Compared to What? Early Brain Overgrowth in Autism and the Perils of Population Norms

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Background: Early brain overgrowth (EBO) in autism spectrum disorder (ASD) is among the best replicated biological associations in psychiatry. Most positive reports have compared head circumference (HC) in ASD (an excellent proxy for early brain size) with well-known reference norms. We sought to reappraise evidence for the EBO hypothesis given 1) the recent proliferation of longitudinal HC studies in ASD, and 2) emerging reports that several of the reference norms used to define EBO in ASD may be biased toward detecting HC overgrowth in contemporary samples of healthy children.

Methods: Systematic review of all published HC studies in children with ASD. Comparison of 330 longitudinally gathered HC measures between birth and 18 months from male children with autism ($n = 35$) and typically developing control subjects ($n = 22$).

Results: In systematic review, comparisons with locally recruited control subjects were significantly less likely to identify EBO in ASD than norm-based studies ($p < .001$). Through systematic review and analysis of new data, we replicate seminal reports of EBO in ASD relative to classical HC norms but show that this overgrowth relative to norms is mimicked by patterns of HC growth age in a large contemporary community-based sample of US children ($n \sim 75{,}000$). Controlling for known HC norm biases leaves inconsistent support for a subtle, later emerging and subgroup specific pattern of EBO in clinically ascertained ASD versus community control subjects.

Conclusions: The best-replicated aspects of EBO reflect generalizable HC norm biases rather than disease-specific biomarkers. The potential HC norm biases we detail are not specific to ASD research but apply throughout clinical and academic medicine.

Key Words: Autism, bias, CDC, head circumference, systematic review, WHO

An atypical pattern of brain growth during early postnatal life was first reported in children with autism over a decade ago (1). Since then, numerous studies have used head circumference (HC) measures or in vivo structural magnetic resonance imaging estimates of brain size to test for early brain overgrowth (EBO) in children with autism spectrum disorder (ASD).

The EBO hypothesis, which states that ASD is associated with an abnormal acceleration of brain growth within the first 2 years of life (2), has received considerable empirical support, leading to the speculation that EBO might be a potential biomarker for ASD (3). The influence of EBO reports on ASD research is evidenced by recent use of the link between brain enlargement and ASD to validate or interpret 1) animal models for putative genetic (4) and epigenetic (5) risk mechanisms in ASD; 2) studies of postmortem brain tissue from individuals with ASD (6,7); 3) reported associations between a given genetic variant and risk for ASD (8); and 4) in vivo neuroimaging and electrophysiological studies of altered brain connectivity in ASD (9–11). Two recent developments urge reappraisal of the evidence base for EBO in ASD, however.

First, several new longitudinal studies of early brain growth in ASD have become available since the topic last underwent systematic review (12). Longitudinal data are critical for testing the EBO hypothesis, which hinges on the presence of an atypical pattern of brain size change in ASD (13). Currently, the largest available body of evidence regarding early brain growth in ASD comes from studies of HC, which serves as an excellent proxy for brain size in infants and preschool-aged children (14,15) and provides cost-effective access to large bodies of retrospective longitudinal data about brain growth in ASD during the first years of postnatal life. There are now 11 longitudinal HC studies of brain growth in ASD within the hypothesized phase of EBO (15–25), which together provide 17 times (~3000:180) more observations than the two existent longitudinal structural neuroimaging studies of preschoolers with ASD (26,27). As 10 of these 11 longitudinal HC studies have been published since the topic of EBO was last systematically reviewed (12), there is a pressing need to formally integrate the now much expanded evidence base regarding patterns of early brain growth in ASD. Such integration could also help clarify recently posed questions regarding the selectivity of EBO for certain ASD subgroups [e.g., as defined by sex or clinical status (22)] and the extent to which EBO in ASD is part of more generalized somatic overgrowth (21).

The second recent development that could significantly modify our understanding of EBO in ASD comes from multiple studies outside the field of ASD, which report discrepancies between HC growth reference norms commonly used to test the EBO hypothesis in ASD and contemporary patterns of HC growth (28–33). The best replicated of these discrepancies concerns Center for Disease Control and Prevention (CDC) norms (34): to date, five large independent contemporary samples of healthy children have been reported to show trajectories of HC growth during the first year of life that are abnormally accelerated

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relative to the CDC norms (29–33). This discrepancy is strikingly similar to the pattern of HC overgrowth relative to CDC norms that constitutes the principal finding in five of the most commonly cited sources of empirical support for the EBO hypothesis in ASD (15,16,19,20,35). This convergence raises a critical question—might reports of HC growth in ASD that diverge from CDC norms reflect a systematic bias in CDC norms rather than any specific association between ASD and an abnormal acceleration of early brain growth? Existing studies of bias in CDC norms point towards possible limitations in HC data collection and modelling (30). Concerns also arise regarding potential biases in other popular HC norms, given robust and convergent evidence that the tempo of human HC growth can show robust intergenerational change and that such secular changes in HC growth can emerge within time frames that have commonly separated the construction of these HC norms and their application in ASD research [United Kingdom (28,36), China (37), Netherlands (38), Finland (32), Japan (39), and Korea (40)]. The influence of HC norm use on early brain growth findings in ASD is yet to be systematically assessed however, despite carrying significant consequences for the EBO hypothesis in ASD, and more generally, for the application of population reference norms in clinical and academic medicine.

In the present report, we reappraise evidence for EBO in ASD through an updated systematic review of all HC studies in children with ASD and analysis of HC data from a recently assembled cohort of children with autism and typically developing control subjects (41). Our study builds on the last systematic review of the EBO hypothesis (12) in two main ways. First, we incorporate the expanded evidence base regarding EBO in ASD, which has been enriched by multiple longitudinal studies capable of quantifying those changes in brain size that are so critical to the EBO hypothesis. Second, we provide a detailed methodological annotation of published research, so that available evidence for and against the EBO hypothesis can be considered in light of pertinent study features including 1) age range; 2) temporal density of measures used to generate group HC estimates; 3) extent of control for potential HC modifiers such as body size, sex, and ethnicity; and 4) source of control data with which ASD HC measures are contrasted.

The relationship between control group selection and HC findings in ASD is a major empirical focus in both our systematic review and analysis of new HC data, which we address by 1) comparing EBO findings in ASD studies that rely exclusively on HC norms with ASD studies that include locally recruited control children as a comparison group; 2) comparing EBO findings in ASD across multiple HC reference norms; and 3) using the common reference frame of CDC norms to integrate reported patterns of early HC growth in children with ASD and locally recruited control subjects and then compare these trajectories with the largest (~400,000 HC measures on ~75,000 children ages 0 to 18 months) and most current description of HC growth in a community-based sample of US children (Primary Care Network [PCN] norms) (30).

Methods and Materials

Systematic Review

Three authors (A.R., G.L.W., L.A.) independently carried out an electronic literature search (PubMed [National Library of Medicine, Bethesda, Maryland], EMBASE [Elsevier, Amsterdam, The Netherlands]; start of records until June 30, 2012) and manual bibliography search to identify all available studies of HC in children with ASD. Electronic literature search terms included: AUT*, ASPERGER*, ASD, PERVASIVE DEVELOPMENTAL DISORDER, PDD, HEAD CIRCUMFERENCE, OFC, and OVERGROWTH. For a study to enter our initial pool, it had to include 1) children with ASD under age 5 years or an ASD group with mean age ≤10 years; and 2) a comparison of ASD HC values with those in control children or HC norms. Our requirements regarding study age were designed to capture all studies including children. Of the 43 studies thus identified (Figure S1 in Supplement 1), 34 survived exclusion criteria (Table 1). Three authors (A.R., G.L.W., L.A.) independently abstracted data from all 34 studies using a common set of rules (Table S2 in Supplement 2), and any interrater inconsistencies were resolved by consensus.

To graphically integrate reported early-life HC trajectories for children with ASD and control subjects, we averaged reported mean group HC estimates across studies at standard pediatric health surveillance checkpoints (birth, 2, 4, 6, 9, 12, 15, and 18 months). Whenever averaging HC values (e.g., HC centile or macrocephaly rate) across studies, each reported HC value was weighted by the number of HC observations per month upon which it was based. This weighting is needed to reflect the fact that 100 children aged 10 months ± 2 weeks provide a more valid estimate of mean HC at 10 months than 100 children aged 10 months ± 4 months.

Chi-squared tests were used to quantify the relationship between cross-sectional study outcome (report of statistically significant evidence of HC enlargement in ASD versus report of no such evidence) and use of HC growth norms (HC norms vs. recruited control subjects) (see text in Supplement 1 for further details). This approach was adopted after testing for and ruling out the presence of an association between ASD sample size and study outcome ($p = .5$ for macrocephaly reports, $p = .3$ for HC centile reports).

Analysis of New HC Data

Participants. We included a total of 57 male subjects, who were enrolled at approximately 4 years of age and comprised 22 locally recruited typically developing control subjects, and 35 clinically ascertained children with ASD who met DSM-IV diagnostic criteria for autistic disorder. Full details of procedures for participant recruitment, screening, medical investigation, and cognitive assessment are provided in Supplement 1. In all cases, written informed consent was obtained from the participant's parent(s). A National Institutes of Health Institutional Review Board approved this study.

Head Circumference Data. Head circumference data were retrospectively gathered for all participants from medical records. As expected, HC measures were clustered at birth and 2, 4, 6, 9, 12, 15, and 18 months of age [as per American Academy of Pediatrics Recommendations for Preventative Pediatric Health Care (42)]. Our sample included a total of 330 HC measures (201 ASD, 129 control subjects). Head circumference values were analyzed in both their raw form and after conversion to age- and sex-normed HC centile using CDC (34), World Health Organization (WHO) (43), and PCN (30) norms.

We note that the number of participants and overall HC measurements in our sample was smaller than some prior reports (Table 1) and therefore less powered to identify statistically significant group differences in HC. However, in the context of our systematic review/meta-analysis of prior data, the main purpose of analyzing our own raw HC data was to 1) determine if our newly derived HC trajectories would independently replicate our systematic review findings; 2) allow illustration of different HC norm effects on the same raw data; and 3) allow illustration of the distributional properties that arise when normally distributed raw HC data are converted to centile.