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Study shows how microscopic changes to brain cause schizophrenic behavior in mice

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The findings are being published in an Early Edition of the journal *Proceedings of the National Academy of Sciences* this week.

"We found several microscopic pathologies and behavioral traits that are hallmarks of schizophrenia, says Ulrich Mueller, Ph.D., a professor at Scripps Research who was senior author of the study. "These findings in mice may help shed light on how schizophrenia, an often severe and debilitating disease, emerges in humans."

In the study Mueller, Research Associate Claudia Barros, and colleagues also showed that the schizophrenic mice could recover normal behavior when treated with clozapine, a decades-old drug sometimes used to treat schizophrenia in people. This suggests that these mice might provide researchers with a good model system for studying schizophrenia and testing new drugs designed to treat people suffering from it.

Schizophrenia affects millions of Americans — about one percent of all people in the United States, according to the National Institute of Mental Health — and manifests in symptoms like hearing imaginary voices, paranoia, delusions of grandeur, severe apathy, and incoherent speech. Despite its prevalence, however, the causes of schizophrenia are not entirely understood.

The scientific consensus is that the disease results from a combination of genes and other factors. Schizophrenia runs in families, which is strong evidence that inherited genes play a role, but the disease is not

completely genetic. Some identical twins, for instance, are discordant — one will have the disease while the other will not. The fact that it can strike one genetically identical twin to the exclusion of the other means that there are more than just genes involved. Development may be another factor.

People with schizophrenia usually do not begin showing signs of the disease until their late teens or early 20s. One of the current scientific hypotheses regarding schizophrenia, however, is that the disease is caused by developmental defects that occur in the brain long before the signs of the disease emerge. The mice that Mueller, Barros, and colleagues studied would seem to lend credence to this hypothesis.

In the new paper, the team describes what happens to the mice when they lose the function of a brain protein called neuregulin — an important developmental protein that helps the brain form its distinct structures early in development. Genetic studies have linked inherited forms of this protein and its receptors to schizophrenia and numerous other mental health problems.

Mueller, Barros, and colleagues managed to effectively remove the function of neuregulin by eliminating the receptor to which it binds. Because this is such an important developmental protein, they expected that eliminating its receptor would severely impact the development of the mouse's brain. To the researchers' surprise, that did not happen. Overall, the brains were normal. Microscopically, however, the loss of neuregulin tells another story.

To understand what happens when you hamper the action of neuregulin, Mueller says, you have to understand something about how neurons in the brain form and communicate. Humans, mice, and other mammals have brains that develop through multiple intricate stages, bursts, and crawls. Brain tissue first forms without neurons, as a sort of scaffold,

and then the neurons grow, creep into place, and connect to each other.

When it is finished, the average human brain has some 100 billion neurons — a highly intricate, overlapping web of branched structures that communicate with one another (and the outside world). They have tree-like networks of extensions called "dendrites" that receive input from other neurons, as many as ten thousand inputs for a single neuron. The structure that enables one neuron to contact another is called a dendritic spine. These humble structures look like a little fingers coming off the dendrites, and their proper formation may be one of the keys to schizophrenia.

In their study, the scientists discovered that when mice are deprived of neuregulin, their dendritic spines start to form, but do not mature completely — instead falling apart while the brain matures. The effect of this loss is evident in behavior tests, where mice display hallmarks of schizophrenia, such as social interaction problems and reduced anxiety. Loss of the spines also leads to the loss of the ability to adapt to and anticipate a startling noise — a classic sign of a schizophrenia-like state in mice.

This study provides support for a hypothesis about schizophrenia that implicates what are known as "glutamatergic" neurons. All neurons communicate by releasing particular chemicals called neurotransmitters into synapses, the tiny gaps in between two neurons. One longstanding hypothesis concerning schizophrenia implicates neurons that release the neurotransmitter dopamine. Another hypothesis is that glutamatergic neurons, which release the neurotransmitter glutamate, are also important in schizophrenia. The study supports the second hypothesis, says Mueller, because the mice had problems with their glutamatergic synapses, which are located at dendritic spines.

More information: "Impaired maturation of dendritic spines without

disorganization of cortical cell layers in mice lacking NRG1/ErbB signaling in the central nervous system," Ulrich Mueller et al., *PNAS*.

Source: Scripps Research Institute