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Autism with Intellectual Disability Related to Dynamics of Head Circumference Growth during Early Infancy

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ABSTRACT

BACKGROUND: It is not yet definitively known whether dynamic features of head circumference growth are associated with autism. To address this issue, we carried out a nested matched case-control study using data from national well baby clinics in Finland; autism cases were identified from the Finnish Hospital and Outpatient Discharge Registry.

METHODS: A nonparametric Bayesian method was used to construct growth velocity trajectories between birth and 2 years of age in autism cases and matched control subjects ($n = 468$ in main analyses, 1:1 matched control subjects). Estimates of odds ratios for autism risk in relation to the growth velocities were obtained using conditional logistic regression.

RESULTS: Growth velocity of head circumference at 3 months of age, adjusting for gestational age at birth and maternal age, is significantly associated with autism ($p = .014$); the finding was observed in subjects with comorbid intellectual disability (ID) ($p = .025$) but not in those without ID ($p = .15$). Height growth velocity among subjects with autism and without ID is significantly associated with autism at 6 months ($p = .007$), and weight growth velocity at 18 months without ID ($p = .02$) and 24 months without ID ($p = .042$) and with ID ($p = .037$).

CONCLUSIONS: Acceleration in head circumference growth is associated with autism with comorbid ID at 3 months but not subsequently. This association is unrelated to acceleration in height and weight, which are not strongly associated with autism until after 6 months.

Keywords: Autism, Development, Epidemiology, Growth Velocity, Head Circumference, Trajectories

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Evidence is accumulating of a strong association between autism and extreme growth of head circumference (HC) during early infancy. We studied the association between HC growth and autism with the aim of shedding light on the dynamic features of HC growth that relate to autism. We focus on rates of growth (i.e., growth velocity) rather than cumulative growth, and we also take into account growth velocities of height and weight. The main difficulty in studying dynamic features of HC growth related to autism has been a lack of sufficiently large cohorts to allow accurate comparisons of growth velocity trajectories between cases and control subjects. The main contribution of the article is to utilize high-quality longitudinal well baby clinic data from a large nested matched case control study, the Finnish Prenatal Study of Autism (FiPS-A), along with a novel statistical technique to allow direct comparisons of HC growth velocities between cases and control subjects.

In an intriguing study, Chawarska *et al.* (1) examined the trajectory of early growth in boys with autistic disorder compared with typically developing boys. Cases were found to have significantly larger HC in the first year of life, reflecting a generalized process that also included elevated height and weight. General morphologic between-group differences, however, may not be apparent until after accelerated growth has had time to accumulate, so the present study is complementary: our focus is on growth velocity. Indeed, growth rate acceleration is distinct from cumulative growth—for example, depending on the starting point, children who were smaller at birth may be able to catch up with typical peers and never lead to macrocephaly or macrosomy. Earlier studies that found elevated HC growth in autism are complementary to our study in the same way. Dawson *et al.* (2) found a significant increase in HC from birth to 12 months in autism spectrum disorder (ASD) cases, adjusting for height. Fukumoto *et al.* (3) reported significantly larger HC in the ASD group at 6 and 9 months after birth. Courchesne *et al.* (4) observed markedly increasing separation of HC in ASD and control subjects from 6 to 14 months. Hazlett *et al.* (5) found increased HC beginning at 12 months, adjusting for body mass index. Accelerated HC growth was also found in the first year of life (6) and from 2 to 3 years (7).

In addition to Chawarska *et al.* (1), other studies found no differences in HC either alone or after adjusting for height and/or weight. Mraz *et al.* (8) reported larger HC in ASD beginning at 6 months, persisting at every age interval until

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25 months, though significance was lost controlling for length and weight. van Daalen *et al.* (9) found no significant difference in HC from 4 to 11 months. Constantino *et al.* (10) found increases in head growth from birth to 15 months in ASD cases compared with sibling cases and control subjects, but the findings fell short of statistical significance. No differences were found in HC in another study (11). In a Norwegian birth cohort, Suren *et al.* (12) found similar mean head growth in boys with autism as for control subjects, though variability and the proportion with macrocephaly were greater in boys with autism. Among girls, HC was smaller at birth and mean head size was lower in the first year, though there were no significant differences with control subjects. Schrieken *et al.* (13) found a smaller HC relative to height over the first year in autistic cases. Nordahl *et al.* (14) found a pronounced increase in cross-sectional HC in male ASD cases with regression relative to typically developing control subjects starting at 4 to 6 months of age, persisting through 19 months. There was no difference in cross-sectional HC between ASD cases without regression and typically developing (TD) control subjects. In analyses of longitudinal changes in HC, the rate of HC growth was larger in the autism with regression group than TD and autism without regression groups. The rates of HC growth relative to TD before 4.5 months were only slightly but statistically significantly increased in the ASD groups without regression and with regression. There were no differences in HC growth trajectory from birth to age 3 in girls alone. Webb *et al.* (15) found no differences in rate of growth between ASD cases with and without regression. Gray *et al.* (16) found no difference in HC between autism cases and the Centers for Disease Control and Prevention norm median up to 18 months of age; an increase in HC was observed at 18 months in male subjects. These analyses were restricted to male subjects given the small number of female subjects. No differences in HC were found between autism cases and subjects with developmental delay but without autism. The pattern of HC growth was significantly increased in probands with ASD compared with siblings (17). In that study, subjects with increasingly extreme HC demonstrated increasingly lower mean IQ scores. Moreover, autism symptom severity increased with HC. Probands with larger HC also had earlier onset of first words and were more likely to have had regression. Early generalized overgrowth of HC, height, and weight in boys was related to more severe symptoms and greater deficits in adaptive social functioning (1).

Some previous studies suggest that increased body growth is also a feature of autism. In a previous study, the rates of height growth in ASD were significantly increased compared with control subjects up to age 2 (8). In another study, increased growth in height was found in boys with ASD versus control subjects, with significant effects from 4.8 to 24 months (1). Significantly increased height was also observed from 100 to 400 days postnatally (9). ASD male subjects were significantly heavier than control subjects at 3 to 12 months (3).

Our analytical strategy involved a new nonparametric modeling approach that brings greater flexibility, as well as ease of implementation, to growth trajectory analysis. Repeated measurements of HC were available on most subjects in the FiPS-A study, but it was challenging to gain a detailed understanding of growth patterns. The problem was exacerbated by large fluctuations in growth velocity during early infancy and high between-subject variability. To address this problem, we used a powerful new nonparametric Bayesian inversion method for reconstructing growth velocity curves from sparse temporal data (18,19) (see Supplement 1). We applied this method to examine the relationship between the growth dynamics of head circumference, as well as height and weight, in a large sample of cases and control subjects from a national birth cohort in Finland with longitudinal data on these measures.

METHODS AND MATERIALS

The study used a nested matched case-control design (FiPS-A) described in detail in Lampi *et al.* (20) and summarized here. In this design, the cases and matched control subjects are drawn from the same birth cohort. The cohort consisted of all offspring born in Finland from 1987 to 2005 (n = 1.2 million pregnancies). To identify the autism cases, we conducted a record linkage between the Finnish Medical Birth Register and the Finnish Hospital Discharge and Outpatient Register (FHDR), using personal identification numbers assigned at birth. Cases with childhood autism (ICD-10 F84.0, ICD-9 299.0) in the cohort were followed up from 1987 to 2007. The total number of childhood autism cases in the entire study sample was 1132 (only 7 cases with ICD-9 299.0, the remainder with ICD-10 F84.0). Registry diagnoses of infantile autism from the FHDR were very well validated with the Autism Diagnostic Interview-Revised in a previous study (21). The childhood autism cases were matched 1:1 to control subjects drawn from the birth cohort who were without ASD or severe/profound intellectual disability on date of birth, sex, birthplace, and residence in Finland.

The study was approved by the ethical committees of the hospital district of Southwest Finland, National Institute for Health and Welfare, and the Institutional Review Board of the New York State Psychiatric Institute.

Collection of Data on Head Circumference, Height, and Weight from Well Baby Health Clinics

Parents in Finland have their children evaluated with nationally standardized developmental assessments at well baby centers throughout the country at age 1 month and every 1 to 2 months until 15 months. Toddlers are seen at age 2. Physicians and registered nurses complete a nationally standardized form, including HC, height, and weight measurements at every visit. The clinics where all cases and control subjects received care were identified by registry linkages with the Finnish Medical Birth Register and FHDR. These archived longitudinal data were abstracted manually by public health or research nurses highly trained and experienced in the data acquisition.

Measures

The primary measure was growth velocity of HC at selected intervals from birth to age 2. The analyses were limited to 2 years based on findings from the prior literature (reviewed in

introductory paragraphs). In secondary analyses, the measures included height and weight growth velocities.

Covariates

Covariates consisted of maternal age, paternal age, gestational age, birth weight, previous births, and maternal socioeconomic status (as in Table 1).

Statistical Analysis

Growth velocity trajectories were reconstructed using the Bayesian inversion method developed by Lopez-Pintado and McKeague (18) and McKeague *et al.* (19). The R package (version 1.3; R Foundation for Statistical Computing, Vienna, Austria) growthrate was used to carry out the reconstructions.

Table 1. Demographic Characteristics of the Cases and Control Subjects

Characteristics	Cases (n = 468)	Control Subjects (n = 468)	p Value
Age at Ascertainment (Years)	5.1 (3.4)	NA	
Maternal Age (Years), *n* (%)			.023
<20	3 (.6)	13 (2.8)	
20–24	61 (13.0)	78 (16.7)	
25–29	155 (33.1)	158 (33.8)	
30–34	135 (28.9)	134 (28.6)	
35–39	91 (19.4)	71 (15.2)	
>40	23 (4.9)	14 (3.0)	
Paternal Age (Years), *n* (%)			.13
<20	7 (1.5)	5 (1.1)	
20–24	32 (6.8)	38 (8.1)	
25–29	109 (23.3)	123 (26.3)	
30–34	143 (30.6)	167 (35.7)	
35–39	95 (20.3)	79 (16.9)	
40–49	75 (16.0)	51 (10.9)	
>50	7 (1.5)	5 (1.1)	
Gestational Age (Weeks), *n* (%)			.53
≤31	7 (1.5)	5 (1.1)	
32–37	44 (9.4)	36 (7.7)	
>37	417 (89.1)	427 (91.2)	
Birth Weight (Grams), *n* (%)			.30
<1500	5 (1.1)	2 (.4)	
1500–2500	12 (2.6)	7 (1.5)	
>2500	451 (96.4)	459 (98.1)	
Previous Births, *n* (%)			.82
<2	349 (74.6)	346 (73.9)	
≥2	119 (25.4)	122 (26.1)	
Maternal Socioeconomic Status, *n* (%)			.35
Upper white collar	49 (12.7)	62 (16.4)	
Lower white collar	199 (51.4)	174 (46.0)	
Blue collar	69 (17.8)	67 (17.7)	
Other	70 (18.1)	75 (19.8)	
Sex			NA
Male	361	361	
Female	107	107	

NA, not applicable.

Inclusion Criteria

To provide accurate and complete reconstructions of the growth velocity trajectories, sufficient data on each subject and his/her matched control were necessary. For that purpose, four inclusion criteria for analysis were used: 1) maximum age at first visit is 40 days; 2) at least six visits; 3) age at the sixth visit is at most 2 years; and 4) age at last visit is at least 1.5 years.

Figure 1 shows the reconstructed HC growth trajectories of 50 subjects (left panel) and the 95% credible intervals around the reconstruction for a single subject (right panel). Note that the within-subject variation is negligible compared with the between-subject variation, so the slight uncertainty in HC growth velocity can reasonably be ignored in our analyses below. In these subjects, mean HC at birth and at 2 years was 35.7 cm and 49.6 cm, respectively. Multivariable generalized estimating equations (GEE) were used to assess differences between mean (reconstructed) growth velocities of cases and control subjects, accounting for the possibility of dependence of growth velocity in cases and control subjects due to the matching. Conditional logistic regression analyses were used to estimate odds ratios for autism incidence in relation to the covarying growth velocities (HC, height, and weight at the same age), adjusting for gestational age and maternal age, also accounting for the matching. Statistical significance was judged at $\alpha = .05$. After examining the main effects, we utilized the same statistical method to investigate HC growth velocity at age 3 months for autism cases with and without comorbid intellectual disability (ID) defined by the following ICD-10/ICD-9 codes: F70/317 (mild), F71/318.0 (moderate), F72/318.1 (severe), F73/318.2 (profound), F78 (no ICD-9 code) (other), and F79/319 (unspecified). There were 124 cases (26.4%) with comorbid ID. The GEE and conditional logistic regression analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, North Carolina).

RESULTS

The demographic characteristics of the cases and control subjects are presented in Table 1. Only maternal age differed between the two groups ($p = .02$) and thus all analyses were adjusted for this covariate in addition to gestational age.

The difference in mean HC growth velocity between cases and control subjects as a function of age between birth and 2 years is depicted in Figure 2. This analysis was restricted to the 468 matched pairs in which both the cases and control subjects satisfied the inclusion criteria for HC data availability. The 95% point-wise confidence band, taking dependence within the matched pairs into account, indicates a significant acceleration of HC growth from 2 to 5 months in cases compared with control subjects. There is also a slight acceleration in HC growth from 15 to 18 months but only reaching borderline significance. The minimal detectable effect size (for 80% power, $\alpha = .05$) is .28 cm per year at 6 months of age, which contrasts with the estimated peak in effect size of about .7 cm per year at 2 to 3 months. Figure S1 in Supplement 1 depicts the same plots separately for the 107 female pairs and the 361 male pairs; no observable differences in growth velocity profiles by gender are evident. The corresponding plots for height and weight (broken down by gender) are

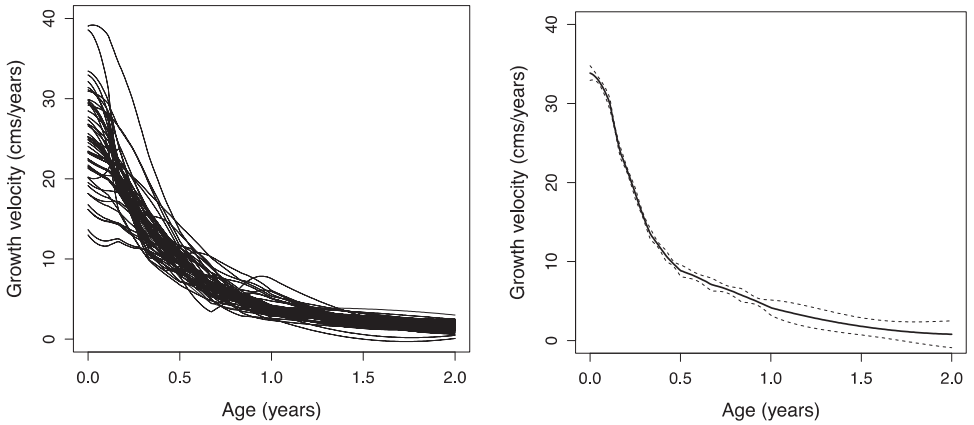

Figure 1. Reconstructed head circumference growth velocity trajectories of 50 subjects selected at random (left panel) and for one subject (right panel); the 95% credible intervals (dashed lines) and the reconstructions are based on the Bayesian inversion method ([18,19]).

provided in Figures S2 and S3 in Supplement 1. Figure S4 in Supplement 1 depicts the same plots separately by the presence of intellectual disability and nonintellectual disability (non-ID). These findings demonstrate that the increase in HC growth velocity at age 3 months for the non-ID cases was less than that of the ID cases. The 95% point-wise confidence band indicates significant acceleration in growth velocity at approximately 2 to 3 months for both ID and non-ID cases, though the result for the non-ID cases is nonsignificant in the adjusted analysis (see end of Results section).

Figures 3 and 4 show the similar confidence bands for height and weight. Significant acceleration in height is associated with autism from 3 to 8 months and with weight from 3 to 8 months and 14 to 24 months of age. The effect of accelerated growth in height and weight appears to be delayed by at least a month compared with the effect of accelerated HC growth. Table 2 reports *p* values corresponding to the HC comparison (Figure 2) for selected months from birth to 2 years. Focusing on the first 6 months, applying a Bonferroni correction to adjust for multiple comparisons (dividing $\alpha = .05$ by 7), the reported association between autism and accelerated HC growth remains significant from 2 to 4 months.

Table 3 reports the results of conditional logistic regression analyses with predictors specified by the growth velocities of HC, height, and weight at the same age both with and without adjustment for gestational age at birth and maternal age. In the adjusted models, significant results were obtained for growth velocities of HC at 3 months ($p = .014$), height at 6 months ($p = .006$), weight at 18 months ($p = .006$), and weight at 24 months ($p = .005$). These results are consistent with the results from GEE. In a subgroup analysis, splitting the sample by the presence or absence of comorbid ID and adjusting for the same covariates, the association of autism with HC velocity at 3 months was only found in the subgroup with comorbid ID ($p = .025$, odds ratio [OR] = 1.17, 95% confidence interval [CI] 1.02–1.34, 124 pairs) (Table 4). For the subgroup without ID, there was no significant effect ($p = .15$, 344 pairs) (Table 5).

Growth velocity of height at 6 months was significantly associated with autism among cases without comorbid ID ($p = .007$, OR = 1.07, 95% CI = 1.02–1.12) but not with ID ($p = .37$) (Table 5). Growth velocity of weight at 18 months was associated with autism among cases without ID ($p = .037$, OR = 1.29, 95% CI = 1.04–1.60) but only at a trend level for cases with ID ($p = .08$), and growth velocity of weight at 24 months was associated with autism among cases with ID ($p = .037$, OR = 1.31, 95% CI = 1.02–1.70) and without ID ($p = .04$, OR = 1.16, 95% CI = 1.01–1.34) (Table 4 and Table 5).

DISCUSSION

The main finding was a strong association between autism, especially with comorbid ID, and acceleration in HC growth

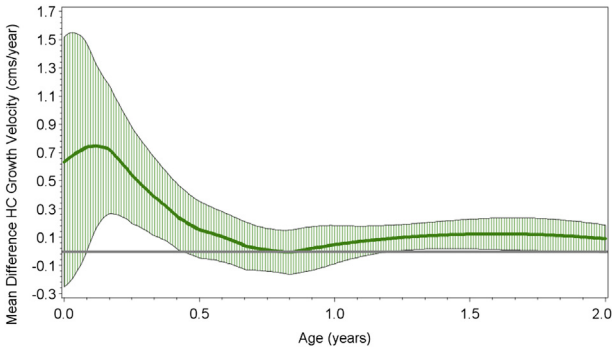

Figure 2. Mean head circumference (HC) growth velocity difference (solid line) between 468 cases and their matched control subjects; 95% confidence limits (dashed lines).

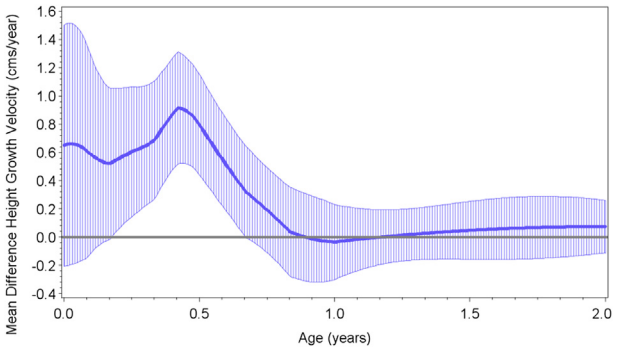

Figure 3. Mean height growth velocity difference (solid line) between 732 cases and their matched control subjects; 95% confidence limits (dashed lines).

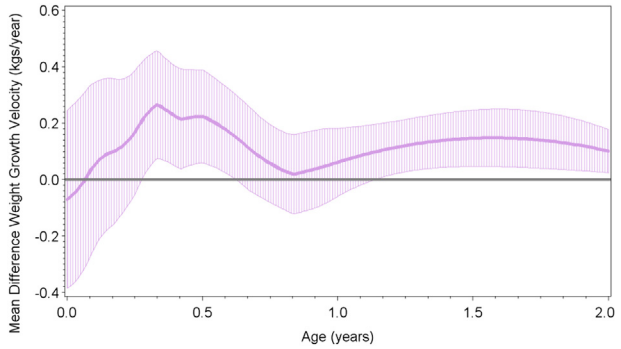

Figure 4. Mean weight growth velocity difference (solid line) between 737 cases and their matched control subjects; 95% confidence limits (dashed lines).

from 2 to 4 months of age, with the association reaching a peak at 3 months. This association was found irrespective of height and weight acceleration, which are not strongly associated with autism until after 6 months of age. The findings persist under Bonferroni correction for multiple testing. In contrast, elevated height growth velocity was significantly increased only in autism cases without comorbid ID, and this occurred at age 6 months. Weight growth velocity was increased in both the ID and non-ID groups at age 18 to 24 months (Tables S1 and S2 in Supplement 1).

One of the major differences between the present and previous studies relates to the timing of the differences in HC growth velocities. The difference in HC growth velocity in our study was statistically significant at age 3 months but had disappeared by age 6 months and did not re-emerge thereafter in adjusted analyses. This is earlier than virtually all previous studies, in which increases were primarily observed after age 6 months and as late as 3 years [see e.g., (2,3,5,14,22)].

Table 2. Mean Head Circumference Growth Velocity (cm/Year) at Different Time Points in Cases and Control Subjects (468 Pairs)

Age in Months	HC Mean Growth Velocity in Cases	HC Mean Growth Velocity in Control Subjects	HC Mean Growth Velocity Difference	*p* Value for HC Mean Growth Velocity Difference Based on GEE
0	24.63	23.99	.63	.16
1	23.52	22.78	.74	.05
2	20.45	19.72	.73	.002
3	16.64	16.10	.54	.001
4	13.80	13.41	.39	.01
5	11.29	11.06	.24	.04
6	9.46	9.32	.15	.15
7	7.93	7.84	.09	.29
8	6.63	6.59	.03	.68
9	5.85	5.84	.01	.91
10	5.11	5.12	−.01	.94
11	4.59	4.57	.02	.80
12	3.92	3.87	.05	.47
14	3.32	3.23	.08	.09
16	2.79	2.68	.11	.02
18	2.39	2.27	.12	.02
20	2.08	1.95	.12	.03
24	1.79	1.70	.09	.07

GEE, generalized estimating equations; HC, head circumference.

These differences may relate to variations in the analytic strategy and research design. First, the present study benefits from several statistical advantages, which allow for analysis of growth velocities; we emphasize that our conclusions (based on growth velocity) are not directly comparable with studies based on cumulative growth. Second, unlike most previous studies, based on the broad phenotype of ASD [see (22) for review], our sample was restricted to childhood autism, the core ASD phenotype. However, over the past year, DSM-IV autistic disorder is no longer in use. Childhood autism requires impairment in receptive or expressive language, social interaction, and functional or symbolic play, while ASD, which also includes Asperger syndrome and pervasive developmental disorders, requires some, but not all, of these criteria. Third, our sample size was substantially larger than those of all previous studies. Most studies consisted of fewer than 100 ASD cases (22) in contrast to over 400 childhood autism cases in the present study. Fourth, some studies had no or relatively small numbers of female subjects (10,13,14,16). Fifth, some studies did not collect data at intervals as frequent as in the current study (6). Sixth, the present study was based on a national birth cohort that is representative of the source population that gave rise to the cases, while most studies were based on clinical samples in which greater potential for selection bias exists (22). Seventh, many previous studies utilized population norms; evidence suggests that this may introduce systematic age-dependent biases (22). Nonetheless, it may be valuable in the future to conduct a meta-analytic replication of these findings using the original datasets from prior studies.

Several hypotheses have been offered to account for increased HC growth in autism. Courchesne *et al.* (4) suggested excess neurons, observed in a later study (23); excess minicolumn numbers; and premature expansion of dendritic and axonal arbors. Increased postnatal growth or diminished synaptic pruning may lead to volumetric anomalies.

In a longitudinal magnetic resonance imaging study, Hazlett *et al.* (24) found significant enlargement in total tissue and both gray and white matter volume in ASD children between age 2 and 4 to 5 years. In children between age 18 to 35 months, significant enlargement was also found for total cerebral cortical volume (5). Courchesne and Pierce (25) provided evidence indicating that within the cerebrum, the frontal and temporal lobes have the greatest growth deviation in autism (26); within the frontal lobes, the dorsolateral and medial frontal cortex were especially deviant (27).

It has been posited that the large integrative and projecting pyramidal neurons in frontal cortex are susceptible to increased brain growth dynamics (25). Pyramidal neurons in cortical layer III have long-range intracortical projections that are overexpressed in humans compared with nonhuman primates. These projections are believed to play a key role in distributed, interconnected association networks. It has been hypothesized that these networks originate from rapid expansion of the cortical mantle during human evolution, leading to

Table 3. Conditional Logistic Regression Analyses of Autism Incidence Predicted by the Growth Velocities of Head Circumference, Height, and Weight at Various Ages

	HC Growth Velocity[a]		HC Growth Velocity Adjusted[b]		Height Growth Velocity[a]		Height Growth Velocity Adjusted[b]		Weight Growth Velocity[a]		Weight Growth Velocity Adjusted[b]	
Age (Months)	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
3	1.07 (1.01–1.13)	.03	1.09 (1.02–1.16)	.014	1.03 (.99–1.06)	.20	1.03 (.99–1.07)	.11	.98 (.91–1.05)	.56	.97 (.90–1.05)	.45
6	1.01 (.92–1.11)	.84	1.01 (.92–1.12)	.81	1.06 (1.02–1.11)	.01	1.07 (1.02–1.11)	.006	1.02 (.93–1.11)	.67	1.03 (.94–1.13)	.49
9	.99 (.88–1.12)	.89	.96 (.85–1.09)	.55	1.02 (.96–1.07)	.59	1.01 (.96–1.07)	.63	1.01 (.9–1.14)	.88	1.035 (.91–1.17)	.59
12	1.05 (.92–1.19)	.46	1.05 (.92–1.19)	.50	.99 (.94–1.05)	.85	1.00 (.95–1.07)	.93	1.00 (.89–1.12)	.99	.98 (.88–1.11)	.78
18	1.16 (.98–1.37)	.09	1.18 (1.00–1.41)	.054	.92 (.85–1.00)	.05	.93 (.85–1.01)	.07	1.32 (1.10–1.58)	.003	1.30 (1.08–1.57)	.0057
24	1.13 (.95–1.34)	.18	1.16 (.97–1.39)	.11	.97 (92–1.03)	.36	.97 (.91–1.03)	.32	1.19 (1.06–1.34)	.004	1.19 (1.05–1.34)	.0053

CI, confidence interval; HC, head circumference; OR, odds ratio.
[a]Adjusted for the other two growth velocities at the same age (468 pairs).
[b]Adjusted for gestational age at birth, maternal age, and the other two growth velocities at the same age (n = 468 pairs).

cortical zones that became untethered from canonical sensory-motor hierarchies present in lower primates and mammals (28). Based on this evolutionary hypothesis, the proposal of Courchesne and Pierce (25), and the findings of the present study, we conjecture that an ontogenetic disruption in the process of association cortex development due to overactive brain growth during the fetal and early postnatal period contributes to the pathogenesis of autism.

In our study, differential acceleration in HC growth between autism cases and control subjects was not found during the period (later in the first year of life) when the earliest observable behavioral symptoms emerge (29). To our knowledge, the earliest findings were demonstrated at age 6 months; these included reduced attention toward faces (30), decreased parent-reported activity levels (31), and diminished postural control (32). However, the finding of an effect as early as 3 months may have important implications for further work, including neuroimaging research: in our view, attempts should be made to examine alterations in the trajectory of brain morphology within more narrow age windows during early infancy. In children aged 7 months, differences in visual orienting were related to individual differences in white matter microstructure of the splenium of the corpus callosum (33). Second, such findings may imply that the aberrant neurodevelopmental processes that underlie increased HC during infancy, such as those reviewed above, may not be directly responsible for symptomatic and behavioral manifestations of autism. Rather, these developmental deviations may increase the vulnerability for the later development of these symptoms, when functional networks that subserve language, social reciprocity, and other behaviors become activated. An analogous theory, involving an early, latent developmental insult has been advocated for schizophrenia (34).

Causes of accelerated growth in HC and body size may include abnormalities of neurotrophins, which regulate glucose metabolism (35) and also promote neuronal growth and survival (36). Insulin-like growth factor-I (IGF-I) is a neurotrophin that modulates somatic growth and metabolism and brain growth and myelination (37). Higher plasma IGF-I, as well as growth hormone binding protein, were observed in autistic children at age 4 to 8 (38), and IGF-I levels were positively correlated with head circumference (39).

We wish to further comment on the differential relationships between HC and height by ID status. In one study, the odds ratio doubled for ASD with ID in infants born 24% above the optimal birth weight (although the findings were not statistically significant) (40). On the other hand, in another study, Abel *et al.* (41) found a stronger association between low fetal growth and ASD for cases with comorbid ID than in cases without ID. While we have no ready explanation for the association between growth velocity of HC and autism among those only with comorbid ID, we speculate that the aberrant

Table 4. Conditional Logistic Regression Analyses of Autism with Intellectual Disability Predicted by the Growth Velocities of Head Circumference, Height, and Weight at Various Ages

	HC Growth Velocity[a]		HC Growth Velocity Adjusted[b]		Height Growth Velocity[a]		Height Growth Velocity Adjusted[b]		Weight Growth Velocity[a]		Weight Growth Velocity Adjusted[b]	
Age (Months)	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
3	1.114 (.99–1.25)	.07	1.170 (1.02–1.34)	.025	.98 (.91–1.06)	.63	1.01 (.93–1.10)	.81	1.00 (.87–1.15)	.99	.98 (.84–1.15)	.81
6	.942 (.79–1.13)	.52	1.00 (.82–1.24)	.97	1.03 (.95–1.12)	.46	1.04 (.95–1.15)	.37	1.06 (.90–1.25)	.48	1.06 (.89–1.28)	.51
9	.88 (.69–1.14)	.34	.855 (.64–1.14)	.29	1.01 (.91–1.12)	.86	1.0 (.89–1.12)	.96	1.06 (.85–1.34)	.59	1.20 (.92–1.56)	.17
12	1.06 (.82–1.36)	.67	1.073 (.81–1.43)	.63	.99 (.89–1.10)	.86	1.00 (.89–1.13)	.95	.91 (.73–1.12)	.37	.89 (.71–1.13)	.34
18	1.02 (.73–1.44)	.89	.95 (.64–1.40)	.78	.86 (.73–1.01)	.07	.87 (.73–1.04)	.11	1.36 (.95–1.96)	.10	1.43 (.96–2.14)	.08
24	1.02 (.73–1.42)	.91	.96 (.67–1.38)	.83	.93 (.83–1.04)	.18	.92 (.82–1.04)	.19	1.28 (1.01–1.62)	.038	1.32 (1.02–1.70)	.037

CI, confidence interval; HC, head circumference; OR, odds ratio.
[a]Adjusted for the other two growth velocities at the same age (n = 124 pairs).
[b]Adjusted for gestational age at birth, maternal age, and the other two growth velocities at the same age (n = 124 pairs).

Table 5. Conditional Logistic Regression Analyses of Autism Without Intellectual Disability Predicted by the Growth Velocities of Head Circumference, Height, and Weight at Various Ages

	HC Growth Velocity[a]		HC Growth Velocity Adjusted[b]		Height Growth Velocity[a]		Height Growth Velocity Adjusted[b]		Weight Growth Velocity[a]		Weight Growth Velocity Adjusted[b]	
Age (Months)	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
3	1.05 (.98–1.13)	.15	1.06 (.98–1.14)	.15	1.04 (1.00–1.09)	.08	1.05 (1.00–1.09)	.06	.97 (.89–1.06)	.54	.96 (.88–1.06)	.43
6	1.03 (.93–1.15)	.57	1.03 (.92–1.15)	.64	1.07 (1.02–1.12)	.007	1.07 (1.02–1.13)	.007	1.00 (.9–1.11)	.97	1.01 (.91–1.12)	.89
9	1.03 (.89–1.18)	.71	1.00 (.87–1.16)	.99	1.02 (.95–1.08)	.63	1.01 (.95–1.08)	.68	.99 (.86–1.14)	.90	1.00 (.87–1.16)	1.00
12	1.04 (.90–1.21)	.60	1.04 (.89–1.21)	.64	1.00 (.93–1.07)	.96	1.00 (.93–1.07)	.92	1.04 (.91–1.19)	.54	1.03 (.90–1.18)	.67
18	1.20 (.99–1.45)	.07	1.21 (1.00–1.48)	.053	.94 (.86–1.04)	.22	.94 (.86–1.04)	.22	1.30 (1.06–1.60)	.012	1.29 (1.04–1.60)	.02
24	1.17 (.95–1.44)	.14	1.20 (.97–1.48)	.1	.99 (.92–1.06)	.76	.99 (.92–1.06)	.77	1.16 (1.01–1.33)	.035	1.16 (1.01–1.34)	.042

CI, confidence interval; HC, head circumference; OR, odds ratio.

[a]Adjusted for the other two growth velocities at the same age (n = 344 pairs).

[b]Adjusted for gestational age at birth, maternal age, and the other two growth velocities at the same age (n = 344 pairs).

neurodevelopmental processes discussed above may be responsible for a more severe subtype of ASD characterized by increased HC growth velocity and comorbid ID. Since there was no comparison group of nonautistic ID cases in the present study, it is possible that the association with accelerated HC growth is not specific to autism. However, in a prior study (1), there was no elevated HC growth up to age 2 among subjects with developmental delay; in another study (15), HC was significantly smaller during the first 7 months in developmentally delayed subjects without autism. With regard to the finding that height growth velocity at 6 months was only related to autism without comorbid ID, we note that, among autism cases with ID, the odds ratio was highest at age 6 months versus all other ages (even though nonsignificant). Thus, the weaker relationship may have been due to lower statistical power due to the smaller number of cases with ID (n = 124) compared with cases with non-ID (n = 344).

Beyond the lack of a comparison group of ID cases without autism, we note additional limitations: 1) the data beyond age 2 were too sparse to follow up the growth trajectories into childhood; 2) no data were available on nutritional intake; 3) a considerable proportion of the sample did not have data available on the outcome measures; however, cases with and without missing data did not differ on covariates tested; 4) diagnoses were based on a psychiatric registry, although the agreement with Autism Diagnostic Interview-Revised diagnoses was very high; and 5) the proportion of autism cases with ID was only 26% in our sample, well below the 67% rate found in childhood autism in a birth cohort study in England (42), which included standardized IQ testing as part of the study. Hence, one reason for the discrepancy is that our study relied on registry diagnoses of ID. While all of the ID diagnoses in our study were based on careful neuropsychological testing, if ID is not consistently entered into the registers, this would have produced an underestimate of comorbidity of ASD and ID. Although not published, it is generally believed that milder cases of ID are most likely to be missing in the Finnish registers. Nonetheless, our finding is consistent with a previous study, cited above, of HC growth and ID in autism (17).

Conclusion

Acceleration in HC growth from 2 to 4 months of age is strongly associated with autism among cases with comorbid intellectual disability, irrespective of acceleration in height and weight at the same age. After 6 months, associations emerge between autism and accelerated height and weight. The association of acceleration in HC growth with autism may occur much earlier than previously reported. Studies on the specificity of altered HC growth dynamics in autism cases are warranted.

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