Mouse model may provide insight into the schizophrenic brain

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Schizophrenia is an incredibly complex and profoundly debilitating disorder that typically manifests in early adulthood but is thought to arise, at least in part, from pathological disturbances occurring during very early brain development. Now, a new study published by Cell Press in the February 25 issue of the journal *Neuron*, manipulates a known schizophrenia susceptibility gene in the brains of fetal mice to begin to unravel the complex link between prenatal brain development and maturation of information processing and cognition in adult animals.

"Although it is clear that multiple factors are involved in schizophrenia, many studies have suggested that variations in disease susceptibility genes might contribute to disruption of high brain functions such as cognition and information processing," explains study author Dr. Akira Sawa from the Department of Psychiatry at the Johns Hopkins School of Medicine in Baltimore. "These genetic factors are believed to be good probes to explore mechanistic links between brain development and adult brain functions."

Dr. Sawa, coauthor Dr. Toshitaka Nabeshima from the Department of Clinical Pharmacology at Meijo University in Nagoya, Japan, and their colleagues showed that a transient reduction of one of the susceptibility genes linked with schizophrenia (Disrupted-in-Schozophrenia-1) in the mouse prefrontal cortex just before or after birth led to aberrant changes in adult animals that are associated with schizophrenia, including perturbation of specific dopaminergic brain pathways, disruption of neural circuitry, and severe behavioral abnormalities.

These findings were significant because they provided a concrete link between a nonlethal genetic disruption during prenatal brain development and specific abnormalities in adult brain maturation. "Prior to our study, the kinds of neurodevelopmental defects that cause the defined anatomical changes observed in schizophrenia patients, clinical onset 15□□ years after birth, psychosis, impaired cognition and information processing and aberrant dopaminergic neurotransmission were not clear," offers Dr. Nabeshima. "However, the model in our study represents a majority of these characteristics."

The authors are careful to caution that while their findings shed some light on how early disease-associated events impact adult brain function, manipulation of one gene cannot fully define the complex neuropathology associated with schizophrenia. "Although it is only one piece of the puzzle, our study may aid molecular understanding of how the initial insults during early development disturb postnatal brain maturation for many years, which results in full-blown onset of schizophrenia or other mental disorders after puberty," explains Dr. Sawa.

More information: Niwa et al.: “Knockdown of DISC1 by In Utero Gene Transfer Disturbs Postnatal Dopaminergic Maturation in the Frontal Cortex and Leads to Adult Behavioral Deficits.” Publishing in Neuron 65, 480-489, February 25, 2010. DOI 10.1016/j.neuron.2010.01.019

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