hallucinations, delusions and disordered thinking, as well as reduced expression of emotions, reduced motivation to accomplish goals, difficulty in social relationships, motor impairment and cognitive impairment.

Symptoms typically start in late adolescence or early adulthood, although cognitive impairment and unusual behaviors sometimes appear in childhood. Current treatments for schizophrenia include antipsychotic drugs which address the symptoms of psychosis, but not the cause.

"One of the major side effects of the drugs used to treat schizophrenia is lack of pleasure and joy," said Dr. Jennifer Erwin, an investigator at the Institute and one of the authors on the report. "In theory, if we could target the dopamine receptor specifically with drugs, that could be a new strategy for treatment that would not limit a patient's joy as much."

Scientists have known for decades that irregular levels of dopamine have some connection to psychosis and are a critical factor in schizophrenia, Alzheimer's disease and other neuropsychiatric disorders. Drugs that increase dopamine in the brain, such as amphetamines, are known to cause psychosis. Drugs that treat psychosis do so by reducing dopamine activity.

These observations have inspired generations of scientists to try to understand whether—and how—an imbalance of dopamine actually relates to schizophrenia. Dopamine transmits information in the brain by interacting with proteins on the surface of brain cells, called [dopamine receptors](#). By studying those receptors, scientists at the Lieber Institute have come up with novel evidence confirming that dopamine is a causative factor for schizophrenia.

The investigators examined hundreds of post-mortem specimen brains donated to the Lieber Institute from over 350 individuals, some with schizophrenia and others without psychiatric illness.

They chose to focus on the caudate nucleus, a part of the brain that is critically important for learning how to make complex ideas and behaviors more automatic and intuitive, but also because it has the brain's richest supply of dopamine. They also studied a region of the human genome that large international genetic studies have identified as being connected with the risk of schizophrenia.

This region contains the genes for the protein receptors that respond to

dopamine, which points to the dopamine-schizophrenia connection. But while [genetic data](#) suggest at most a role of dopamine receptors at risk for schizophrenia, the data are not conclusive and do not identify what the relationship actually is.

The investigators at the Lieber Institute went critically further in discovering the mechanisms that make dopamine receptors a risk factor.

The mechanism exists specifically in a subtype of the dopamine receptor, called the autoreceptor, which lies on the "male" side of the connection between neurons, the presynaptic terminal. This autoreceptor regulates how much dopamine is released from the presynaptic neuron. If autoreceptors are compromised, the flow of dopamine within the brain is poorly controlled, and too much dopamine flows for too long.

The investigators found that decreased expression of this autoreceptor in the brain explains the genetic evidence of risk for illness. This is consistent with the prevailing hypothesis that too much dopamine plays a role in psychosis, and strong evidence that the dopamine-schizophrenia riddle has at last been solved.

The pioneering neuroscientist Dr. Sol Snyder hailed the study as a breakthrough many decades in the making. Dr. Snyder is a distinguished service professor of neuroscience, pharmacology and psychiatry and founder of the Department of Neuroscience at the Johns Hopkins University School of Medicine, which bears his name. He was the scientist who discovered that [antipsychotic drugs](#) work by reducing brain dopamine.

"There's lots of muddled data indicating the relevance of dopamine and dopamine receptors in schizophrenia," said Dr. Snyder, who was not involved in this research project. "The key thing these researchers have done is to collect data that puts it all together and in a fashion that is

persuasive in establishing that dopamine systems are out of kilter in schizophrenia, and that is causal to the disease."

"For decades, people have debated the [dopamine](#) connection to [schizophrenia](#)," Dr. Snyder said. "They used to say, 'Well, this is interesting to speculate about, but there's no solid evidence.' But now that we have much more rigorous data available, we keep coming back to the same story. You don't have to call it a hypothesis anymore."

More information: Jennifer Erwin et al, Analysis of the caudate nucleus transcriptome in individuals with schizophrenia highlights effects of antipsychotics and new risk genes, *Nature Neuroscience* (2022). [DOI: 10.1038/s41593-022-01182-7](https://doi.org/10.1038/s41593-022-01182-7)

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