NEWS

Studies question link between head circumference, autism

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Measuring up: Boys with autism who have bigger heads than their unaffected peers also tend to be taller and heavier, but this pattern occurs in only a small minority.

Having an enlarged head in early childhood is not a reliable marker of autism, according to two new studies published in August in the *Journal of the American Academy of Child and Adolescent Psychiatry*.

In the first study, **Lonnie Zwaigenbaum** and his colleagues tracked head circumference and height from birth to age 3 in hundreds ofyounger siblings of children with autism[1]. These so-called '**baby sibs**' are up to **20 times more likely to develop autism** than children with no family history of the disorder. The researchers found no difference in the rate of head or body growth among baby sibs, including those later diagnosed with autism, compared with controls.

The second study, led by **Katarzyna Chawarska** at Yale University, looked at head circumference, height and weight in the medical records of hundreds of4-year-old children diagnosed with autism[2]. As a group, boys with autism had slightly larger heads than typically developing controls by 8 months of age, but these boys were also slightly taller and heavier. This suggests that some children with autism may have larger bodies overall.

"There's not just one predominant pattern that is universally affecting all children with autism,"

says **Janet Lainhart**, professor of psychiatry at the University of Wisconsin-Madison, who was not involved in either study.

That's because a diagnosis of autism captures a "mixed bag" of biological features, says **Armin Raznahan**, a staff scientist at the National Institute of Mental Health's Child Psychiatry Branch and author of an editorial accompanying the studies[3]. "It's highly likely that different genetic subtypes of autism, for example, have biological differences," Raznahan says. "So the idea of finding a biomarker for all of autism, to my mind, is not a winning strategy."

Head first:

Psychiatrist Leo Kanner included abnormally large head size, known as **macrocephaly**, as a feature of autism in his **1943 description of the disorder**. Since then, findings from postmortem brains and neuroimaging studies have suggested that some children with autism show **accelerated brain growth before age 2**.

Studies that measure head circumference, which is a surrogate for brain size, have **yielded more mixed results**. Last year, Raznahan **led a review** of studies that tracked head size in children with autism over time. Of the seven studies with the most robust designs, four found evidence of abnormal head size and three did not[4]. Researchers have also reported conflicting conclusions about when during childhood abnormal head growth occurs and whether it relates to overall differences in body size.

The new studies address these inconsistencies by tracking changes in head and body growth over time in children who have autism or are at a high risk for developing the disorder. They compared these children with typically developing controls from the same communities. Other studies often rely on existing datasets of head circumference norms published by the World Health Organization and the U.S. Centers for Disease Control and Prevention. But these datasets do not account for geographical variations in head size, which can **skew the results**.

Zwaigenbaum and his colleagues looked at 253 typically developing children with no family history of autism and 442 baby sibs, 77 of whom went on to be diagnosed with autism. The researchers found that both groups of children have similar rates of head and body growth before age 3. This held true even when they split the baby sibs into children with and without autism.

However, by age 3, some slight differences emerge. At this age, baby sibs have heads that are about 4 millimeters larger, on average, than the heads of controls. This difference is not specific to the children who developed autism, however.

It's possible that measurements of head circumference are missing subtle changes in brain growth

captured in neuroimaging studies and postmortem brains, says Zwaigenbaum, associate professor of pediatrics at the University of Alberta in Canada.

“It seems like brain growth is what is truly informative for risk of autism,” he says. “I think that it is important not to put too much weight on any single study, but rather look at the literature as a whole.”

Size matters:

Chawarska’s team compared head size, height and weight among 200 children with autism and 147 controls. All of the children had normal head size at birth, but the rate of head growth among boys with autism accelerated at around 10 months of age such that their heads measured roughly 6 millimeters larger than those of controls by age 2.

When the researchers accounted for variations in the rate of overall body growth, however, the difference in head size was no longer significant.

“We see overgrowth along all dimensions,” says Chawarska, associate professor of pediatrics at Yale University.

The findings fit with those of a 2011 study by the same team, which found that male toddlers with autism tend to be **larger overall than their typically developing peers**[5].

In the new study, Chawarska’s team found overgrowth in 16 percent of the children with autism compared with 3.4 percent of controls. Children with autism who have abnormal growth also tend to have more severe social, verbal and cognitive impairments at age 4 than other children with the disorder, as measured by the Autism Diagnostic Observation Schedule and the Mullen Scales of Early Learning.

The findings suggest that early overgrowth occurs in a small minority of children with autism and is not a reliable risk marker for the disorder, Chawarska says. However, children who have autism as well as a history of abnormal growth during infancy may be at risk for severe verbal and cognitive impairments, she says.

The fact that Zwaigenbaum’s study did not find similar evidence for generalized body overgrowth may be because that study’s participants are from multiplex families, in which more than one child has the disorder. By contrast, most of the children with autism in Chawarska’s study have no family history of the disorder.

“It is possible that the autism in multiplex families might arise through somewhat different genetic mechanisms than we see in sporadic cases,” Chawarska says.

It is also possible that only individuals with certain subtypes of the disorder have enlarged brains or bodies. For example, a 2011 study found **abnormal brain enlargement in boys with regressive autism**[6]. Certain autism-linked mutations are also **associated with macrocephaly**.

Overall, the studies underscore the difficulty of identifying reliable risk markers for autism, as the molecular underpinnings of the disorder can **vary widely from person to person**.

“Lately there’s been this backlash against the notion that there’s abnormal brain enlargement in autism at all,” says **Christine Nordahl**, assistant professor of psychiatry and behavioral sciences at the University of California, Davis. Nordahl led the 2011 study but was not involved in the new work. “I think that one thing that people are missing is the heterogeneity of the disorder.”

References:

1. Zwaigenbaum L. *et al. J. Am. Acad. Child Adolesc. Psychiatry* **53**, 1053-1062 (2014) **PubMed**

2. Campbell D.J. *et al. J. Am. Acad. Child Adolesc. Psychiatry* **53**, 1063-1073 (2014) **PubMed**

3. Raznahan A. *J. Am. Acad. Child Adolesc. Psychiatry* **53**, 1045-1047 (2014) **PubMed**

4. Raznahan A. *et al. Biol. Psychiatry* **74**, 563-575 (2013) **PubMed**

5. Chawarska K. *et al. Arch. Gen. Psychiatry* **68**, 1021-1031 (2011) **PubMed**

6. Nordahl C.W. *et al. Proc. Natl. Acad. Sci. USA* **108**, 20195-20200 (2011) **PubMed**