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Sizing Up the Search for Autism Spectrum Disorder (ASD) Risk Markers During Prenatal and Early Postnatal Life

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The symptom-based diagnosis of autism spectrum disorder (ASD) is characterized by early-emergent impairments of social communication alongside patterns of restricted interests and repetitive behavior. The preschool emergence of ASD symptoms and their strong association with known genetic disorders of early brain development motivate searching for ASD risk markers during prenatal and early postnatal life. Three studies in this month's *Journal* contribute to this search, namely those by Campbell *et al.*,¹ Zwaigenbaum *et al.*,² and Cheslack-Postava *et al.*³

Campbell *et al.* and Zwaigenbaum *et al.* examined one of the most intensely studied early developmental markers in ASD: head circumference (HC). Although HC may seem a relatively crude and indirect way of probing the brain bases of a complex disorder such as ASD, it has retained appeal as an early developmental marker for several reasons. Measures of HC provide a quick, easy, and reasonably accurate proxy for overall brain size in the first years of life. Longitudinal HC measurements are gathered on most children as part of standard pediatric surveillance visits from birth to 3 years of age. Finally, clinical HC data can be easily compared with widely used population norms such as those published by the Centers for Disease Control and Prevention (CDC).

Intense study of HC in ASD was sparked by a highly influential 2003 article that used longitudinal data to identify rapid HC overgrowth in ASD compared with CDC norms during the first 18 months of life.⁴ Subsequent replication of this finding in several independent cohorts made the link between ASD and HC overgrowth one of the most robust biological associations in psychiatry.⁵ However, evidence is mounting that the striking replicability of HC overgrowth and macrocephaly in ASD compared with CDC norms was likely to have been driven by norm-related biases and that the true story regarding HC growth in ASD is much, much murkier.⁵

The HC studies in ASD that avoid norm-related biases (by gathering their own control data) have yielded a highly inconsistent picture regarding HC overgrowth in ASD. Many such studies have failed to find evidence of HC overgrowth in ASD, and those that have found such evidence typically disagree with one another about the timing and magnitude of

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atypical HC growth in ASD; whether abnormal HC growth reflects a more generalized alteration in body growth; and the extent to which abnormal HC growth in ASD differs as a function of sex or symptom profile.⁵ The work of Campbell *et al.* and Zwaigenbaum *et al.* directly addresses several of these outstanding questions.

Campbell *et al.* found evidence for generalized (rather than uniquely cranial) overgrowth in children with ASD versus locally recruited control participants (347 children, 4,400 HC measurements) within the first 24 months of life that was specific to boys. More pronounced generalized overgrowth was associated with poorer social, verbal, and nonverbal skills at 4 years of age. Zwaigenbaum *et al.* compared early HC and body growth between a high-risk group of children who had siblings with ASD and low-risk controls (695 children, 2,600 HC measurements); follow-up to 3 years of age allowed further stratification of the high-risk group by the eventual presence or absence of an ASD diagnosis. Zwaigenbaum *et al.* found no significant group differences in the rate of HC change but did report that, on average, high-risk children (regardless of whether they develop ASD) have a significantly larger HC at 18 years of age than do low-risk children. This difference was driven by male sex and amounted to a 4-mm difference in HC versus low-risk control participants at 36 months. Interestingly, the magnitude of this difference converges with that reported by another recent large family-based study of HC in ASD (4 mm)⁶ and the study by Campbell *et al.* (6 mm). However, in contrast to Campbell *et al.*, Zwaigenbaum *et al.* failed to find any evidence of generalized somatic overgrowth in ASD or a relation between HC growth and clinical outcome.

So, what can and cannot be said about HC growth in ASD given these mixed findings from multiple large-scale studies? First, the diagnosis of ASD is not associated with the gross and replicable pattern of HC overgrowth that was suggested by earlier norm references studies,⁴ but may on average be associated with a subtle (~5-mm) increase in HC by the third year of life. Second, there is some convergent evidence that increased mean HC in ASD is specific to boys. Third, there is currently no consensus regarding whether alterations of HC growth are a feature of ASD or are also seen in unaffected relatives; correlate with clinical outcome in ASD; or exist above and beyond alterations in overall body growth.⁵ It is important to emphasize that these statements concern only the relation between HC and idiopathic ASD considered at the group level. Emerging reports that syndromic forms of ASD can be accompanied by microcephaly and macrocephaly clearly show the limitations of trying to catch biomarkers with a behaviorally defined net such as ASD.⁷

It is tempting to wonder whether the complexities of HC data in ASD will soon be a relic of the past, as we start to gather ever more refined measurements of brain anatomy from in vivo neuroimaging of ever larger cohorts of patients and control participants. Large-scale, longitudinal, and family-based neuroimaging studies, such as the Infant Brain Imaging Study (IBIS) network, have already begun to show subtle and regionally specific brain changes in children who are at risk for but have not yet manifested ASD.⁸ However, although HC's days may be numbered as a developmental marker of interest in ASD, our experience with this humble phenotype—gathered with nothing more than a tape measure about the head—should be in the forefront of our minds as we seek to advance our

understanding of ASD using newer and much more complex phenotypic measurements such as those provided by in vivo neuroimaging.

Although we have studied HC for a much longer time, with much less platform-related measurement errors, in far larger samples, and with far denser repeated measurements than any other biological measurement in ASD, several basic objectives in HC research have continued to elude us. These same objectives will need to be met for any phenotype that we aspire to wield with translational intent in ASD: being able to detect whether differences between control samples are driving study heterogeneity; building robust and generalizable normative models that properly accommodate the complex and interacting influences of age and sex; establishing consensus “best-practice” guidelines for data preprocessing and analysis within the research community to promote internal validity and comparability between studies; gathering clinical samples of sufficient size to allow adequately powered analysis of subgroups with known genotypic or environmental risks; and finding ways to extend human models into the critical but difficult-to-study period of prenatal and early postnatal life.

The study by Cheslack-Postava *et al.* in this month’s *Journal* takes on many of these themes by using a large national birth cohort to examine the relation between interpregnancy interval (IPI), a determinant of the prenatal environment, and risk for ASD in offspring. This article is one of many recent reports coming out of the Finnish Prenatal Study of Autism and exemplifies the power of prospective population-based research within a fully integrated national health care system. By linking back to pregnancy records for 2,272 children later diagnosed with ASD and 5,377 matched control participants, while controlling for a host of familial and perinatal confounds, these investigators provide strong evidence for an “inverted-U” relation between IPI and later risk for ASD. IPIs shorter than 24 months and longer than 60 months were associated with higher rates of ASD in offspring. Interestingly, the association between shorter IPI and ASD was accounted for by subsets of the ASD that are enriched for intellectual disability, and the investigators noted that a short IPI also has been associated with increased risk for schizophrenia. In this sense, IPI findings echo those of another commonly used marker of the prenatal environment—birth weight: large-scale population-based studies also have linked both extremes of fetal growth to greater risk for ASD and schizophrenia.^{9,10}

Taken together, studies of IPI and birth weight suggest a model of risk for neurodevelopmental disorder that emphasizes that 1) absolute distance from an optimum (i.e., standard deviations away from the ideal IPI) may be more relevant to outcome than the “direction” of this distance (i.e., short versus long IPI) and 2) many developmental adversities are often nonspecific for diagnostic outcome (i.e., ASD versus schizophrenia). The first of these observations brings us full circle to the complexities of HC data in ASD: a recent family-based study reported that absolute deviation of HC away from that predicted by genetic potential shows a stronger relation with IQ variation in ASD than raw HC.⁶ Moving forward, it will be valuable to test in large national birth cohorts such as the one used by Cheslack-Postava *et al.* whether ASD is in fact more prevalent in children at the 2 extremes of the HC growth spectrum, and whether extremes of HC growth show any special relation with ASD over other outcomes (e.g., schizophrenia and intellectual disability) that

share many genetic and environmental risks with ASD. Of course, analogous questions could (and should) be asked of more complex measurements of the brain in ASD once the necessary data become available.

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