Disruption in brain connection linked to genetic defect in schizophrenia

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To receive a reward, a mouse in the T-maze had to remember whether it had turned left or right on the previous trial, and turn in the opposite direction. Mice genetically engineered to lack a specific segment of genetic material on Chromosome 22, a known cause of schizophrenia -- like patients with the disorder -- faltered at such working memory tasks, because of poor functional connections between the brain's executive and memory hubs. Credit: Torfi Sigurdsson, PhD, Department of Psychiatry, Columbia University

In what may provide the most compelling evidence to date, researchers at Columbia University Medical Center have illuminated how a genetic variant may lead to schizophrenia by causing a disruption in communication between the hippocampus and prefrontal cortex regions of the brain, areas believed to be responsible for carrying out working

memory. Findings are published in the current online edition of *Nature*.

This discovery coincides with the 15th anniversary of the first identification of the link between schizophrenia and a genetic mutation - a microdeletion on human chromosome 22 - known as 22q11 deletion, by Columbia Psychiatry researcher Maria Karayiorgou, M.D., a coauthor on the research. Previous studies have shown that approximately 30 percent of patients with this deletion will go on to develop schizophrenia.

"We know that this genetic deficit predisposes us to schizophrenia, and now we have identified a clear pathophysiological mechanism of how this deletion confers this risk for schizophrenia," said Dr. Karayiorgou. Dr. Karayiorgou discovered the link between the 22q11 mutation and schizophrenia in 1995. Since then, Dr. Karayiorgou and Joseph A. Gogos, M.D., Ph.D, a senior author on the research, have established and pursued research focusing on the neurobiology of this mutation.

Though schizophrenia is best known for its delusions and hallucinations, it is the disease's impact on such cognitive abilities like working memory - a key element of executive functioning - that best predict how well a person will function in society.

Using a mouse model with the 22q11 deletion, senior authors Joshua Gordon, M.D., Ph.D., and Joseph A. Gogos, M.D., Ph.D., and their teams, recorded the neural activity of the mice while they performed a cognitive task of working memory, and found that their performance was either completely disrupted, or was impaired, compared to that of the healthy mice.

In healthy mice, the hippocampus sends spatial information to the prefrontal cortex, but in the mouse model of the 22q11 mutation there is a breakdown in the connection and this communication is either weakened or fails completely.

As part of the cognitive trial, the mice were tested as they navigated a t-shaped maze. In order to successfully complete the task, the mice had to recall the direction in which they traveled, and then choose to go in the opposite direction to receive their next reward. While the healthy mice easily learned the task, mice carrying the schizophrenia mutation took longer to master it, demonstrating a behavioral deficit of the task in the mouse model of schizophrenia.

"We found that successful completion of the task in our healthy mice required the two regions of the brain - the hippocampus and the prefrontal cortex - to work together, and in our mouse model, the information transfer was less efficient, or was unable to take place at all," said Dr. Gordon.

In addition, the researchers reported that they were able to show the extent of the deficit in individual mice.

"There was a variation in how much of a deficit they showed, and that correlated with the degree of the behavioral deficit, so that for individual mice that have less communication between these structures, there was more of a behavioral deficit," said Torfi Sigurdsson, Ph.D., a postdoctoral research scientist in Dr. Gordon's laboratory at Columbia Psychiatry and a coauthor on the paper.

Recent human imaging studies have suggested the possibility that there may be abnormalities in the functional connectivity between the hippocampus and prefrontal cortex in schizophrenia, however, it remained unclear how such findings related to a cause of the disease, like that of a genetic risk variant, or if they were the result of the disease itself or medications used.

"Here we are really at the level of the individual cells, so our findings extend beyond patient studies by showing how disrupted connectivity

can arise at the level of single neurons, as a result of a genetic risk variant," said Dr. Sigurdsson.

Another strength of the study, according to the researchers, is that the communication can be measured directly between the two regions.

"It unequivocally establishes a deficit in that communication in a way that the early studies could not - not only because we can isolate the genetics of the disease, but we can also measure the connectivity between these structures directly," said Dr. Gordon.

"The 22q11 deletion mouse model allows us to explore how these mutations alter brain function and the abnormal behavior that we see in schizophrenia patients. This is exactly what our study and our research program on 22q11, in general, has accomplished," said Dr. Gogos.

"We now know that one of the consequences of that deletion is to disrupt functional communication between these two brain regions, and we have evidence from the study that the disruption actually has an impact on a cognitive behavior that is disrupted in patients, so it gives us a really strong indication of how the deletion can contribute to the development of schizophrenia," he added. "It is possible that similar abnormalities in functional connectivity may also account for other symptoms of the disease, and can be used to better assess treatment response, and, most importantly, to develop new medications."

Next, the researchers plan to test the structural links between the hippocampus and prefrontal cortex, since it appears likely that synchrony between these two regions is mediated through anatomical connections. The researchers will examine how the anatomical and synaptic properties of these connections change in this mouse model and will aim to identify the genes that account for this change.

Authors of the *Nature* study are Torfi Sigurdsson, Kimberly L. Stark, Maria Karayiorgou, Joseph A. Gogos and Joshua A. Gordon.

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Contrary to popular belief, schizophrenia is not a split personality; it is a chronic, severe, and disabling brain disorder that affects just over one percent of the adult population and is characterized by loss of contact with reality (psychosis), hallucinations (usually, hearing voices), firmly held false beliefs (delusions), abnormal thinking, a restricted range of emotions (flattened affect) or inappropriate and disorganized behavior, social withdrawal, and diminished motivation.

The disease often strikes in the early adult years, and although many individuals experience some recovery, many others experience substantial and lifelong disability. People with schizophrenia often have problems functioning in society and in relationships and are over-represented on disability rolls and among the homeless and imprisoned.

What precisely causes schizophrenia is not known, but current research suggests a combination of hereditary and environmental factors. Fundamentally, however, it is a biologic problem (involving changes in the brain), not one caused by poor parenting or a mentally unhealthy environment.

More information: Impaired hippocampal-prefrontal synchrony in a genetic mouse model of schizophrenia. Sigurdsson T, Stark KL, Karayiorgou M, Gogos JA, Gordon JA. Nature. 2010 April 1.