NEWS

Striatum, the brain’s reward hub, may drive core autism traits

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Restricted interests and repetitive behaviors are hallmarks of autism. They can take many forms: Some autistic people flap their arms or rock back and forth; others ritualistically line up objects or insist on a rigid daily schedule.

Several studies have suggested that repetitive behaviors originate in the striatum, a cluster of neurons in the center of the brain that helps initiate and execute movements. In support of this idea, people who have a damaged striatum show autism traits, including repetitive, inflexible behaviors and various movement problems.

In the past two decades, however, scientists’ understanding of the striatum has expanded, yielding tantalizing hints that the region is involved in the characteristic social difficulties seen in autistic people.

“The common, long-canonical view was that the striatum either excited or inhibited movement,” says **Ann Graybiel**, professor of brain and cognitive sciences at the Massachusetts Institute of Technology. “But [it] might also be dealing with mood, motivation, approaching good or avoiding bad, reward-based learning — all kinds of things like that.” Autistic people often have problems with mood, motivation or the reward system, all of which may make them **uninterested in interactions** with others.

The region also appears to be key for learning to make eye contact and discerning which sensory information warrants attention. This new view comes from studies that have traced the striatum’s connections to other parts of the brain, including areas that process sensory information, thoughts,

feelings and emotions. And mutations in many genes linked to autism **impair the striatum**'s structure and function. Studies in animals shore up the evidence: Disrupting neurons in a mouse striatum, for instance, triggers both repetitive behaviors and social problems[1].

"The more we know, the more we realize it's much more complicated than the field originally thought," says **David Sulzer**, professor of neurobiology at Columbia University.

Striatal pathways:

The striatum is part of the basal ganglia — clusters of neurons deep in the center of the brain. The basal ganglia receives signals from the cerebral cortex, which controls cognition and social behavior.

The striatum in particular processes signals from the cortex about desired goals and prompts other neurons in the basal ganglia to initiate actions to achieve those goals. Separately, it also alerts the thalamus — a brain region that processes sensory information and communicates with the cerebral cortex — forming a loop that controls how a person starts and stops an action. The thalamus also sends signals directly to the striatum, in addition to the cortex, so the entire circuit is composed of multiple interconnected loops.

The striatum was first implicated in autism in 1978, when doctors reported widespread "disturbances of motility" in autistic children[2]. These disturbances include rhythmic and tic-like gestures, unusual posture and gait, and 'striatal toes' — an unusual upward extension of the big toes. Many of these problems bear a striking resemblance to those seen in people and lab animals with a damaged striatum.

Brain imaging studies, too, support the link between autism and the striatum. For instance, some parts of the striatum are enlarged in people with the condition[3]. The striatum typically shrinks as a child matures, but one report suggests **it keeps growing** in autistic children and young adults[4]. The enlargement tracks with the severity of repetitive behaviors in children with the condition[5].

Autistic people also show unusually low activity in the striatum when they complete tasks that offer a social reward. And their striata have **unusually weak connections** with brain regions involved in processing reward. Difficulties with **processing social reward** may explain why some people with autism seem to have **little interest in social interactions**.

Genetic studies of autism implicate the striatum, too. Many of the genes mutated in people with autism are **highly expressed in the striatum**. And mice with mutations in these genes show alterations in the striatum that resemble those seen in autistic people.

For instance, mice with a mutation in **SHANK3**, a top autism gene that is highly expressed in the striatum, groom themselves obsessively and have social difficulties. A portion of the striatum is enlarged in these mice and weakly connected to the cerebral cortex, and the neurons show **impaired excitatory signaling**.

Wiring the brain:

Other autism genes may be needed for proper wiring of the striatum. **FOXP1**, which helps turn other genes on and off, is highly expressed in the striatum. Mice missing a copy of this gene make fewer ultrasonic calls than usual after being separated from their mothers[6]. And some of their striatal neurons fire more easily than usual.

“We think that FOXP1 is really important for setting up the developmental programs that build the striatum,” says lead investigator **Genevieve Konopka**, associate professor of neuroscience at the University of Texas Southwestern in Dallas. She and her colleagues are now studying a different set of mice, which lack FOXP1 in only their striatal neurons. The team’s unpublished results suggest the gene is critical for the striatum to develop properly.

Sulzer’s team is focusing on another gene called mTOR — which is unusually active in some children with autism — and its role in the developing striatum. Hyperactive mTOR leads to an **excess of neuronal connections** in the cerebral cortex; Sulzer’s team is exploring whether similar changes occur in the striatum.

A better understanding of the striatum’s development may help solve a vexing problem facing researchers who study this brain area: Its structure is “very complicated,” Sulzer says. “Autism is a developmental [condition], so people should be looking at development.”

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