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Uncovering secrets of how intellect and behavior emerge during childhood

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Scientists from the Florida campus of The Scripps Research Institute (TSRI) have shown that a single protein plays an oversized role in intellectual and behavioral development. The scientists found that mutations in a single gene, which is known to cause intellectual disability and increase the risk of developing autism spectrum disorder, severely disrupts the organization of developing brain circuits during early childhood. This study helps explain how genetic mutations can cause profound cognitive and behavioral problems.

The study was published in the November 9, 2012, issue of the journal *Cell*.

The genetic mutations that cause developmental disorders, such as intellectual disability and autism spectrum disorder, commonly affect synapses, the junctions between two nerve cells that are part of the brain's complex electro-chemical signaling system. A substantial percentage of children with severe intellectual and behavioral impairments are believed to harbor single mutations in critical neurodevelopmental genes. Until this study, however, it was unclear precisely how pathogenic genetic mutations and synapse function were related to the failure to develop normal intellect.

"In this study, we did something no one else had done before," said Gavin Rumbaugh, a TSRI associate professor who led the new research. "Using an animal model, we looked at a mutation known to cause intellectual disability and showed for the first time a causative link

between abnormal synapse maturation during brain development and life-long cognitive disruptions commonly seen in adults with a neurodevelopmental disorder."

Losing Balance

The study focused on a critical synaptic protein known as SynGAP1. Mutations in the gene that encodes this protein cause disabilities in an estimated one million people worldwide, according to the paper.

"There are a few genes that can't be altered without affecting normal cognitive abilities," Rumbaugh said. "SynGAP1 is one of the most important genes in cognition—so far, every time a mutation that disrupts the function of SynGAP1 has been found, that individual's brain simply could not develop correctly. It regulates the development of synaptic function like no other gene I've seen."

Using animal models that were missing just one copy of SynGAP1, as seen in some patients with intellectual disability, the scientists found that certain synapses develop prematurely in the period shortly after birth. This dramatically enhances what is known as "excitability"—how often brain cells fire—in the developing hippocampus, a part of the brain critical for memory. The balance between excitability and inhibition is especially critical during early developmental periods, when neural connections that ultimately give rise to normal cognitive and behavioral functions are forming.

"You might think this accelerated development of brain circuits would make you smarter," Rumbaugh said. "But the increased excitability actually disorganizes brain development. We think that early maturation of these excitatory synapses disrupts the timing of later developmental milestones. It rains down chaos on this complex process, preventing normal intellectual and behavioral development."

A Critical Window

Interestingly, inducing these mutations after the critical development period was complete had virtually no impact on normal synapse function and repairing these pathogenic mutations in adulthood did not improve behavior or cognition.

"A key finding is we were able to remove the mutation and restore SynGAP protein levels in adult mice with obvious cognitive and behavioral problems, but this intervention did not benefit the animals," Rumbaugh said.

These results imply that very early intervention is essential in neurodevelopmental disorders, particularly for cognitive problems. The team is now aggressively searching for the optimal period during development in which repairing these mutations is most beneficial.

Rumbaugh speculates that successfully defining these treatment windows, combined with the fast-approaching ability to identify potential pathogenic mutations in utero, will provide a possible path toward eradicating this type of intellectual disability and lowering the risks for autism. "We believe a cure is possible," he said. "It is likely that there are many other single mutations out there that cause distinct forms of these spectrum disorders. Our strategy could be applied to these disorders as well."

More information: "Pathogenic SYNGAP1 Mutations Impair Cognitive Development by Disrupting the Maturation of Dendritic Spine Synapses," *Cell*, 2012. DOI: 10.1016/j.cell.2012.08.045

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