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Evidence of Brain Overgrowth in the First Year of Life in Autism

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BEHAVIORAL SIGNS AND SYMPTOMS during the second and third years of life, including delayed speech, unusual social and emotional reactions, and poor attention to and exploration of the environment, raise warnings that a child might have autism.¹⁻⁵

Autism is a neurobiological disorder,⁶⁻⁸ and neurobiological abnormalities must necessarily precede the first behavioral expressions of the disorder. However, such neurobiological early warning signs have not yet been discovered for autism. Knowledge of such signs could lead to objective, quantifiable, and reliable clinical tests for autism; earlier identification and intervention; and eventually insight into the original causes and/or mechanisms present at the earliest stages of the disorder.

One neurobiological abnormality, increased brain volume, is detectable at an age when clinical signs are becoming apparent.⁹ Ninety percent of 2- and 3-year-old children had brain volumes larger than the healthy average,⁹ as well as abnormally large head circumferences (HCs).¹⁰ Another study reported that brain size in 4-year-old children with autism exceeded the healthy average.¹¹ Excessive brain size was primarily due to increased white matter volumes in the cerebellum and cerebrum⁹ and increased gray matter volume in the cerebrum, within which frontal lobes were most abnormal.¹² A

Context Autism most commonly appears by 2 to 3 years of life, at which time the brain is already abnormally large. This raises the possibility that brain overgrowth begins much earlier, perhaps before the first clinically noticeable behavioral symptoms.

Objectives To determine whether pathological brain overgrowth precedes the first clinical signs of autism spectrum disorder (ASD) and whether the rate of overgrowth during the first year is related to neuroanatomical and clinical outcome in early childhood.

Design, Setting, and Participants Head circumference (HC), body length, and body weight measurements during the first year were obtained from the medical records of 48 children with ASD aged 2 to 5 years who had participated in magnetic resonance imaging studies. Of these children, 15 (longitudinal group) had measurements at 4 periods during infancy: birth, 1 to 2 months, 3 to 5 months, and 6 to 14 months; and 33 (partial HC data group) had measurements at birth and 6 to 14 months (n=7), and at birth only (n=28).

Main Outcome Measures Age-related changes in infants with ASD who had multiple-age measurements, and the relationship of these changes to brain anatomy and clinical and diagnostic outcome at 2 to 5 years were evaluated by using 2 nationally recognized normative databases: cross-sectional normative data from a national survey and longitudinal data of individual growth.

Results Compared with normative data of healthy infants, birth HC in infants with ASD was significantly smaller ($z=-0.66$, $P<.001$); after birth, HC increased 1.67 SDs and mean HC was at the 84th percentile by 6 to 14 months. Birth HC was related to cerebellar gray matter volume at 2 to 5 years, although the excessive increase in HC between birth and 6 to 14 months was related to greater cerebral cortex volume at 2 to 5 years. Within the ASD group, every child with autistic disorder had a greater increase in HC between birth and 6 to 14 months (mean [SD], 2.19 [0.98]) than infants with pervasive developmental disorder-not otherwise specified (0.58 [0.35]). Only 6% of the individual healthy infants in the longitudinal data showed accelerated HC growth trajectories (>2.0 SDs) from birth to 6 to 14 months; 59% of infants with autistic disorder showed these accelerated growth trajectories.

Conclusions The clinical onset of autism appears to be preceded by 2 phases of brain growth abnormality: a reduced head size at birth and a sudden and excessive increase in head size between 1 to 2 months and 6 to 14 months. Abnormally accelerated rate of growth may serve as an early warning signal of risk for autism.

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discriminant function analysis revealed that 95% of 2- to 5-year-old children with autism were separately classified from children without autism based on cerebral and cerebellar mag-

netic resonance imaging (MRI) volume measurements (N.A., unpublished data, March 2003).

Whether pathological brain overgrowth precedes, co-occurs with, or fol-

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lows the onset of the first clinical behavioral signs of autism is unknown. Given that HC throughout the first years of life is an accurate index of brain size,¹³⁻¹⁵ an important observation is that birth HCs in children with autism are not abnormally large.^{9,16-18} Because excessive brain size is not present at birth but is present by 2 to 3 years,⁹ this overgrowth must begin sometime between these 2 ages.

In this study, we aimed to determine whether pathological brain overgrowth precedes the first behavioral expressions of autism and whether abnormal growth trajectories predict the neuroanatomical and clinical outcomes of children with autism. To establish relationships between growth during infancy and later neuroanatomical outcome, we included all 2- to 5-year-old children with an autism spectrum disorder (ASD), which included autistic disorder (AD, more severe form of ASD) and pervasive developmental disorder-not otherwise specified (PDD-NOS, milder form of ASD), on whom we had quantitative MRI measurements (R.C., unpublished data, May 2003; N.A., unpublished data, March 2003)^{9,10,12,19} and requested birth and first year HC measurements from each child's medical records. Due to variability in procedures across pediatricians, the exact ages at which HC was measured varied from patient to patient. Because medical records for some patients were unavailable and others did not include regular HC measurements, our final sample size was about half that of our original MRI study sample.

Despite the confines imposed by such a design, our study had a number of significant strengths. First, the critical HC measurement was obtained in an unbiased fashion. The measurements were recorded by medical staff in ordinary clinics, not clinics specializing in suspected developmental disorders. These individuals were unaware that the infants would develop an ASD. The measurements were recorded by different individuals, which eliminates the possibility of any systematic error in measurement biasing the results. The

methods and individuals involved in acquiring infant HC and developmental outcome brain size on MRI were also completely independent of each other. Second, our study is a contemporary sample of children with ASD now being observed in clinics. Third, our sample was diagnosed with rigorous contemporary methodology by using a prospective, longitudinal diagnostic follow-up design. Full descriptions of this design have been published previously.⁹ By using a sample of children with ASD on whom we had MRI data, we were in the unique position to examine relationships between HC changes during the first year and MRI-based measurements of the brain at a later developmental age, namely 2 to 5 years.

To establish at what ages HC in infants with ASD differs from that in healthy infants, we compared our HC measurements of children with ASD to the Centers for Disease Control and Prevention (CDC) growth charts of the United States.²⁰ To determine how often healthy developing infants show extreme growth deviations in HC during the first year and whether longitudinal growth trajectories differ between individual healthy infants and those with ASD, we compared our longitudinal HC measurements from infants with ASD to those available from a nationally recognized, contemporary cohort of healthy infants.²¹

METHODS

The study was approved by the institutional review board of San Diego Children's Hospital Research Center. All participants were recruited from community advertisements and referrals, and informed consent was obtained from the parents of the children.

Participants

A total of 48 children with ASD aged 2 to 5 years participated; 92% of them were white. Each had been a participant in previous MRI studies reporting age-related changes in the brain in autism (R.C., unpublished data, May 2003; N.A., unpublished data, March 2003).^{9,12,19}

The diagnosis of ASD was based on multiple criteria as previously described,⁹ resulting in a conservative selection of participants that would be expected to lead to better agreement than clinical diagnosis alone.²² All children met inclusionary criteria for the diagnosis of AD or PDD-NOS based on the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*²³; the Autism Diagnostic Interview²⁴ or the Autism Diagnostic Interview-Revised²⁵; and the Autism Diagnostic Observation Schedule.²⁶ For 1 child, the Autism Diagnostic Observation Schedule was not completed, but a diagnosis of AD was made based on clinical observation, the Autism Diagnostic Interview-Revised, and collateral records. Of the total 48 children with ASD, 40 met criteria for AD and 8 for PDD-NOS. Diagnostic and IQ data at the age of MRI scan (ages 2-5 years) are given in TABLE 1. All patients were full term at birth and negative for fragile-X, except 9 who did not receive this test. Patients with concurrent medical conditions were excluded.

HC Data

Physicians, clinics, and hospitals involved in the treatment of each of the 48 children with ASD were contacted to obtain all available medical records containing clinical HC, length, and weight measurements. Of the 48 patients with ASD, 15 (12 males and 3 females) had pediatric HC measurements at 4 age periods: birth, 1 to 2 months (mean [SD] age, 1.6 [0.5] months), 3 to 5 months (4.2 [0.6] months), and 6 to 14 months (10.6 [2.6] months) and were termed the longitudinal group. The remaining 33 children (29 males and 4 females) were termed the partial HC data group because they had HC measurements at birth and 6 to 14 months (n=7) and at birth only (n=28). Also, 2 did not have a birth HC measurement but did have an HC measurement at 2 weeks of age.

Birth HC, body length, and body weight did not significantly differ between the longitudinal and partial HC data groups (TABLE 2). However, birth HC was significantly smaller in both

ASD groups compared with the CDC average of healthy infants (longitudinal group: $z = -0.66$, $t_{14} = -3.94$, $P = .001$; partial HC data group: $z = -0.41$, $t_{32} = -3.07$, $P = .004$). In contrast, neither length nor weight of all infants were smaller than the CDC averages of healthy infants.

Clinical and MRI Characteristics of Longitudinal and Partial HC Data Groups

To further determine whether those infants who had their head frequently measured by their pediatrician differed from those infants who did not, we compared clinical and MRI characteristics of the longitudinal and partial HC data groups (Table 2 and TABLE 3). *t* Tests revealed that there were no significant group differences with any of these clinical or MRI variables.

Statistical Analyses and Normative Databases

Statistical analyses were carried out by using SPSS statistical software version 10 (SPSS Inc, Chicago, Ill); $P \leq .05$ was considered statistically significant. Head circumference, length, and weight measurements were normalized across sex and age by converting to *z* scores based on the CDC averages of healthy infants.²⁰ Head circumference data from 51 infants born between 1980 and 2001 from the Fels Longitudinal Study²¹ were made available to us for comparison with the ASD sample. The infants from the Fels Longitudinal Study included 26 males and 25 females and were a subset of the more extensive Fels Longitudinal Study sample. All were white infants recruited from middle-class families in southwestern Ohio.

RESULTS

HC Growth During the First Year

The Longitudinal Group vs CDC Data. To identify when during the first year HC in infants with ASD deviated significantly from averages of healthy infants, data from the longitudinal group were compared with the CDC data. A repeated measures analysis of variance of HC *z* scores at birth, 1 to 2 months,

3 to 5 months, and 6 to 14 months showed a statistically significant effect of age ($F_{3,42} = 16.87$, $P < .001$). This age-related change was because of a sudden increase in HC measurement be-

ginning after 1 to 2 months (FIGURE 1). Follow-up analyses showed that HC was significantly smaller than healthy measurements at birth ($z = -0.66$, 25th percentile). However, between 1 to 2

Table 1. Diagnostic and IQ Data for All Participants With ASD*

	Longitudinal Group (n = 15)	Partial HC Data Group (n = 33)
Age at first concern, mo	17.93 (5.8)	19.97 (6.11)
Age first sought advice, mo	22.57 (7.53)	24.39 (6.58)
Age first diagnosis, mo	30.07 (7.11)	31.57 (7.98)
Diagnosis, No. (%)		
Autism	11 (73)	29 (88)
PDD-NOS	4 (27)	4 (12)
ADI-R		
Social	20.47 (6.21)	23.45 (4.92)
Nonverbal	10.07 (3.45)	10.52 (3.32)
Verbal†	16.5 (3.66)	17.30 (4.37)
Repetitive	6.47 (2.70)	6.47 (2.06)
CARS	34.37 (8.59)	35.26 (6.13)
IQ		
Nonverbal‡	75 (22.56)	86.97 (20.91)
Verbal ≥70, No. (%)§	3 (20)	10 (30)

Abbreviations: ADI-R, Autism Diagnostic Interview-R; ASD, autism spectrum disorder; CARS, Childhood Autism Rating Scale²²; HC, head circumference; PDD-NOS, pervasive developmental disorder-not otherwise specified.

*Data are presented as mean (SD) unless otherwise specified.

†Subscale limited to children with functional language (longitudinal group [n = 8] and partial HC data group [n = 22]).

‡Based on the Leiter International Performance Scale²³; Stanford-Binet-IV²³; Wechsler Intelligence Scale for Children-II²³; or Mullen Scales of Early Learning.³¹ The specific tests administered were selected on a case-by-case basis depending on the age and level of ability of the child.

§Based on the Stanford-Binet-IV²³ or Wechsler Intelligence Scale for Children-III²³; 14 of the participants with lower functioning were not able to achieve above basal level on the verbal tests.

Table 2. Birth Measurement Data for All Children With ASD

Birth Measurements	Longitudinal Group (n = 15)		Partial HC Data Group (n = 33)	
	Mean (SD)	<i>z</i> Score	Mean (SD)	<i>z</i> Score
HC, cm	34.33 (1.33)	-0.66*	34.89 (1.76)	-0.41*
Length, cm	51.35 (3.03)	0.57	51.78 (3.2)	0.65†
Weight, kg	3.48 (0.37)	-0.02	3.66 (0.66)	0.29

Abbreviations: ASD, autism spectrum disorder; HC, head circumference.

*Smaller than Centers for Disease Control and Prevention averages of healthy infants (longitudinal group, $P = .001$; partial HC data group, $P = .004$).

†Larger than Centers for Disease Control and Prevention averages of healthy infants ($P = .002$).

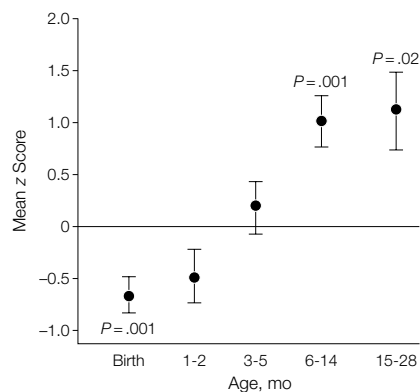
Table 3. Magnetic Resonance Imaging Data for All Male Infants With ASD at 2 to 5 Years

Volume, mL	Mean (SD)	
	Longitudinal Group (n = 12)	Partial HC Data Group (n = 29)*
Intracranial (brain+CSF)	1385.56 (94.62)	1399.85 (125.84)
Whole brain	1275.64 (90.57)	1292.54 (111.88)
Whole brain white matter	348.46 (34.53)	351.37 (40.92)
Whole brain gray matter	927.18 (62.53)	941.17 (75.51)
Cerebral white matter	279.45 (30.51)	282.06 (34.19)
Cerebral gray matter	756.87 (51.46)	769.34 (63.12)
Cerebellar white matter	32.07 (3.08)	31.71 (3.79)
Cerebellar gray matter	101.39 (12.92)	101.30 (13.25)

Abbreviations: ASD, autism spectrum disorder; CSF, cerebrospinal fluid.

*Separate white and gray matter volumes for the cerebellum were not obtainable from 1 patient in this group.

Figure 1. Age-Related Changes in Head Circumference During Infancy in Autism Spectrum Disorder



ASD indicates autism spectrum disorder; HC, head circumference. At birth and at 1 to 2 months of age, HC in the longitudinal-ASD group was statistically significantly below the Centers for Disease Control and Prevention (CDC) mean for healthy infants, but by 6 to 14 months of age, it was more than 1.0 SD (84th percentile) above the mean for healthy infants. The CDC mean of healthy infants at each age is 0. Error bars are SEM.

months and 3 to 5 months, HC increased by 0.66 SDs to a mean *z* score of 0.18; between 3 to 5 months and 6 to 14 months, HC increased by 0.83 SDs to a mean *z* score of 1.01. Between birth and 6 to 14 months of age, the mean HC of infants with ASD increased from the 25th to the 84th percentile, an increase of 1.67 SDs.

Body length and weight at birth and 1 to 2 months were not significantly smaller than averages of healthy infants, and at 3 to 5 months and 6 to 14 months were not significantly larger than averages of healthy infants; therefore, none of the significant HC deviations from healthy averages in the infants were explained by differences in body length and body weight at any of the 4 age groups.

Nine of these 15 longitudinal group infants also had at least 1 pediatric HC measurement between 15 and 28 months (mean [SD], 19.22 [4.38]). Although HC at this age range was significantly greater than the CDC data of healthy infants (mean [SD] *z* score, 1.10 [1.12], 86th percentile), it was not a statistically significant increase over the mean *z* score for HC at 6 to 14 months.

Longitudinal Changes in Infants With ASD vs Individual Fels Longitudinal Study Infants. Of the 51 Fels Longitudinal Study infants, only 6 had pediatric HC measurements at the same 4 age periods as the longitudinal group; therefore, a within-participant longitudinal comparison to our longitudinal group infants at 4 age periods was not possible. However, 31 of the Fels Longitudinal Study infants had 1 HC measurement at birth to 2 months (mean [SD], 0.4 [0.6] months) and a second at 6 to 14 months (10.1 [1.5] months). Seven infants with ASD from the partial HC data group who had both birth and 6 to 14 month HC measurements were added to the longitudinal sample, providing a total of 22 infants with ASD with HC measurements at 2 similar age periods, namely, birth and 6 to 14 months (10.3 [2.7] months). The HC measurements from the 31 Fels Longitudinal Study infants were converted to *z* scores based on the CDC averages of healthy infants; however, the birth HC in the CDC averages of healthy infants were based entirely on the Fels Longitudinal Study data set, and the CDC averages for HC at all other age periods were based on a national survey collected separately from and independently of the Fels Longitudinal Study data.

Comparison of the 31 Fels Longitudinal Study infants and the 22 infants with ASD showed that the increase in HC between birth and 6 to 14 months was significantly greater for the infants with ASD (ASD vs Fels Longitudinal Study infants: mean (SD) *z* score, 1.82 [1.11] vs 0.76 [0.74]; $t_{51}=4.18$; $P<.001$).

Measurements at Birth vs Later Clinical Indices and MRI Measurements

A priori hypotheses⁹ suggested that the magnitude of brain changes of abnormal nature during infancy in autism might be related to later clinical and brain size outcome. To test this hypothesis, the 2 main HC effects (ie, reduced birth HC and the HC increase during infancy) were used. To increase statistical power, the infants with ASD ($n=22$)

who had both birth and 6 to 14 month HC measurements were examined.

Clinical Indices. A median split was performed on the birth HC of these infants, resulting in 1 subgroup with a mean (SD) birth HC *z* score of -1.27 (0.44) (10th percentile) and another with a *z* score of 0.07 (0.46) (53rd percentile). A median split was also performed on the birth to 6 to 14 month HC increase in these infants, resulting in 1 subgroup with an HC increase of 0.94 (0.48) (73rd percentile) and another with an HC increase of 2.71 (0.79) (97th percentile). Among patients with functional language, smaller birth HC was associated with a worse verbal score on the Autism Diagnostic Interview (19.6 vs 14.4; $t_{10}=2.81$; $P=.02$). A greater increase in HC measurement during infancy was associated with a significantly worse score on the stereotyped and repetitive behaviors scale of the Autism Diagnostic Observation Schedule (3.6 vs 2.0; $t_{20}=-2.21$; $P=.04$); a strong trend toward a later age of onset for first words (44 vs 30 months; $t_{15}=-2.00$; $P=.06$); and a trend toward a higher score on the Childhood Autism Rating Scale,²⁷ a clinical index of the severity of autistic symptoms (38 vs 31; $t_{20}=-1.93$; $P=.07$).

MRI Outcome. TABLE 4 shows correlations between HC measurements in the first year and quantitative MRI measurements of the brain at 2 to 5 years. Only male infants were considered in analyses of MRI outcome measurement. Smaller birth HC was significantly correlated with smaller cerebellar gray matter volumes in childhood after controlling for age at MRI ($r=0.53$; $df=14$; $P=.04$); a strong trend was observed for cerebellar white matter volume ($r=0.49$; $df=14$; $P=.06$). Birth HC was not significantly correlated with any cerebral measures. Conversely, a greater increase in HC during the first year was significantly correlated with greater cerebral gray matter, whole brain gray matter, and whole brain volumes (all correlations $r\geq 0.48$; $df=15$; $P\leq .03$) but not with any white matter measures or cerebellar measures (Table 4). Additionally, HC measurements at 6 to 14

Table 4. Partial Correlation Coefficients Between HC Measurements During the First Year and MRI Outcome Measurements at 2 to 5 Years of Age, Controlling for Age at MRI

MRI Outcome Measurements, Volume	Correlation Coefficient					
	Birth HC (n = 15)	P Value	HC at 6 to 14 Months (n = 15)	P Value	Change in HC From Birth to 6 to 14 Months (n = 15)	P Value
Whole brain	0.388	.12	0.784	<.001	0.481	.051
Whole brain white matter	0.35	.17	0.538	.03	0.264	.31
Whole brain gray matter	0.378	.13	0.829	<.001	0.534	.03
Cerebral white matter	0.27	.29	0.545	.02	0.334	.19
Cerebral gray matter	0.323	.21	0.817	<.001	0.565	.02
Cerebellar white matter*	0.489	.055	0.027	.92	-0.326	.22
Cerebellar gray matter*	0.530	.04	0.538	.03	0.169	.53

Abbreviations: HC, head circumference; MRI, magnetic resonance imaging.

*For each correlation with cerebellar measurements, n = 14.

months was significantly correlated with greater cerebral gray matter (FIGURE 2), cerebral white matter, whole brain gray matter, whole brain white matter, whole brain volumes (all correlations $r \geq 0.54$; $df = 15$; $P \leq .03$), and cerebellar gray matter ($r = 0.54$; $df = 14$; $P = .05$) (Table 4).

AD vs PDD-NOS Outcome. Among the 22 infants with ASD with both birth and 6 to 14 month HC measurements, 17 were diagnosed with AD and 5 with PDD-NOS. Birth HC measurements of mean (SD) z score were not significantly different between the 2 groups (AD: -0.55 [0.83], 29th percentile; PDD-NOS: -0.48 [0.83], 32nd percentile). However, there was a striking difference in the HC measurement increase because from birth to 6 to 14 months, the infants with AD increased 2.19 (0.98), reaching the 95th percentile, while the infants with PDD-NOS increased only 0.58 (0.35), reaching only the 54th percentile (FIGURE 3).

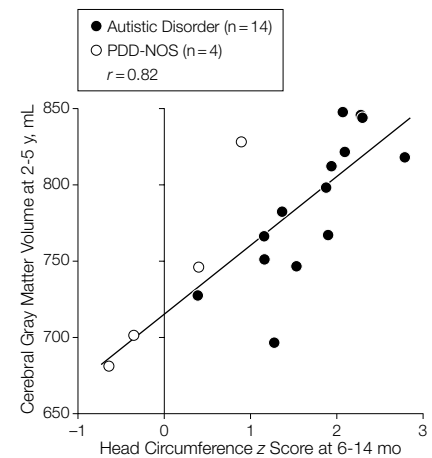
Furthermore, for 71% of the infants with AD, the magnitude of the increase was greater than 1.5 SDs with 59% of the infants having increases between 2.0 and 4.3 SDs. None of the infants with PDD-NOS had increases more than 1.0 SDs. Among the 31 healthy Fels Longitudinal Study infants in our analyses, only 9% had increases of more than 1.5 SDs, with 6% having increases of more than 2.0 SDs. As a result of the large increase in HC by 6 to 14 months, 15 (88%) of the 17 infants with AD had HC values that ex-

ceeded the 87th percentile ($z \geq 1.15$) and 9 (53%) of 17 were at or above the 97th percentile ($z \geq 1.87$).

FIGURE 4 shows the growth curve for the male infants with AD (14 of the total 17) relative to the CDC 10th, 50th, and 90th percentile curves for healthy male infants; all HC measurements at birth, 1 to 2 months, 3 to 5 months, and 6 to 14 months from these 14 male infants with AD were used to calculate the best fit curve.

COMMENT

This is the first study to our knowledge to find a potential early warning neurobiological sign for autism and to link it to a later brain abnormality. Specifically, we found a rapid and excessive increase in HC measurements, and therefore, presumably, brain size, beginning several months after birth. This abnormally accelerated rate of increase in HC measurements in infants with ASD was evident in comparisons to 2 nationally recognized normative databases, one a national cross-sectional survey and the other a longitudinal study of growth patterns in healthy infants. In our study, head size increased from the 25th percentile based on the CDC averages of healthy infants to the 84th percentile in 6 to 14 months. This excessive increase occurred well before the typical onset of clinical behavioral symptoms. Moreover, this increase by the end of the first year was strongly correlated with greater cerebral and cerebellar volumes by 2 to 5 years of age. These re-

Figure 2. Head Circumference of Male Infants at 6 to 14 Months Correlating With Cerebral Gray Matter Volume at 2 to 5 Years

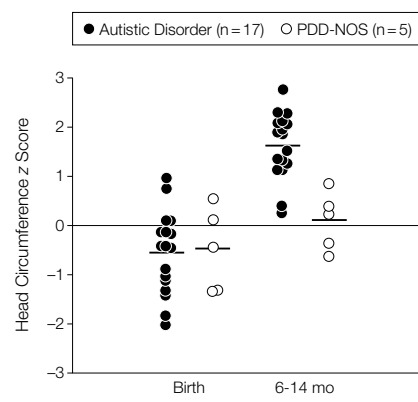
PDD-NOS indicates pervasive developmental disorder not otherwise specified. The larger the head circumference of male infants at 6 to 14 months, the greater the cerebral gray matter volume at 2 to 5 years of age.

sults suggest that growth dysregulation in 2 major cortices and underlying white matter in the brain underlies the increase in HC.

The cellular bases of the brain volume increases remains to be determined and could reflect any of a number of possibilities, including excessive numbers or rates of growth of neurons and/or glial cells, excessive numbers of minicolumns, excessive and premature expansion of dendritic and axonal arbors, excessive numbers of axonal connections, and/or premature myelination. The causes also remain to be

identified and could reflect an abnormal acceleration of postnatal growth processes or a failure of late prenatal and early postnatal regressive processes. The brain volume increases could also reflect either aberrant compensatory responses to adverse prenatal conditions

Figure 3. Increase in Head Circumference From Birth to 6 to 14 Months of Age Between Infants With Autistic Disorder and Infants With PDD-NOS



PDD-NOS indicates pervasive developmental disorder not otherwise specified. At each age and for each group, short horizontal bars indicate mean HC. The infants with autistic disorder had a greater rate of growth in head circumference between birth and 6 to 14 months of age than did those with PDD-NOS.

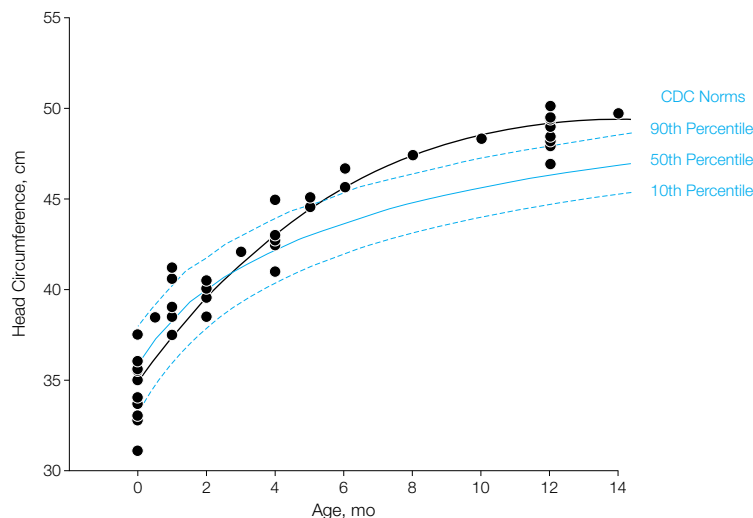
or deviant biological mechanisms that are first expressed in early postnatal life. Events and conditions, such as measles, mumps, and rubella vaccinations, childhood exposure to environmental toxins or pathogens, or unusual gastrointestinal or allergic reactions to food, that occur after the overgrowth are not logically plausible as causes. Although some may argue that such later occurring events might be important as aggravating factors, the key question remains—what triggers the abnormal brain overgrowth in the first months of life initially?

In our study, this overgrowth was also a reliable neurobiological phenomenon among the children with AD within our sample of infants with ASD. Among the infants who have the more severe form of autism, 71% showed increases during their first year of more than 1.5 SDs, with 59% showing increases between 2.0 and 4.3 SDs. Such high percentages were not observed in the typically developing infants in the Fels Longitudinal Study sample. Our sample of infants with ASD also included a very small number of children with PDD-NOS, a milder condition of autism. In contrast with the children with AD, all of the children with

PDD-NOS showed small increases, in which their HC measurement increased from less than the 50th percentile up to the 54th percentile. This contrast between infants with the more and less severe forms of autism is compatible with our previous hypothesis⁹ that an earlier onset, faster rate, and longer period of excessive brain growth might be associated with poorer outcome (eg, AD), and the converse, later onset, slower rate, and shorter period of excessive growth, might be associated with a better outcome (eg, PDD-NOS). Larger samples of infants with ASD will be needed to further support this clinically and neurobiologically relevant hypothesis.

Our analyses of the Fels Longitudinal Study data suggest that although extreme HC measurement increases may occur occasionally in healthy developing infants, they are much less common (6% of cases) than in infants later diagnosed with AD (59% of cases). Aberrantly excessive head size in infants may also occur in disorders, such as hydrocephalus, benign megalencephaly, tumor, and subdural hematoma; therefore, it is important for physicians to rule out these types of conditions via physical, imaging, and biological examinations. Although an abnormally large increase in HC in an infant cannot be viewed as a certain and unique marker of autism, it nonetheless does appear to be an important signal that an infant is at significantly heightened risk for the disorder. If further research verifies this result, it may become an important observation in the clinic alerting the physician to the need for follow-up tests for possible autism. Further research may identify a combination of biological (eg, biochemical, MRI, genetic) and behavioral signs that together compose an accurate and early diagnostic prognosis, which might make it possible to begin treatment 2 or 3 years earlier than is now commonly the protocol. However, as demonstrated by some animal models (eg, monocular deprivation)³² and human disorders (eg, phenylketonuria)³³ of brain development, a sub-

Figure 4. Growth of Head Circumference Measurements in Male Infants With Autistic Disorder by Age



Longitudinal data from male infants with autistic disorder (n=14) from Figure 3 (2 to 4 points per child). Thick line indicates head circumference change through these points; 10th, 50th, and 90th percentile averages for healthy male infants, as indicated (blue).²⁰ Data from different infants overlap at some measurement ages.

stantially improved outcome can result from appropriate interventions begun before aberrant neural circuit configuration and function have been irreversibly established. Similarly, identifying novel early treatments for autism should result in a better outcome than is currently possible.

There appear to be at least 4 phases of brain growth in autism. The first phase involves a slight undergrowth of the prenatal brain because, at birth, the average HC measurement is at the 25th percentile. This is not due to overall decreases in prenatal body growth because body length and weight at birth are not less than the values of healthy infants. Although the brain volume decrease at birth is small, it coincides with speculations about prenatal neural defects inferred from adult autistic postmortem brains.^{6,34-40} The second growth phase involves the rapid and large overgrowth within the first year described in the current study. The third phase appears to last about 2 to 4 years, during which the overall rate of brain growth slows, so that by ages 4 to 5 years, brain size in autism reaches its near maximum.⁹ Importantly, this maximum brain size in young children with autism (approximately 1350 mL) is similar to that achieved by healthy children (approximately 1360 mL), but about 8 years too soon.⁹ The fourth phase involves a gradual decline in overall brain size and extends from middle or late childhood through to adulthood. By adolescence and adulthood, brain size in autism is not significantly different from the healthy average.^{9,10}

A new MRI study of 8- to 46-year-old patients with autism and healthy patients has confirmed that the brain in autism is only slightly larger than average size by late childhood, and that by adolescence and adulthood, it does not differ significantly in size.⁴¹ The evidence indicates, therefore, that autism is a disorder involving a transient period of postnatal pathologically rapid brain growth. Only during the very first years of postnatal life in autism is the brain abnormally enlarged and not before (eg, at birth) or after (eg, adoles-

cence and adulthood). There are exceptions to this rule. Of the 48 infants with ASD in our study, 2 had birth HC measurements at more than the 80th percentile. There also are rare cases of autism in which brain volumes of infants exceed all healthy patients of all age groups.^{9,42}

This early, yet transient, period of brain overgrowth must be an important factor in causing the emergence of autistic behavior because it occurs at the beginning of an important period of developmental neuroplasticity and learning. Evidence from studies of developmental neuroplasticity^{32,43-49} leads to the conclusion that the developing human brain is designed to benefit from an extended period of experience-guided growth. The long period of plasticity provides the opportunity for a multitude of experiences in the form of sensations, emotions, thoughts, and actions to direct axonal and dendritic growth, and to create, reinforce, or eliminate synapses as needed. Such extended experience-guided growth inevitably leads to the emergence of refined higher order neurobehavioral functions, such as those cognitive, emotional, linguistic, and motor skills necessary for understanding and actively socially engaging others. In autism, the brain may compress for a short time an amount of overall growth that takes many years in typically developing children to unfold.^{9,12,50-54} Thus, there is aberrantly rapid and disordered growth without guidance that produces in too short a time too many connections that may not be adaptive. Faced with the neural noise that would be the result of such rapidly changing aberrant connections, the infant would lose the ability to make sense of its world and withdraw. Not until later, when the excessive growth rate slows, would the now autistic child have a chance to use experience-guided processes to select whatever connections might still be useful and to eliminate those that are not. By that time, however, the extended period of plasticity that allows the exquisite and graceful complexity of the human brain to emerge will have passed.

There is large literature emphasizing the heterogeneity, particularly of behavioral outcome, in autism. Yet, in the current study, 76% of the children with AD had HC measurements below the 50th percentile at birth, 88% showed early postnatal brain overgrowth with HC measurements exceeding the 87th percentile by 6 to 14 months, and 59% showed extreme (>2.0 SD) increases during the first year. In other studies of autism, 95% of cases had elevated blood levels of brain growth factors at birth⁵⁵; more than 95% of cases have cerebellar pathology^{6,35-37,39}; more than 95% of 2- to 5-year-old patients were correctly distinguished from healthy measurements on the basis of only cerebellar and cerebral white matter volumes (N.A., unpublished data, March 2003); and 100% of cases have increased neuron packing density in limbic structures.³⁶ Such biological consistencies, along with the relatively uniform onset age and excessive rate of brain growth reported in the current study, raise the interesting possibility that some biological factors leading to autism might be similar across the majority of patients. Perhaps the outcome heterogeneity might have more to do with the multitude of genetic and nongenetic background factors that differ between patients.

In conclusion, our study found evidence of neonatal brain undergrowth followed by rapid and excessive postnatal brain growth beginning in the first few months that precedes the clinical behavioral onset of autism. The degree, rate, and/or duration of the overgrowth may be related to neuroanatomical and clinical outcome. The HC overgrowth in infants later diagnosed with AD holds potential for clinical application because it is early, rapid, substantial, common across patients, and may eventually prove to be distinctive from other forms of head and brain enlargement, and also because its detection is simple, inexpensive, noninvasive, objective, and reliable. The existence of such a pronounced biological early warning signal, if confirmed by future studies, offers hope that the causes will be equally pronounced leading to

very early diagnosis and effective biological intervention or even prevention of autism.

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