Researchers reveal how brain circuits are affected by infections in mothers and newborns

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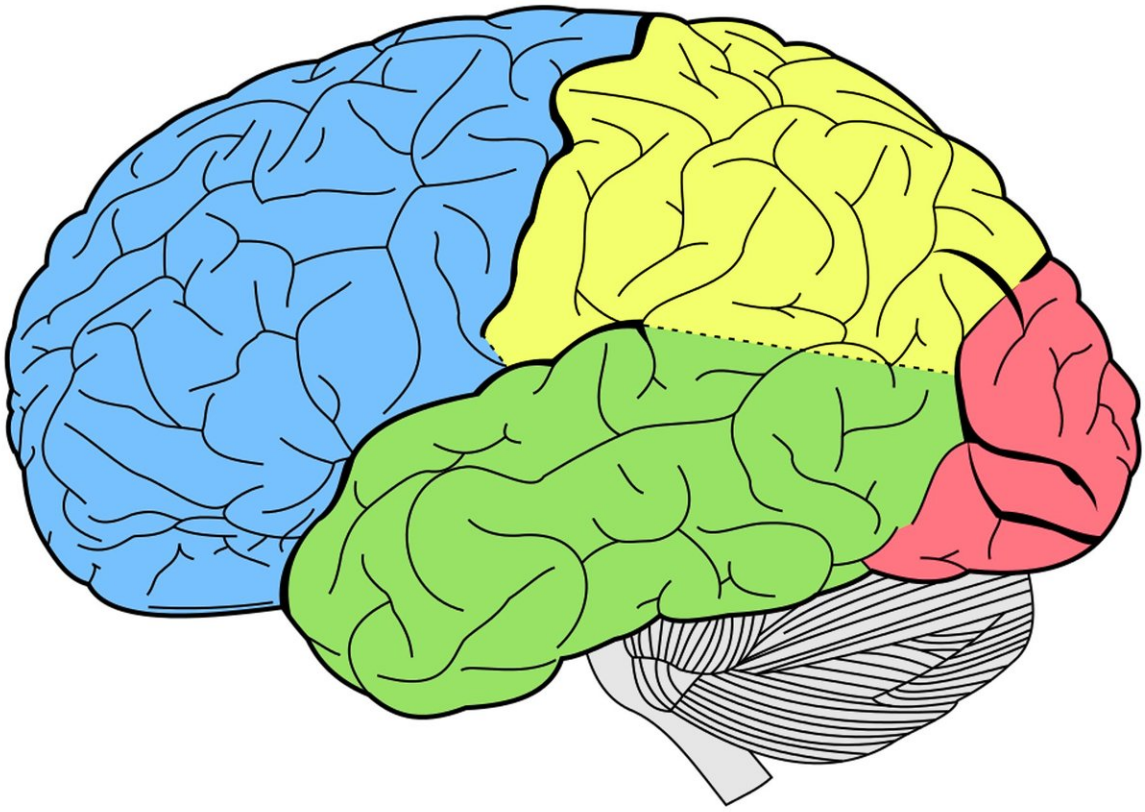

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McLean Hospital neuroscientists have found that immune system

activation during pregnancy and right at birth can cause alterations in the brain's neural circuits during young adulthood that are consistent with behavioral symptoms common in autism spectrum disorder (ASD) and other developmental conditions. The detailed findings are available in the March 28, 2018, issue of the *Journal of Neuroscience*.

"Mounting evidence suggests that immune activation, such as prenatal viral infections and postnatal bacterial infections, can impact later-life brain development in humans," said Vadim Bolshakov, PhD, director of the Cellular Neurobiology Laboratory at McLean Hospital and co-senior author of the paper. "While previous studies at McLean and elsewhere have focused on the behavioral symptoms produced by such immune activation, this study goes deeper, going to the cellular level to show how the brain's neural circuits are affected."

"Previous studies have helped demonstrate the types of things that can happen behaviorally as a result of immune system activation," added Bill Carlezon, PhD, chief of the Division of Basic Neuroscience at McLean Hospital, and co-senior author of the paper. "This research, however, is distinguishable in that it is an important step in telling us the biological basis of how these symptoms develop."

To explore the impact of immune activation on the developing brain, the researchers induced either maternal or postnatal immune activation, or gave both treatments, in groups of pregnant mice and their offspring. Pregnant mothers were treated with polycytidylic acid, a chemical that simulates the effects of a viral infection, at a time point that approximates the third trimester of pregnancy in humans. The offspring were treated with a lipopolysaccharide (LPS), a chemical that simulates a bacterial infection and causes a temporary (1-3 day) activation of the immune system. The LPS was given at a time point that approximates the stage of brain development in humans right at the time of birth, thus mimicking the development of a bacterial infection during delivery.

Long after the treatments were applied, during a time point in mice that approximates young adulthood in humans, the investigators examined the impact of the simulated infections on the brain, comparing their results to those from mice that had received inactive injections. Focusing on the neural pathway from the brain's prefrontal cortex to the amygdala, they combined optogenetics—a technique that uses light to control the activity of neurons in living tissue—with behavioral testing, a methodology that allows researchers to study functional connections between different regions of the brain. Behaviorally, the researchers found a strong connection between immune activation and symptoms of enhanced anxiety-like behavior and decreased social interactions. Correspondingly, they found that neural circuits in the brain that contribute significantly to the control of anxiety and social interactions were significantly affected in the immune-activated mice.

While the group that received the combined maternal and postnatal treatment showed the largest behavioral effects, electrophysiology tests easily distinguished the pathway effects in each of the four treatment groups. According to Bolshakov, Carlezon, and fellow study researcher Yan Li, PhD, this ability to definitively detect and distinguish electrophysiological changes suggests that this study's methodology provides a stronger link between immune activation and brain disorders versus studying behavioral effects alone.

"The results are novel, as this sensitive and comprehensive testing has revealed how prenatal and early postnatal immune activation may regulate core behavioral signs associated with ASD and certain other developmental disorders through changes in signal flow between different structural components of behavior-driving neural circuits," said Bolshakov. "These findings may be of a significant translational value, as they provide important clues to understanding the mechanisms of these disorders and potentially their treatment."

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