Motor coordination issues in autism are caused by abnormal neural connections

24 November 2014

Quinn, an autistic boy, and the line of toys he made before falling asleep. Repeatedly stacking or lining up objects is a behavior commonly associated with autism. Credit: Wikipedia.

Abnormal connections between neurons are the likely cause of motor coordination issues seen in autism spectrum disorder. Using a mouse model of autism, scientists from the University of Chicago identified a malfunctioning neural circuit associated with reduced capacity for motor learning. This appears to arise from an inability to eliminate unneeded neural connections in the brain. They report their findings Nov. 24 in *Nature Communications*.

"We have identified synaptic abnormalities that may play a role in motor problems typically seen in children with autism," said study senior author Christian Hansel, PhD, professor of neurobiology at the University of Chicago. "Autism is sometimes described as intense world syndrome - too many, too strong excitatory connections that lead to enhanced sensory input. The results of our study might shed light on this phenomenon."

Social and behavioral criteria are used to diagnose autism spectrum disorder (ASD), but around 80 percent of children with autism have motor coordination issues that include clumsiness and difficulties with gaze or eye movement control.

The underlying cause of these motor deficits is poorly understood. To investigate, Hansel and his team utilized a mouse model for one of the most common genetic abnormalities known in autism, the human 15q11-13 chromosomal duplication. They focused on the cerebellum, a brain region heavily involved in motor control.

The researchers found ASD model mice have similar cerebellums to normal mice, but demonstrated motor deficits in the form of an unstable gait and impaired motor learning. To test this, researchers taught normal mice to associate a short light signal with a puff of air to the eye. The mice learned to blink in response to the light, even without an air puff. ASD model mice, however, were much slower to learn in this eye blink test and made mistakes more frequently.

Can't stop the signal

To figure out why, the team looked at Purkinje cells, a type of neuron heavily involved in motor learning. Purkinje cells can either strengthen or depress the efficacy of their synapses - sites of connection between neurons where signals are passed. This ability is one of the primary mechanisms for learning and memory, as it allows neural pathways to be reinforced or weakened.

In ASD model mice, the ability of Purkinje cells to depress the efficacy of their synapses was greatly reduced. This hindered their ability to help fine-tune movements and contribute in motor learning. The team found that a likely cause of this state was impaired synaptic pruning, a developmental process that enables the trimming of unneeded synapses as the brain develops.

Purkinje cells receive signals about environmental errors or disturbances - such as an air puff reaching the eye - from neuronal projections known as climbing fibers. This signal triggers a corrective motor response. When pruning is working normally, each Purkinje cell in an adult brain receives only one climbing fiber input. ASD model mice, however, possessed an overabundance, altering the efficacy of this instructive 'error signal.'

"Inefficient synaptic pruning seems to be a common motif in autism," Hansel said. "There are not many types of synapses in the brain where pruning can be measured easily, but climbing fibers provide an excellent model and allow us to make predictions about synaptic pruning deficits elsewhere in the brain as well."

Hansel and his team demonstrated that these synaptic abnormalities are associated with the delayed eye blink response seen in ASD model mice. This represents a powerful new tool for autism researchers, as changes to a relatively simple neural circuit can now be connected to changes to a behavioral action in an animal model.

"A direct link between synaptic studies and behavioral output is almost impossible to do with social behaviors, but we can now accomplish this," he said. "This is due to the relative simplicity of the motor system, and because the cerebellum is evolutionarily conserved, allowing for comparisons between mice and man."

Hansel's work highlights the role of abnormalities in synaptic function in developmental brain disorders. The researchers hope that these studies will eventually pave the way for clinical trials that focus on the treatment of synaptic dysfunction.

More information: "Cerebellar plasticity and motor learning deficits in a copy-number variation mouse model of autism," *Nature Communications*, 2014.

Provided by University of Chicago Medical Center

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