A mouse model offers new evidence to support the theory that schizophrenia may arise from disrupted communication between different brain regions. Using genetic engineering and brain probes, researchers have taken another step toward understanding the causes and mechanisms of schizophrenia.

The first piece is a genetic mutation: the 22q11.2 microdeletion, in which a stretch of DNA on chromosome 22 containing 30 to 40 genes is deleted. The consequence of this mutation is variable. Several studies have confirmed that people who carry this mutation have a 30-fold increased risk of developing schizophrenia.

Although it is not possible to test whether a mouse is psychotic, it is possible to measure the mouse's impairment in working memory; this is analogous to a cognitive deficit observed in human patients with schizophrenia. In this study, mice were trained in a spatial task, which required them to retrieve recently learned information. First, a mouse was directed to turn in one of two possible directions in a T-shaped maze. Next, the animals had to remember which direction they took before and turn in the opposite direction to find food. Thus, how quickly a mouse learned to perform the task is a measurement of its working memory.

Compared with mice without genetic mutation (the wild-type mice), the genetically engineered mice with the microdeletion were significantly slower to learn the task, suggesting that their working memory was impaired.

The third piece of the puzzle was how well the neural activities in the hippocampus and prefrontal lobe were synchronized when a mouse was performing the working-memory task. The electrical firings of the neurons in both regions were directly measured using tiny electrodes surgically implanted in the mouse brain.

As expected, the mutant mice had significantly lower synchrony between neurons in the hippocampus and those in the prefrontal lobe compared with the wild-type mice.

"Not only was the prefrontal-hippocampus connectivity during the task associated with how well [the mice] performed it, but even before they learned the task, the mutant mice showed reduced baseline connectivity," said Joshua Gordon, M.D., Ph.D., an assistant professor at Columbia University and a psychiatrist at the New York State Psychiatric Institute, in an interview with *Psychiatric News*. Gordon is one of the authors of this study.

Previous brain imaging and electroencephalogram studies have shown a disconnection in the activities between the temporal and frontal lobes in people with schizophrenia. However, those are relatively crude measurements, as these instruments are able to show only the collective neural activities on a larger scale. "With the implanted microelectrodes, we can record the activities on the level of single neurons," said Gordon.

Recreate Genetic Risk in Mice

By itself, "the 22q11.2 microdeletion accounts for up to 2 percent of nonfamilial cases of schizophrenia, [which is] the majority of cases with schizophrenia," Joseph Gogos, M.D., Ph.D., a coauthor of the study, told *Psychiatric News*. "This is not a negligible portion ... [in part because] great insights in other neurological diseases such as Alzheimer’s and Parkinson’s disease came from mutations for an equal or smaller proportion of cases."

Gogos and Maria Karayiorgou, M.D., have been working on animal models of schizophrenia for over a decade. They decided to develop a mouse model engineered to carry a genetic deletion that is analogous to the 22q11.2 mutation in humans—that is, this deletion in mice and in humans is expected to have the same functional effects.

Karayiorgou is a professor of psychiatry at the Center for Human Genetics at Columbia University Medical Center (CUMC). Gogos is an associate professor of physiology and cellular biophysics and of neuroscience at CUMC.

"It has become clear from the work in our lab as well as other labs that schizophrenia is a highly [genetically] heterogeneous disorder—much more so than people anticipated," according to Gogos. Hundreds of genetic variants, including very rare mutations that occur in a few individuals, may confer risks of schizophrenia, he explained. How did these different variants result in the symptoms of schizophrenia? Now, the goal for research is "to identify the common physiological brain pathways affected by the plethora of these mutations," said Gogos.

Given the results from the study and clues from past research evidence, Gordon said, he and his colleagues are fairly confident that the 22q11.2 microdeletion was responsible for the abnormal connectivity between the two brain regions in the mice.

Model Cognitive Symptoms in Mice

To make the leap from mice to man, not only did the researchers have to "recreate" the genetic risk for schizophrenia, they also had to ensure that the symptoms and physiological mechanisms observed in mice were analogous to those in humans.
"Positive and negative symptoms in schizophrenia are very hard to model in mice," said Gogos. Instead, he and his colleagues focused on impaired cognitive functions, a hallmark symptom of patients with schizophrenia. "Although it is not one of the DSM diagnostic criteria, cognitive symptoms are invariably present and can predict functional outcome of the disease," said Gogos. They felt that studying cognitive impairment in mice, which is quantifiable in behavioral experiments, could reveal the pathophysiology also relevant in humans.

Previous research has shown that the brain regions associated with working-memory-related learning are similar between human and mouse, according to Gordon. "There is a body of literature to support the behavioral model. Others have shown that the prefrontal and hippocampal regions must work together to perform the cognitive function properly," he said.

**Taking Leap to Human Pathophysiology**

"We hypothesize that cognitive deficits [in schizophrenia] are likely mediated by the same abnormal physiological processes as other symptoms," Gogos explained. By understanding what goes wrong in cognitive impairment, they hope to "offer some general insights into the pathophysiology."

"We can say with certainty that the disconnectivity between the hippocampus and prefrontal lobe, as a result of the 22q11.2 microdeletion, contributes to the cognitive deficit," said Gogos. "It is less certain how this disconnectivity can lead to psychosis."

Gogos hypothesized that in schizophrenia the neural disconnectivity may affect more areas than the prefrontal lobe and hippocampus. Perhaps "other symptoms can be understood mechanistically as a consequence of abnormal connectivity that results in abnormal information flow and inability to accurately interpret incoming sensory input," he said. In other words, schizophrenia may be a disorder of miscommunication between different neurological components.

This study is believed to be the first to use an animal model to string together the genetic cause, physiological mechanism, and behavioral symptom in one package.

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*An abstract of “Impaired Hippocampal-Prefrontal Synchrony in a Genetic Mouse Model of Schizophrenia” is posted at [www.nature.com/nature/journal/v464/n7289/abs/nature08855.html](http://www.nature.com/nature/journal/v464/n7289/abs/nature08855.html)*

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