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Boys with regressive autism, but not early onset autism, have larger brains

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In the largest study of brain development in preschoolers with autism to date, a study by UC Davis MIND Institute researchers has found that 3-year-old boys with regressive autism, but not early onset autism, have larger brains than their healthy counterparts.

The study is published online today in the Proceedings of the National Academy of Sciences Early Edition. It was led by Christine Wu Nordahl, a researcher at the UC Davis MIND Institute and an assistant professor in the Department of Psychiatry and Behavioral Sciences and David G. Amaral, Beneto Foundation Chair, MIND Institute Research Director and University of California Distinguished Professor in the Department of Psychiatry and Behavioral Sciences.

"The finding that boys with regressive autism show a different form of neuropathology than boys with early onset autism is novel," Nordahl said. "Moreover, when we evaluated girls with autism separately from boys, we found that no girls — regardless of whether they had early onset or regressive autism — had abnormal brain growth."

Brain enlargement has been observed in previous studies of autism. However, prior to this study, little was known about how many and which children with autism have abnormally large brains.

"This adds to the growing evidence that there are multiple biological subtypes of autism, with different neurobiological underpinnings.," Amaral said.

Autism is a neurodevelopmental disorder whose symptoms include deficits in language and social interaction and communication. The condition affects 1 in 110 children born today, according to the U.S. Centers for Disease Control and Prevention. It is diagnosed more frequently in male children than female children, at a ratio of 4 to 1.

The current study is one of the first published from data collected by the UC Davis MIND Institute Autism Phenome Project (APP). The project's goal is to recruit and enroll as many very young children as possible in order to collect sufficient biological and behavioral information to characterize different autism subgroups and to explore different neural, immunologic and genetic signatures of autism.

For the study, the authors enrolled a total of 180 children between age 2 and 4 who were enrolled in the APP. One hundred and fourteen of the participants had autism spectrum disorder; the remaining participants were 66 age-matched typically developing controls. Of the children with autism, 54 percent were diagnosed with the regressive form and 46 with the non-regressive type.

The researchers collected magnetic resonance imaging (MRI) scans on 180 participants at age 3. To evaluate the rate of brain growth prior to age 3, the researchers analyzed head circumference measurements taken from pediatric well-baby visits from birth through 18 months. Roughly half of the children with autism were reported by their parents as having experienced a regression, characterized by the loss of previously acquired language and social skills.

MRIs were carried out on study participants during natural, nighttime sleep using protocols developed specifically for the Autism Phenome Project by Nordahl.

"Obtaining MRI scans in 3-year-old children without the use of sedation

may seem quite challenging. But, by working closely with the parents, we actually were successful more than 85 percent of the time. Patience on the part of everyone and the dedication of the families was so critical for our success," Nordahl said.

The study found that accelerated head growth and brain enlargement was consistently observed only in the subset of children diagnosed with regressive autism. Specifically, total brain volume in 3-year-old males with regressive autism was more than 6 percent larger than that of age-matched typically developing peers. Twenty-two percent of boys with regressive autism, as opposed to 5 percent of boys without regressive autism, had enlarged brains, the study found.

Changes in brain size were not apparent in boys who did not experience a regression. Girls with autism, regardless of autism onset status, also did not show abnormal brain growth. The study findings suggest that abnormalities in overall brain growth are specific to male children with the regressive type of autism, and that rapid brain growth may be a risk factor for regression, the researchers said.

While brain size was clearly larger at age 3, the study also determined when the precocious growth began, by examining records of head circumference that provides a reasonable estimate of brain size in young children. These analyses clearly indicated that brain growth diverged from normal at around 4 to 6 months of age. This is of particular interest, because many families believe that the trigger that led to their child's regression took place close to the time that the regression happened. But the data reported in this paper indicate that the process leading to the enlarged brain, which is presumably also associated with the onset of autism, started when the child was a newborn.

Much remains to be elucidated regarding brain changes associated with autism, the authors note. In the current study, not all boys with regression

demonstrate the precocious brain growth. The investigative team also continues efforts to define the underlying brain pathology in children with early onset autism and in girls with autism.

"It is not clear how many different types of autism will be identified," Amaral said. "The purpose of defining different types of autism is to more effectively study the cause of each type and eventually determine effective preventative measures and better, individualized treatments. This is a first step in defining autism subtypes based on the data from the Autism Phenome Project, but it certainly will not be the last. There are already indications that other subtypes of autism will be more closely associated with immunological differences or genetic alterations."

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