NEWS

Mounting evidence implicates cerebellum in autism

BY **SARAH DEWEERDT**

6 JANUARY 2014

Young children who don't point at interesting objects or make eye contact may be showing early warning signs of autism. Adults with autism may not shake hands or perform other actions rooted in social skills.

All of these behaviors are, in the most basic sense, **movements**. Yet a major brain structure tasked with coordinating movements, the cerebellum, has been relatively ignored in studies of autism.

"The traditional notion of the function of the cerebellum was [that it is] primarily contributing to motor control," says **Stewart Mostofsky**, director of the Laboratory for Neurocognitive and Imaging Research at the Kennedy Krieger Institute in Baltimore.

In other words, the cerebellum was thought to be responsible only for actions such as walking, reaching and grasping, and pedaling a bicycle. The subtleties of social interaction and language belonged to the cerebral cortex.

But **that view is changing**, say Mostofsky and others. "There's an emerging body of data that the cerebellum is important for a lot more than regulating your motor movements," says **William Dobyns**, professor of genetic medicine at the University of Washington in Seattle, who cares for children with malformations of the cerebellum. "It regulates your emotions as well — your affective state — and your attention."

This new view is rooted in observations that individuals with tumors, injuries or birth defects affecting the cerebellum have a range of difficulties, including emotional outbursts, attention problems, difficulty understanding social cues, mood changes and **repetitive behaviors**. Many of these features are frequently seen in people with autism.

Meanwhile, researchers are increasingly uncovering abnormalities in **cerebellar structure** and **function in individuals with autism**.

Four studies published over the past year provide genetic and mouse model evidence bolstering a link between the cerebellum and autism-related behaviors. The studies represent disparate dispatches from an emerging field, and don't yet tell a unified story. But they do suggest that the cerebellum is likely to play a bigger role in autism than many had assumed.

Clique candidates:

In one study published last January, researchers identified cerebellar abnormalities in children who carry a deletion of an autism-linked chromosomal region, 22q13[1]. Deletion of this region causes **Phelan-McDermid syndrome**, characterized by developmental delay and, often, severe language impairment. Many of these individuals are also diagnosed with autism.

The researchers analyzed brain scans of ten individuals with a 22q13 deletion. Eight of them have a smaller-than-normal vermis, the connection between the two halves of the cerebellum; an enlarged posterior fossa, the cavity the cerebellum sits within; or both, the researchers found. Both of these anomalies have also been identified in people with autism[2, 3].

Analysis of the participants' DNA suggests that two genes in the 22q13 region, PLXNB2 and **MAPK8IP2**, are most closely linked to cerebellar abnormalities in these individuals.

However, the gene in this region that is most strongly implicated in autism, **SHANK3**, seems to have less impact on the cerebellum: One participant with a deletion that affects only SHANK3 has a normal cerebellum, the researchers found.

Evidence from one individual is far from definitive, cautions Dobyns, the lead investigator. "At this point, I don't know whether they're linked," he says. But, he adds, the results suggest that cerebellar malformation is part of a cluster of disorders and abnormalities — including autism, schizophrenia, **epilepsy**, intellectual disability and having a **small or absent corpus callosum** — that often occur together and may sometimes share an underlying genetic cause.

Another study suggests that not just one or two but whole suites of autism genes are at work in the cerebellum. In this study, published in *PLoS Computational Biology* in July, researchers analyzed the expression of more than 3,000 genes in the mouse brain, based on data from the **Allen Mouse Brain Atlas**[4]. Among these, **a group of 26 autism candidate genes** is expressed together more than would be expected by chance alone.

That's not so surprising, says study leader **Partha Mitra**, professor of neuroscience and theoretical biology at Cold Spring Harbor Laboratory in New York. What's more unexpected, Mitra says, is that the researchers also identified two 'cliques,' or groups of genes with similar expression patterns, that contain a high proportion of autism candidate genes. And both of these cliques are expressed in the cerebellum, the researchers found.

One of the groups includes the autism-linked genes **PTCHD1**, **GALNT13**, **DPP6** and **ASTN2**. The other, smaller group includes ASTN2 and **RIMS3**.

"There has been this emphasis on the [cerebral] cortex" in studies of autism, Mitra notes. "I wasn't expecting the cerebellum to come out in such a robust way."

An unpublished analysis by Mitra's team zeroes in on where in the cerebellum these cliques of autism-linked genes are most active. "We see that these expression patterns appear to be localized in the granule cell layer," he says.

Granule cells are tiny neurons found tightly packed together in the outer region of the cerebellum. The finding contrasts with other studies that have implicated cerebellar Purkinje cells in autism, but Mitra cautions that this analysis is preliminary.

Purkinje pathways:

In fact, **a reduced number of Purkinje cells** is one of the most consistent findings from postmortem studies of autism brains. These cells represent the main output of nerve signals from the cerebellum, with elaborately branching neuronal projections that travel to various regions of the cerebral cortex.

The Purkinje cell "may be a particularly vulnerable cell type" says **Michael Gambello**, chief of medical genetics at Emory University School of Medicine in Atlanta.

Earlier this year, Gambello and his colleagues reported that mice lacking an autism-linked gene, **TSC2**, in Purkinje cells show social deficits reminiscent of autism[5].

The work replicates findings from a study last year showing that removing a closely related gene, **TSC1**, from Purkinje cells also **leads to autism-like behaviors in mice**[6].

In both studies, researchers found that loss of the gene results in Purkinje cell degeneration. The mutant mice also display increased repetitive behavior and decreased interest in social interaction compared with controls. Finally, both teams showed that rapamycin, a drug that inhibits a signaling pathway boosted by the two genes, prevents Purkinje cell loss and the development of autism-like behaviors in the mice.

“Taken together, it's very strong evidence for the importance of the TSC genes in Purkinje cell viability, and that somehow the loss of these cells is affecting some important connection between the cerebellum and the rest of the brain,” says Gambello.

Next, Gambello’s team plans to study the effects of removing TSC2 from cells in the thalamus or the prefrontal cortex, two of the brain structures with the strongest connections to the cerebellum.

The prefrontal cortex has been **strongly implicated in autism**. Parts of it are involved in thinking, planning, memory and social behavior, notes **Charles Blaha**, director of experimental psychology at the University of Memphis in Tennessee.

Blaha and his colleagues have found that in control mice, stimulating a part of the cerebellum called the dentate nucleus results in release of dopamine in the prefrontal cortex. This occurs through two pathways of roughly equal strength: One goes through a part of the brain called the ventral tegmental area and the other through the thalamus.

“Not too many people have paid too much attention to dopamine and its relationship to autism,” says Blaha. But he points out that this chemical messenger is linked to cognitive functions. Problems with dopamine circuits in the cerebellum could contribute to difficulties with cognitive skills such as **theory of mind**, learning and memory, which many people with autism struggle with.

Blaha and his colleagues have studied Lurcher mice, which carry a mutation in the gene **GRID2** that causes them to lose all of their Purkinje cells over the first two to three weeks of life. They also studied mice that model **fragile X syndrome**, the most common inherited cause of intellectual disability and autism. Both mouse models have deficits in learning and memory. The researchers reported in *Cerebellum*in August that the mice also have abnormal dopamine circuits[7].

In both sets of mice, stimulating the dentate nucleus results in much lower dopamine release in the prefrontal cortex compared with controls, and in a shift in the relative strength of the two dopamine pathways. The team plans to conduct similar studies in other mouse models of autism.

Some researchers view the many studies on the cerebellum as evidence that the region underlies many features of the disorder.

“Cerebellar dysfunction may be contributing to impaired coordination of social actions in parallel to the ways it contributes to impaired coordination of motor actions,” says Mostofsky, who has found that the degree of motor impairment in individuals with autism is **linked to their degree of social impairment**.

Others are more circumspect, but say the cerebellum is likely to be important in autism even if it only explains some cases. “We know that autism is such a heterogeneous phenotype,” says Gambello. “I think that there is very likely a percentage of children out there with autism where the

cerebellum is playing a major role.”

References:

1.Aldinger K.A. *et al. Am. J. Med. Genet. A.* **161A**, 131-136 (2013) **PubMed**

2. Courchesne E. *et al. N. Engl. J. Med.* **318**, 1349-1354 (1988) **PubMed**

3. Courchesne E. *et al. Neurology* **44**, 214-223 (1994) **PubMed**

4. Menashe I. *et al. PLoS Comput. Biol.* **9**, e1003128 (2013) **PubMed**

5. Reith R.M. *et al. Neurobiol. Dis*. **51**, 93-103 (2013) **PubMed**

6. Tsai P.T. *et al. Nature* **488**, 647-651 (2012) **PubMed**

7. Rogers T.D. *et al. Cerebellum* **12**, 547-556 (2013) **PubMed**