New clues about autism subtypes

December 17 2020

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Two groundbreaking studies at the UC Davis MIND Institute provide clues about possible types of autism linked to brain structure, including size and white matter growth.

The research is based on brain scans taken over many years as part of the

Autism Phenome Project (APP) and Girls with Autism, Imaging of Neurodevelopment (GAIN) studies. It shows the value of longitudinal studies that follow the same children from diagnosis into adolescence.

"There is no other single site data set like ours anywhere," said Christine Wu Nordahl, associate professor in the Department of Psychiatry and Behavioral Sciences, MIND Institute faculty member and co-senior author on both papers. "In one of the studies we have over 1,000 MRI scans from 400 kids, which is unheard of. It's been 15 years of work to get here."

Big brains: An autism subtype?

In the first study, published in *Biological Psychiatry*, the researchers used magnetic resonance imaging (MRI) to track brain size (volume) in 294 children with autism and 135 children without autism between the ages of 3 and 12. In children with autism, they found evidence of larger brain size relative to height—or disproportionate megalencephaly—a subtype that has been linked to higher rates of intellectual disability and poorer overall prognosis.

Previous cross-sectional research had found that children with autism have larger brains at early ages, but no evidence of larger brains in later childhood. The widely accepted theory is that these brains "normalized" or shrank as the children grew up.

The MIND Institute study found that wasn't the case. The children who had bigger brains at age 3 still had bigger brains at age 12. Why? Unlike most research, which studies different individuals at different time points, this research studied the same children longitudinally, or over time.

Also, unlike most other studies, this one includes children with

significant intellectual disabilities. These were the children who tended to have the "big brain" form of autism.

David Amaral, co-senior author on both studies, suggested that the difference between this and previous research was that children with intellectual disability were left out of previous cross-sectional studies focused on older children.

"Bigger brain size in autism has been linked to lower IQ, and children with intellectual disabilities are harder to scan as they get older," said Amaral, a distinguished professor of psychiatry and behavioral sciences and MIND Institute faculty member. "It's a matter of sampling bias and the previous "dogma" appears to be an artifact of who got scanned when," he explained.

Children under age 5 can be scanned while they're asleep, but Nordahl and her team have created unique, innovative protocols that allow researchers to more easily scan older children with intellectual disabilities while they're awake.

"It's so critical that we include those aspects of the autism spectrum that most impact quality of life, such as intellectual disability, anxiety and verbal functioning." said Joshua Lee, postdoctoral scholar at the MIND Institute and the lead author on the study. "It's important to capture everyone who has autism, not just the ones who are easiest to get images from."

White matter: Connecting the clinical dots

The second study, also published in *Biological Psychiatry*, linked changes in the brain's white matter growth with autism traits in some children.

The researchers used a type of MRI scan called diffusion-weighted

imaging, which allowed them to look at white matter regions, or tracts, in the brain. White matter provides the structural connections in the brain, allowing different regions to communicate with each other. The study included 125 children with autism and 69 typically developing children who served as controls, between the ages of 2.5 and 7.

The researchers found that the development of the white matter tracts in the brain was linked to changes in autism symptom severity. They observed slower development in children whose symptom severity increased over time, and faster development in those with decreased severity over time.

"From a biological standpoint, this emphasizes the role of white matter development in autism and autism symptoms," said Derek Sayre Andrews, postdoctoral scholar at the MIND Institute and lead author on the paper. "We hope that in the future, measurements like this can identify children who would benefit from more intensive intervention—and serve as a marker to determine the effectiveness of an intervention for a particular child," he said.

Changes in autism severity over time

The white matter research builds on a previous MIND Institute study, which found that while many children experience fairly stable levels of autism symptoms throughout childhood, a significant portion can be expected to increase or decrease in their symptom severity over time.

"This new analysis provides an important clue about the brain mechanism that may be involved in some of these changes," said Amaral.

Studying sex differences

The studies are unusual not only because they include children with severe intellectual disability, but also because they include a larger number of girls, who tend to be under-represented in autism research.

"For the first time, we are able to have a large enough sample of girls, where we are able to evaluate their brain trajectories separate from boys to see how they're different," said Nordahl. "For example, we don't see the big brain subtype as frequently in girls, but we do see subtle differences in how autistic girls' brains are growing."

Nordahl, who has also studied the role amygdala size may play in psychiatric challenges for young girls, noted that the MIND Institute's longitudinal data set is likely to play a key role in many future studies about sex differences in autism.

"Collectively, I believe these studies are so important because they get us closer to a point where we can use our understanding of the underlying biology of autism to directly improve the quality of life for individuals in the autistic community," Andrews said. "And that really is the ultimate goal of our research."

More information: Joshua K. Lee et al, Longitudinal Evaluation of Cerebral Growth Across Childhood in Boys and Girls with Autism Spectrum Disorder, *Biological Psychiatry* (2020). DOI: 10.1016/j.biopsych.2020.10.014

Derek Sayre Andrews et al. A Longitudinal Study of White Matter Development in Relation to Changes in Autism Severity Across Early Childhood, *Biological Psychiatry* (2020). DOI: 10.1016/j.biopsych.2020.10.013

Provided by UC Davis