Study shows a solitary mutation can destroy critical 'window' of early brain development

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Scientists from the Florida campus of The Scripps Research Institute (TSRI) have shown in animal models that brain damage caused by the loss of a single copy of a gene during very early childhood development can cause a lifetime of behavioral and intellectual problems.

The study, published this week in the *Journal of Neuroscience*, sheds new light on the early development of neural circuits in the cortex, the part of the brain responsible for functions such as sensory perception, planning and decision-making.

The research also pinpoints the mechanism responsible for the disruption of what are known as "windows of plasticity" that contribute to the refinement of the neural connections that broadly shape brain development and the maturing of perception, language, and cognitive abilities.

The key to normal development of these abilities is that the neural connections in the brain cortex—the synapses—mature at the right time.

In an earlier study, the team, led by TSRI Associate Professor Gavin Rumbaugh, found that in mice missing a single copy of the vital gene, certain synapses develop prematurely within the first few weeks after birth. This accelerated maturation dramatically expands the process known as "excitability"—how often brain cells fire—in the hippocampus, a part of the brain critical for memory. The delicate balance between excitability and inhibition is especially critical during early developmental periods. However, it remained a mystery how early maturation of brain circuits could lead to lifelong cognitive and behavioral problems.

The current study shows in mice that the interruption of the synapse-regulating gene known as SYNGAP1—which can cause a devastating form of intellectual disability and increase the risk for developing autism in humans—induces early functional maturation of neural connections in two areas of the cortex. The influence of this disruption is widespread throughout the developing brain and appears to degrade the duration of these critical windows of plasticity.

"In this study, we were able to directly connect early maturation of synapses to the loss of an important plasticity window in the cortex," Rumbaugh said. "Early maturation of synapses appears to make the brain less plastic at critical times in development. Children with these mutations appear to have brains that were built incorrectly from the ground up."

The accelerated maturation also appeared to occur surprisingly early in the developing cortex. That, Rumbaugh added, would correspond to the first two years of a child's life, when the brain is expanding rapidly. "Our goal now is to figure out a way to prevent the damage caused by SYNGAP1 mutations. We would be more likely to help that child if we could intervene very early on—before the mutation has done its damage," he said.

More information: Clement, J., SYNGAP1 Links the Maturation Rate of Excitatory Synapses to the Duration of Critical-Period Synaptic Plasticity, *Journal of Neuroscience*, 19 June 2013, 33(25): 10447-10452; doi: 10.1523/JNEUROSCI.0765-13.2013.

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