When Is the Brain Enlarged in Autism? A Meta-Analysis of All Brain Size Reports

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Background: *Multiple studies have reported increased brain size in autism, while others have found no difference from normal. These conflicting results may be due to a lack of accounting for age-related changes in brain enlargement, use of small sample sizes, or differences in data acquisition methods.*

Methods: *Reports of autism head circumference (HC), magnetic resonance imaging (MRI), and post-mortem brain weight (BW) that met specific criteria were identified and analyzed. Percent difference from normal values (%Diff) and standardized mean differences (SMD) were calculated to compare brain size across studies and measurement methods. Curve fitting, analysis of variance, and heterogeneity analyses were applied to assay the effects of age and measurement type on reported brain size in autism.*

Results: *A fitted curve of HC and MRI %Diff values from 15 studies revealed a largely consistent pattern of brain size changes. Specifically, brain size in autism was slightly reduced at birth, dramatically increased within the first year of life, but then plateaued so that by adulthood the majority of cases were within normal range. Analysis of variance of MRI and post-mortem %Diff values by age group (young child, older child, adult) and measurement type (MRI, BW) revealed a significant main effect of both age and measurement type, with the youngest ages (2–5) showing the greatest deviation from normal. Random effects heterogeneity analysis revealed a significant effect of age on HC and MRI SMD.*

Conclusions: *These findings reveal a period of pathological brain growth and arrest in autism that is largely restricted to the first years of life, before the typical age of clinical identification. Study of the older autistic brain, thus, reflects the outcome, rather than the process, of pathology. Future research focusing on this early process of brain pathology will likely be critical to elucidate the etiology of autism.*

Key Words: Brain growth, structural imaging, MRI, post-mortem, head circumference, autism

Autism is a complex neurodevelopmental disorder of whose etiology remains unknown, though progress has been made in elucidating some of the neurobiological underpinnings (for review see Courchesne et al 2004). Although a great deal of research and discussion has focused on whether brain and head size are abnormal in autism, the majority of studies have not addressed age-related changes. The few existent developmental studies (Aylward et al 2002; Courchesne et al 2001) raise the possibility that brain size is enlarged at younger, but not older, ages. Through meta-analysis of head circumference, MRI, and post-mortem brain size reports, the present study will be the first to comprehensively examine age-related changes in brain size in autism from birth to adulthood and to examine the consistency of brain size findings within and across age groups and types of measurement.

Autism researchers have used three avenues of study to examine brain size: head circumference (HC), post-mortem, and MRI. HC studies typically report a higher incidence of macrocephaly (head size greater than two standard deviations (SD) above the mean) in children and adults with autism (Bailey et al 1995; Bolton et al 1994; Davidovitch et al 1996; Lainhart et al 1997; Miles et al 2000 Woodhouse et al 1996). However, HC-MRI correlation studies suggest that HC is an accurate index of brain volume only at young ages. Post-mortem studies comparing brain weights of autistic cases to normative data have reported a high incidence of megalencephaly (brain weight greater than 2 SD above the mean); one reports megalencephaly in 14% (Courchesne et al 1999) of autism cases examined and another in 75% (Bailey et al 1993). Postmortem findings have been difficult to interpret for two reasons. First, one normative study of postmortem weight, Dekaban and Sedowski (1978), has typically been used to judge whether brain weight in autism is excessive, but that study reports SD values that are $1/10^{th}$ that of nearly all other contemporary normative brain weight studies. Thus, comparisons of autism brain weights with the Dekaban and Sedowski SD values would lead to an inappropriate increase in the number of brains classified as megalencephalic. Second, when the brain is weighed at autopsy, cerebrospinal fluid (CSF) in the leptomeninges is included in the weight measurement, which may lead to an erroneous overestimation of actual brain weight. An advantage of in vivo structural MRI studies is the ability to provide measurements of total brain volume excluding CSF (Courchesne et al 2000; Sowell et al 2002). However, a disadvantage is that the methodology of MRI studies can vary substantially on several dimensions, including type of scanner, segmentation programs, and anatomical boundary definitions. Furthermore, due to the late age of diagnosis, no MRI data exists for autistic children younger than age 18 months. Thus, while each acquisition method has certain strengths, their weaknesses preclude a complete and generalizable picture of age-related changes in brain size across the autistic lifespan from one single study.

In the current study, we aimed to circumvent these limitations through a meta-analysis of all current HC, MRI, and post-mortem reports meeting specific inclusion criteria. Although MRI and post-mortem methods of measuring brain size are more accurate than HC methods, these measures are not ordinarily obtainable during the first two years of life because a clinical diagnosis of autism is often not made until a later age. Thus, we included retrospective HC measures from children between birth and 2 years of age. To examine age-related changes in brain size from the age of diagnosis through adulthood, MRI brain volume and post-mortem brain weights were included in the analyses. How-

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ever, as direct comparisons of absolute MRI brain volumes across studies would be misleading due to the varying methodologies used, we calculated percent difference values (%Diff) and standardized mean differences (SMD) between mean autism and control brain sizes within each study. To determine if brain weight differences between autistic and normal cases are consistent with brain volume differences in MRI studies, percent differences were calculated between brain weights of individual autism post-mortem cases and age- and sex-matched mean normative brain weights. Moreover, to ensure the best estimate of normative brain weights, not biased by any one single study, ten normative studies were used as comparison, ranging in ages from birth to late adulthood for a total of over 11,000 individual brain weight values. Thus, in the present analysis, we aimed to establish the most complete characterization to date of age-related changes in brain size in autism from birth through adulthood.

Methods and Materials

MRI, HC, and post-mortem studies were identified through literature searches on Medline, PsycInfo, and Web of Science. Brain weight data were requested from authors if the weights were not reported in the paper. Information on additional autopsy cases was provided by the Autism Tissue Program.

MRI Studies

We collected and analyzed measures from 12 MRI studies (Aylward et al 1999, 2002; Carper et al, unpublished data; Courchesne et al 2001; Hardan et al 2003; Haznedar et al 2000; Herbert et al 2003; Kates et al 2004; Piven et al 1995; Rojas et al 2002; Sparks et al 2002; Tsatsanis et al 2003). Studies were included only if whole brain volume measures for both an autism and control group were provided. Multiple studies from the same research group were included only if data were acquired from different participants. Four studies were matched for full scale IQ (Aylward et al 1999, 2002; Hardan et al 2003; Tsatsanis et al 2003); one study stated only that IQ was greater than 80 for both groups (Herbert et al 2003). The mean ages ranged from 2.4 to 46 years (Table 1). Although six studies included a small sample of female participants (Aylward et al 2002; Hardan et al 2003; Haznedar et al 2000; Kates et al 2004; Rojas et al 2002; Sparks et al 2002), the autism and control groups were matched on number of female participants and the proportion of female participants never exceeded 14% of the total sample.

Head Circumference Studies

Although MRI and post-mortem methods provide more sensitive measures of brain size than HC, HC is a good measure of brain volume in neonates (Lindley et al 1999) and children less than 7 years of age (Bartholomeusz et al 2002), but not in adulthood (Bartholomeusz et al 2002; Friedman et al 2000). Furthermore, at present, HC is the only practical measure of brain size during the first two years of life in autism. Thus, in order to examine brain size changes before the age of clinical diagnosis, studies providing HC measures between birth and 3 years were included. With these criteria, three HC studies were identified (Courchesne et al 2003; Gillberg and de Souza 2002; Lainhart et al 1997).

Conversion of HC to Brain Volume. Mean HC values from both autism and normative control data were converted to brain volume using equations derived from the method described below:

$$\text{A (Autism): HC} = 27.987 + .019\ \text{BV}\ (R^2 = .957, p < .0001)$$

$$\text{B (Control): HC} = 27.903 + .019\ \text{BV}\ (R^2 = .987, p < .0001)$$

These equations were determined by regression of brain volume and head circumference measures from a sample of autistic and control boys, aged 1.72 years to 7.03 years, involved in an MRI study within our lab. HC measures were taken by measuring 3D MRI brain volumes using a procedure described elsewhere (Bartholomeusz et al 2002). Because these equations were needed to derive brain volumes from head circumferences before the age at which MRIs are available (i.e. before 1.72 years of age) 30 mean normative HC values (Kuczmarski et al 2000) and 30 normative brain weight values (Voigt and Pakkenberg 1983) from birth to 2 years were added to the data. Brain weight values were first converted to brain volume by dividing the brain weight in grams by 1.036 (1.036 grams of brain weight corresponds to approximately 1 milliliter of brain volume; see Courchesne et al 2000). For the regression, a total of 104 whole brain volume and head circumference measurements (49 autistic, 25 control, 30 mean normative) were exported into the SPSS statistical software program. Two separate regressions were run, one with normative values and autism data and a second with normative values and control data.

Brain Weight

All data on brain weights of autistic patients that were available to us were analyzed. These data included 55 post-mortem brains (44 male) ranging in age from 3 to 65 years (Table 2). Twenty-seven weights were taken from previously published cases (Bailey et al 1998; Casanova et al 2002; Courchesne et al 1999; Darby 1976; Rodier et al 1996), 22 were from the Autism Tissue Program, and 6 were from brain tissue from our lab (Center for Autism Research). Ten cases from the ATP were excluded for diagnoses of Asperger's or unconfirmed autism (3), co-morbid psychiatric disorders (2 ADD, 1 Bipolar, 1 ALS, 1 OCD), or severe mental retardation (2). The excluded cases had brain weights of a similar range and mean to the included sample (1150, 1420, 1640, 1530, 1400, 1780, 1700, 1312, 1340, and 1550 grams, respectively). Seizure disorder was reported in 22 of the cases and mental retardation in 10 cases (Table 2). To assure a representative comparison sample, ten normative brain weight studies published after 1900 were used (Blinkov and Glezer 1968 [Tables 111, 113, and 115]; Chrzanowska and Beyben 1973; Coppoletta and Wolbach 1933; Dekaban and Sadowsky 1978; Harper and Mina 1981; Ho et al 1980; Pakkenberg and Voigt 1964; Voigt and Pakkenberg 1983). Mean normative brain weight values were averaged across each normative study and then averaged within the following age groups for males and females separately; 3–4, 5–6, 7–12, 13–20, 21–30, 31–40, 41–50, 51–60, and 61–70. These age groups were chosen based on previous studies of normal brain size changes with age (Courchesne et al 2000) such that changes in brain size within the groups would be minimal and comparable across the groups.

Normalization of Data to %Diff

In order to normalize the data across study and measurement type, percent difference values were created by dividing the difference between autistic and control mean brain size values by control brain size values. In order to eliminate differences created by the varying methodologies across MRI studies, %Diff values were calculated for each study (or age groups within study) by dividing the difference between autistic and control mean brain volumes by mean control volumes. For head circumference studies, mean autism HC values and mean normative HC

Table 1. HC and MRI Study Information

Study	Study #	Age Range	Mean (or Median) Age (yrs)	Percent Difference	Sex	AUT *n*	CON *n*	AUT IQ	CON IQ
Gillberg 2002	1	Birth	0	−13.08	M,F	42 (5F)	CDC	69	N/A
Courchesne 2003	2	Birth	0	−13.76	M	32	CDC	PIQ: 75 (22.56)	N/A
Lainhart 1997	3	Birth	0	−2.74	M	41	FELS		N/A
Courchesne 2003	2	1–6 mo	.333	6.73	M	9	CDC	PIQ: 75 (22.56)	N/A
Courchesne 2003	2	7–12 mo	.666	9.76	M	20	CDC	PIQ: 75 (22.56)	N/A
Courchesne 2003	2	13–18 mo	1.143	10.84	M	9	CDC	PIQ: 75 (22.56)	N/A
Courchesne 2003	2	19–24 mo	1.75	9.98	M	4	CDC	PIQ: 75 (22.56)	N/A
Courchesne 2001	4	2–4 yr	3	10.09	M	30	12	VIQ: 40–90	VIQ: 86–132
								PIQ: 36–122	PIQ: 90–140
Sparks 2002	5	3–4 yr	3.5	9.54	M,F	45 (7F)	26 (8F)	DD by Mullen	
Courchesne 2001	4	5–7 yr	6	−1.03	M	15	14	VIQ: 40–90	VIQ: 86–132
								PIQ: 36–122	PIQ: 90–140
Kates 2004	6	5–14 yr	8.3	−3.71	M,F	9	16	69.6 (18.7)	123.6 (9.7)
Courchesne 2001	4	7–11 yr	9	−1.39	M	10	14	VIQ: 40–90	VIQ: 86–132
								PIQ: 36–122	PIQ: 90–140
Herbert 2003	7	7–11 yr	9	6.33	M	17	15	IQ > 80	IQ > 80
Aylward 2002	8	8–12 yr	10	4.81	M,F	23 (4F)	28 (3F)	102.7 (15.5)	107.0 (12.5)
Aylward 2002	8	12–16 yr	15	.97	M,F	20 (1F)	27 (1F)	102.7 (15.5)	107.0 (12.5)
Hardan 2003	9	8–45 yr	19	2.64	M,F	40 (2F)	41 (2F)	103.1 (14.6)	104.2 (9.7)
Piven 1995	10	13–29 yr	19	6.74	M	22	20	PIQ: 90.8 (22)	PIQ: 103.4 (9.9)
Tstasanis 2002	11	8–40 yr	19.5	.93	M	12	12	106 (18.3)	108.8 (15.6)
Aylward 1999	12	11–37 yr	20.4	2.37	M	14	14	106.4 (11.71)	108.5 (12.6)
Carper, submitted	13	11–42 yr	24.2	−2.02	M	19	41	PIQ: 90.22 (17.70)	VIQ: 113 (12.03)
								VIQ: 79.50 (25.10)	PIQ: 114.21 (13.04)
Haznedar 2000	14	27.7 yr	28	.08	M,F	10 (?F)	17 (2F)	55–125	88–136
Rojas 2002	15	17–47 yr	30	−7.36	M,F	15 (2F)	15 (2F)	94.93 (21.62)	124.80 (7.98)
Aylward 2002	8	18–46 yr	32	.30	M,F	24 (4F)	28 (3F)	102.7 (15.5)	107.0 (12.5)

Autism and control participant information from the 3 head circumference (HC) and 12 magnetic resonance imaging (MRI) studies is displayed here.
CDC, Center for Disease Control and Prevention Normative Data; FELS, data from the FELS longitudinal data set; CON, control; AUT, autistic patients; DD, developmental delay; N/A, information was not available in the paper; Performance (PIQ), Verbal (VIQ), or full scale IQ values are given either as range or mean (standard deviation).

values were converted to brain volumes using the above equations. The Courchesne et al (2003) and Gillberg and de Souza (2002) studies were compared against Center for Disease Control (CDC) normative data while the Lainhart et al (1997) data were compared against the Fels longitudinal data, as those were the norms used within the latter study. For brain weight data, %Diff values were calculated by comparing individual brain weights with the normative values for the appropriate sex and age group.

Statistical Analyses

Based on the few existing developmental MRI studies in autism (Aylward et al 2002; Courchesne et al 2001), we predicted that younger children with autism would show a greater deviation from normal than older children and adults with autism. To qualitatively examine age-related changes, a curve was fitted to HC and MRI percent difference data using a least squares fitting algorithm in Matlab6.5.1.

To quantitatively test our prediction, post-mortem brain weight and MRI brain volume %Diff data were binned into 3 age groups: "young child," "older child," and "adult." Because of the differences in sample availability between the two methods, the "young child" group consisted of 3–5 year olds for post-mortem data but 2–4 year olds for MRI. Additionally, all nonbirth HC %Diff values were added to the "young child" group. "Older child" was characterized as 6–12 years for both data types and "adult" was 13–70 years for post-mortem but 13–46 years for MRI. A 2 × 3 analysis of variance was run on %Diff data. The independent factors included measurement method (post-mortem, MRI) and age group (young child, older child, adult).

To account for variation in sample sizes and standard deviations across HC and MRI studies, random effects standardized mean differences (SMD), also known as effect sizes, were calculated using RevMan Analyses (RevMan Analyses 2002) for each study (or age group if a study contributed multiple groups). SMD calculation was not necessary for brain weight data because raw, individual values were available. SMD and weights for all MRI data and one HC study (Courchesne et al 2003) were calculated using standard deviations and sample size. Two HC studies (Gillberg and de Souza 2002; Lainhart et al 1997) could not be included in this analysis because raw HC values were not available and thus standard deviations in brain volume could not be calculated. In the third HC study, sample size and standard deviation for the control group were estimated from the autism sample because the autism data were compared to normative reference data.

A random effects heterogeneity analysis was performed on weighted effect sizes to determine if the observed variance across studies was due to sampling error alone. Specifically, based on our prediction of age-related changes in brain size, we computed a regression with mean age of sample as the potential effect modifier variable. From this output, a Q_b statistic was derived based on the sums of squares model and compared against a chi-square distribution of expected variance due to sampling error.

Table 2. Post-Mortem Case Information

ID	Source	Sex	Age	AUT BW (g)	Mean CON BW (g)	Percent Diff	Seizures	MR	Cause of Death
UMB1627	ATP	F	5	1390	1120	24.11	No		Auto trauma
BCH-AUT-88-2	Casanova 2002	F	7	1306	1266	3.17	No	Yes	Drowned
	Courchesne 1999	F	7	1350	1266	6.65	No	No	
UMB 1174	ATP	F	8	1180	1266	−6.78	Yes	Yes	Seizure
UMB 1182	ATP	F	10	1605	1266	26.80	No		Smoke inhalation
BCH-AUT-84	Casanova 2002	F	10	1202	1266	−5.04	Yes	Yes	Peritonitis
b5342	ATP	F	11	1480	1266	16.92	Yes		Seizure and Drowning
	Bailey 1998[a]	F	16	1330	1298	2.44			
BTB3924	ATP	F	16	1230	1298	−5.26	Yes	Yes	Seizures
	Rodier 1996	F	21	1380	1301	6.10			
	Bailey 1998[a]	F	"young adult"	1400	1301	7.64			
BTB4029	CAL	M	3	1389[b]	1196	16.10			
BTB4021	CAL	M	3	1330	1196	11.17	No	No	
1	Bailey 1998/1993	M	4	1525	1196	27.91		Yes	
BCH-AUT-89-3	Casanova 2002	M	5	1386	1306	6.15	Yes	Yes	Found dead in bed
	Darby 1976	M	5	1550	1306	18.71			
BTB3871	ATP	M	5	1360	1306	4.16	Yes		Seizure
UMB1349	CAR	M	5	1620	1306	24.07	Yes	Yes	Seizure
BCH-AUT-91	Casanova 2002	M	6	1460	1306	11.81	Yes	Yes	Asphyxiation (drowning)
b5013	ATP	M	7	1575	1361	15.73	No		Drowning
BB3007	ATP	M	8	1525	1361	12.06	Yes		Myocarditis
BTB4231	CAL	M	8	1570	1361	15.37			Drowning
UMB1315	CAL	M	9	1240	1361	−8.88	No	Yes	Drowning
UMB 797	ATP	M	9	1175	1361	−13.66	No		Drowning
b4925	ATP	M	9	1320	1361	−3.00	Yes		Seizure
BCH-AUT-85	Casanova 2002	M	9	1454	1361	6.84	Yes		
B5666	ATP	M	11	1570	1361	15.37	No		Sarcoma
BB3003	ATP	M	12	1500	1361	10.22	Yes	Yes	Auto trauma
BCH-AUT-87-3	Casanova 2002	M	12	1352	1361	−0.65	No	No	Bone tumor metastasized to lung
B5535	ATP	M	13	1470	1434	2.51	Yes		Seizure
b4323	ATP	M	14	1615	1434	12.62	No	Yes	Hypothermia
B5223	ATP	M	16	1990	1434	38.77	No	Yes	Stopped breathing
CAL103	Courchesne 1999	M	19	1880	1434	31.10	No	No	
b5144	ATP	M	20	1420	1434	−0.98	No	Yes	Auto trauma
5	Bailey 1998	M	20	1405	1434	−2.04	Yes	Yes	
2	Bailey 1998/1993	M	22	1600	1456	9.83	Maybe		
4	Bailey 1998/1993	M	24	1805	1456	24.28	Yes		
6	Bailey 1998	M	24	1820	1456	24.99	Yes		
	Courchesne 1999	M	25	1456	1456	−0.02	No	Yes	
BTB3711	ATP	M	25	1220	1456	−16.23	Yes		Epilepsy
3	Bailey 1998/1993	M	27	1450	1456	−0.44	Yes	Yes	
	Williams 1980	M	27	1430	1456	−1.83			
BCH-AUT-87	Casanova 2002	M	28	1354	1456	−7.03	No	Yes	Cardiac arrest (diabetic)
b5173	ATP	M	29	1230	1456	−15.54	Yes		GI bleeding
	Bailey 1998[a]	M	"young adult"	1299	1456	−10.79			
	Bailey 1998[a]	M	"young adult"	1400	1456	−3.89			
	Bailey 1998[a]	M	"young adult"	1449	1456	−0.48			
	Bailey 1998[a]	M	"young adult"	1529	1456	5.00			
b4871	ATP	M	31	1600	1434	11.54	No	No	Shooting
CAL101	Courchesne 1999	M	35	1367	1434	−4.70	Yes	Yes	
CAL102	Courchesne 1999	M	39	1545	1434	7.70	Yes	No	
CAL104	CAL	M	41	1385	1421	−2.52	Yes	Yes	Food aspiration

Table 2. (continued)

ID	Source	Sex	Age	AUT BW (g)	Mean CON BW (g)	Percent Diff	Seizures	MR	Cause of Death
UMB1582	ATP	M	42	1476	1421	3.88	No	No	Cardiac arrest
B4498	ATP	M	55	1630	1401	16.36	No	Yes	Sudden myocardial infarct
B5183	ATP	M	65	1450	1401	3.51	Yes		Sepsis

Individual autopsy cases are listed by their identifier (if given) and source from which the data were acquired. Cause of death and seizure data are listed if available. ATP, Autism Tissue Program; CAL, Courchesne Autism Lab; MR, mental retardation.

[a]Six of the cases from Bailey 1998 provided only brain weight information but not tissue for analysis.

[b]Brain weight was estimated from post-mortem magnetic resonance imaging (MRI) volume (mL).

Results

Qualitative Changes in Brain Size with Age

To assess qualitative changes in brain size differences between autism and control groups from birth to adulthood, HC and MRI percent differences were plotted by mean age of study group and a curve was fitted to these data. The equation with the least squares and highest correlation with the %Diff data is given below:

$$\%\text{Diff} = -21.18e^{-3.372(\text{Age})} + 13e^{-.1203(\text{Age})}$$

This fit accounts for 78.1% of the variance in the %Diff data (r = .88). As seen from the plot of this line in figure 1, the data reveal the two greatest differences in brain size within the first year of life. Birth head circumference in autism is 13% smaller than that of controls but by the end of the first year of life, the %Diff has peaked at 10% greater than control volumes. By adolescence the %Diff drops to approximately 2% greater, and by adulthood the curve shows brain volumes of patients with autism at about 1% greater than normal.

Quantitative Analyses of Brain Size Changes with Age

To quantitatively test the effect of age on brain size two different methods were used; 1) The MRI and post-mortem %Diff data were analyzed by a 2 × 3 (Measurement method × Age group) analysis of variance; and 2) a random effects heterogeneity analysis with age as the potential effect modifier.

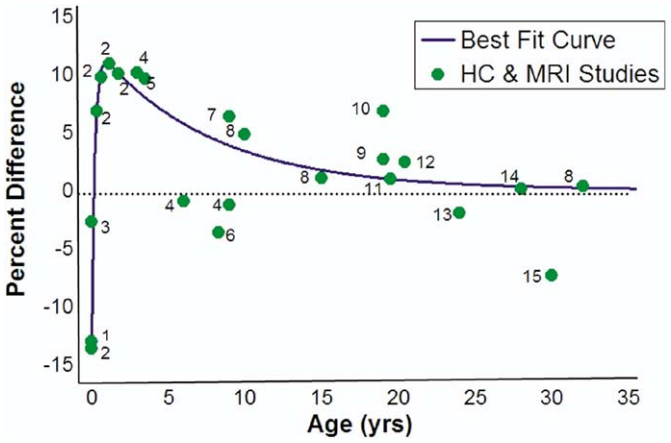

Figure 1. HC and MRI percent difference (%Diff) by age. %Diff values from all HC and MRI studies are plotted by the mean age of the study. The best fitted curve shows the most rapid rates of increased deviation from normal brain size in autism within first year of life and the greatest rates of decrease in deviation from normal during middle and late childhood. Study number, as listed in Table 1, is given next to each percent difference value. HC, head circumference; MRI, magnetic resonance imaging.

Analysis of Variance. Figure 2 shows a higher mean and median %Diff in the young child versus older child and adult age groups for both MRI (Figure 2A) and post-mortem (Figure 2B) data across age bins. The 2 × 3 analysis of variance revealed a main effect of age group ($F(2,75) = 51.08$, $p = .019$) and a main effect of measurement type ($F(1,75) = 26.60$, $p = .007$) but not a significant interaction. Contrasts between age groups revealed a significant effect ($p = .003$) of the "young child" age group but not "older child" or "adult" across both measurement types.

Heterogeneity Analyses. The overall effect across 21 HC and MRI sample age groups was not significant ($Z = 1.80$, $p < .07$) as seen in figure 3. The test for heterogeneity was significant ($p < .0001$), suggesting variance in SMD is not due to sampling error alone. Based on our prediction that brain size shows the greatest deviations in size at younger, but not older, ages, we conducted a random effects homogeneity analysis with age as a potential effect modifier on all HC and MRI SMD. Weighted regression analyses with mean age as a dependent variable and weighted SMD as the independent variable were used to calculate a Q_b statistic, or sums of squares regression. Chi-square analyses of the Q_b statistic revealed a significant effect of age ($\chi^2(20, n = 21) = 34.20$, $p < .05$). Thus, age is a significant predictor of standardized mean differences between brain sizes of autistic and control participants.

Discussion

Several studies have identified the presence of brain enlargement during childhood in autism (Aylward et al 2002; Courchesne et al 2001; Sparks et al 2002). According to a recent study, this brain enlargement may begin as early as the first year of life (Courchesne et al 2003). The present study, using all data available from the autism brain size literature, shows the entire developmental course of brain enlargement in autism and reveals that it is time-delimited to the first 2–4 years of life. Specifically, reduced or normal brain size at birth is followed by an early rapid rate of brain growth and then an abrupt cessation of growth by 2–4 years of age. This early cessation of growth results in a 2–4 year old autistic brain size that is not different from a normal adolescent or adult in the majority of cases. Thus, at the age of typical clinical diagnosis of the disorder (i.e. 3–4 years), the period of pathological growth and arrest has likely already passed, leaving clinicians and researchers with an outcome, rather than process, of pathology for study and treatment intervention.

The strength of this study lies in its large sample size (n = 531), which allows for the power to detect age-related changes in brain size in autism and to concurrently examine

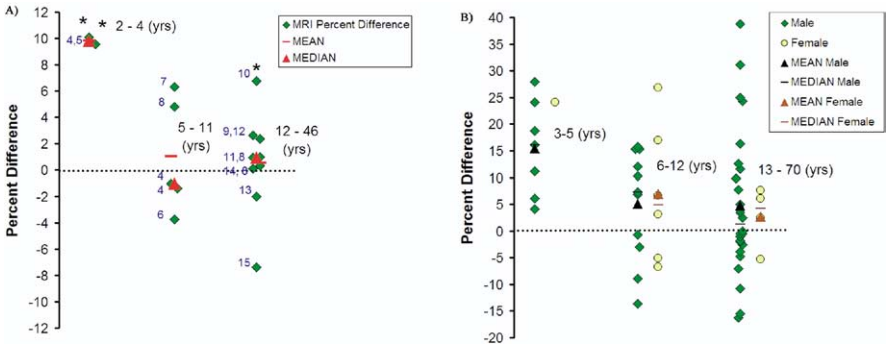

Figure 2. Magnetic resonance imaging (MRI) brain size differences by age group. MRI brain volume **(A)** and post-mortem brain weight **(B)** percent difference (%Diff) data were binned into three age groups of "young" (5 and younger), "child" (6-12), and "adult" (older than 12). %Diff values in the "young" group are significantly higher than in the other two age groups for the MRI and post-mortem data combined. Post-mortem autism data show significantly greater percent difference from normal as compared to MRI data. In **(A)**, MRI studies in which autism brain volumes were significantly different from normal are noted by an asterisk. MRI study number, as listed in Table 1, is given next to each percent difference value.

the consistency of findings across measurement type and research study. Certain limitations are often introduced when using meta-analytic techniques, such as the publication bias against null findings. However, of the 15 HC and MRI studies, 10 reported nonsignificant findings of brain volume differences. A second concern can arise in meta-analyses when the majority of studies provide the minority of data points leading to a lack of independence in the analysis. However, out of the 15 HC and MRI studies, only a minority of the studies (3) contributed multiple data points.

Between measurement types, post-mortem %Diff values were found to be significantly higher than MRI %Diff values. As seen in Figure 2, mean %Diffs for post-mortem weights are consistently 3–5% higher than MRI %Diff for each age group examined. This difference may simply be a sampling effect between the two methods. For example, MRI studies require relatively high functioning patients that are able to remain still within a scanner and withstand an unusual, heightened sensory experience, unless sedation is used. Post-mortem subjects, on the other hand, have a high incidence of seizures and mental retardation and deaths are often due to medical complications or a result of asphyxiation during drowning. These differences in patient characteristics, not measurement type, may account for the subtle differences in brain size. Alternatively, there may be a neurobiological explanation for these differences. In adult patients, CSF is included in brain weight but not MRI and thus increased brain weight in the adult cases may be a result of increased CSF in addition to increased parenchyma in the autism population. Previous studies have reported increased ventricular volumes (Hardan et al 2001; Piven et al 1996) and one study shows increased cerebral and cerebellar CSF volumes in autistic adults (Carper, unpublished data). However, the CSF remaining in the leptomeninges of child postmortem cases would be negligible and thus, an alternative neurobiological mechanism is needed to explain the nearly 5% increase in percent difference values in the young post-mortem group. Perhaps this increase may be due to increased myelin. Indeed, white matter volumes have been reported to be greater in autistic toddlers (Courchesne et al 2001) and children (Herbert et al 2003). Increased myelination could explain increased white matter volumes and heavier brains in the autism group.

The present study shows that postnatal brain overgrowth is a robust phenomenon in autism across multiple study samples and measurement methods. These findings suggest that conflicting reports of brain size may be largely an effect of age. Despite the method of acquisition, when brain size findings are organized according to age, a clear pattern of early brain overgrowth followed

	Autism		Control		Standardized Mean Differences (SMD)		SMD
Study (Age)	N	Mean (SD)	N	Mean (SD)		Weight (%)	[95% Confidence Interval]
Courchesne (birth)	32	388.86 (70.57)	32	450.46 (70.57)		5.61	-0.86 [-1.38, -0.35]
Courchesne (1-6 mo)	9	763 .16 (141.32)	9	715.03 (141.32)		3.92	0.32 [-0.61, 1.26]
Courchesne (7-12 mo)	20	1039.04 (68.39)	20	947.11 (94.36)		4.96	1.09 [0.42, 1.76]
Courchesne (13-18 mo)	9	1162.43 (94.36)	9	1048.68 (94.36)		3.62	1.15 [0.13, 2.16]
Courchesne (19-24 mo)	4	1218.92 (102.08)	4	1108.27 (102.08)		2.26	0.94 [-0.59, 2.47]
Courchesne (2-4 yr)	30	1298.00 (88.30)	12	1179.00 (83.10)		4.69	1.34 [0.61, 2.08]
Sparks (3-4 yr)	45	1326.09 (94.73)	26	1210.62 (110.47)		5.59	1.13 [0.61, 1.65]
Courchesne (5-7 yr)	15	1347.00 (101.23)	14	1361.47 (126.51)		4.71	-0.12 [-0.85, 0.61]
Kates (8 yr)	9	1310.94 (146.53)	16	1361.49 (103.34)		4.32	-0.41 [-1.23, 0.42]
Courchesne (7-11 yr)	10	1342.59 (123.69)	14	1361.49 (105.42)		4.37	-0.16 [-0.97, 0.65]
Herbert (7-11 yr)	17	1453.96 (136.98)	15	1367.44 (106.17)		4.76	0.68 [-0.03, 1.40]
Aylward (8-12 yr)	23	1355.40 (136.40)	28	1293.24 (91.49)		5.41	0.54 [-0.02, 1.10]
Aylward (12-16 yr)	20	1341.12 (116.83)	27	1328.19 (121.57)		5.34	0.01 [-0.56, 0.59]
Hardan (8-45 yr)	40	1350.46 (123.68)	41	1315.78 (134.78)		5.92	0.27 [-0.17, 0.70]
Piven (13-29 yr)	22	1339.90 (127.80)	20	1255.30 (94.90)		5.14	0.73 [0.10, 1.36]
Tsatsanis (10-37 yr)	12	1440.02 (63.80)	12	1426.76 (39.15)		4.41	0.24 [-0.56, 1.05]
Aylward (11-37 yr)	14	1363.10 (128.30)	14	1331.60 (120.20)		4.65	0.25 [-0.50, 0.99]
Carper (11-42 yr)	20	1279.19 (115.04)	41	1305.27 (105.25)		5.52	-0.24 [-0.77, 0.30]
Haznedar (27.7 yr)	10	1315.00 (220.00)	17	1314.00 (122.00)		4.77	0.01 [-0.71, 0.72]
Rojas (19-47 yr)	15	1237.60 (127.80)	15	1335.86 (30.74)		4.55	-1.03 [-1.80, -0.26]
Aylward (18-46 yr)	24	1273.33 (165.16)	28	1269.33 (125.59)		5.48	0.03 [-0.52, 0.57]
Total (95% CI)	405		412				
Test for heterogeneity: $Chi^2 = 72.15$, df = 20 (P<.00001), $I^2 = 72.3\%$							
Test for overall effect: Z = 1.80 (P = .07)							
					-5 0 +5		
					Favors Control	Favors Autism	

Figure 3. HC and MRI standardized mean differences (SMD) between autism and control brain volumes. Autism and control SMD are given by study age group. The forest plot displays SMD and their 95% confidence intervals. HC, head circumference; MRI, magnetic resonance imaging.

by normal brain size in adulthood emerges. However, several autopsy cases and one MRI study (Piven et al 1995) in this report do reveal enlarged brain size during adulthood in autism. Given the robust pattern of early brain overgrowth seen in the current study, enlargement in adulthood may be the result of excessive pathological growth early in life. For example, the brain volume of one 3 year old autistic child measured within our lab was 1816 mL (Courchesne et al 2001), which is larger than any reported normative adult volume (see Courchesne et al 2000). Thus, if this child were measured as an adult, there would be evidence of brain enlargement, even though the period of deviant growth may have passed years earlier. In order to study the process of neural maldevelopment in autism, it is clear that the important question for autism research now becomes not whether the brain is enlarged, but when precisely does brain enlargement begin, peak and cease.

The present results of early brain overgrowth and cessation of growth highlight the urgency in developing accurate and sensitive early-warning signals for clinical identification and research study. Progress has been made in identifying some early behavioral warning signs of autism through use of retrospective home videos (Osterling and Dawson 1994), parent report (Lord 1995), prospective screening forms such as the CHAT (Baron-Cohen et al 1992) or CSBS (Wetherby 2004), and rare prospective case studies (Dawson 2000). However, behavioral signs alone lack specificity. For example, while 100% of toddlers with autism fail to respond to their own name at 18 months of age, 54% of normally developing toddlers also fail to respond (Wetherby 2004). Thus, identifying early neurobiological warning signs within the first year of life for use in conjunction with behavioral indices will likely prove necessary in identifying children at risk for autism.

Identification of early warning signals will give researchers the opportunity to study the neurobiological processes underlying autism as it unfolds. Analyses of retrospective HC measures have been used to estimate brain size from birth through the age of clinical diagnosis (Courchesne et al 2003; Gillberg and de Souza 2002; Lainhart et al 1997; Stevenson et al 1997). However, these measures are only a two-dimensional estimate of brain size and do not allow for a more detailed picture of brain abnormalities (such as regional and gray and white matter volumes), which may offer clues to the etiology of autism. While MR imaging is able to provide these measures, acquiring MR images can be costly. Even so, prospective MRI studies are realistic if conducted on children at risk for developing autism, such as younger siblings of autistic children or children referred by pediatricians based on current behavioral and biological markers of autism. Of course, as more neurobiological and behavioral markers of autism are identified, prospective studies will become increasingly feasible, allowing for a more complete characterization of brain pathology during this critical period of brain overgrowth.

While it is unclear what triggers this postnatal brain overgrowth, it is clear that knowing the underlying mechanism and timing (pre-, peri-, or post-natal) of this trigger is crucial. Evidence from family studies and genetic linkage studies strongly suggests a genetic component to the disorder (Bailey et al 1995; Muhle et al 2004). However, evidence also points towards environmental factors (Hultman et al 2002; Juul-Dam et al 2001). In addition, evidence from a mouse model of autism suggests prenatal viral infection may trigger postnatal brain overgrowth (Fatemi et al 2002). Interestingly, these mice also displayed many of the behavioral characteristics seen in autism (Shi et al 2003). Identifying neural factors underlying this early brain overgrowth will likely prove useful in understanding the mechanism underlying the emergence of autism. One study suggests brain overgrowth in 2–4 year old autistic children may be the most severe in frontal cortex, with less overgrowth in white matter of parietal cortex and gray matter of temporal cortex, and no difference from normal in occipital cortex (Carper et al 2002). These findings suggest an anterior to posterior gradient of overgrowth (Carper et al 2002). Thus, genetic or environmental factors that result in regionally and temporally specific brain abnormalities are likely candidate mechanisms (i.e. Fgf2; Vaccarino et al 1999; and HGF/SF; Levitt et al 2004; Powell et al 2003).

The timing of this brief, postnatal overgrowth may be critical to the emergence of the autistic neurobehavioral phenotype. The window of pathological brain growth coincides with the time of synaptic exuberance and pruning in the normal child in which cortical connections are developed, refined, and stabilized; a process which Greenough has termed "experience-expectant information storage" (Greenough et al 1987). However, the acceleration and then abrupt cessation of brain growth in autism would not allow for the normal developmental course of experience-expectant information storage. Courchesne and Pierce (2005) hypothesized that the rapid growth will differentially affect large, integrative neurons that normally require protracted maturation, for example neurons within the later maturing frontal cortex (Huttenlocher and Dabholkar 1997). These integrative neurons have large dendritic arbors, making them critical to long-distance cortico-cortical and cortico-cerebellar connectivity. Similarly, rates of myelination within later maturing association cortices of frontal and temporal cortex are more protracted when compared to posterior sites (Kinney et al 1988). Thus, the rapid rate and abrupt cessation of growth early in life could shorten the normal window of experience-expectant changes and curtail development of later maturing and myelinating associative cortices. Once the window for experience-expectant storage has passed, the system must rely on experience-dependent mechanisms of learning. Greenough and colleagues (Greenough et al 1999) have shown that experience-dependent mechanisms can produce local levels of synapse generation and pruning dependent on environmental input, at least for sensory systems (Greenough et al 1999). These later-developing, local synapse changes coupled with earlier reductions in integrative neurons and aberrant white matter development would further constrain the brain in autism towards a strategy of local processing rather than coherent, contextual processing. In fact, a recent fMRI study of sentence comprehension shows reduced functional connectivity in the autism group as compared to controls (Just et al 2004). Reductions in long-distance connectivity would be particularly detrimental to higher-order social and communicative functions requiring coherent integration of information from multiple sensory and cognitive domains. This neurobiological profile is consistent with the behavioral model of weak central coherence proposed by Frith and Happé (Frith and Happe 1994) and the temporal binding deficit proposed by Brock and colleagues (Brock et al 2002), in which local or featural processing is enhanced at the expense of global processing due to an inability to integrate across domains.

We have demonstrated a pattern of brain size changes across the autistic lifespan through analysis of the current literature on brain size in autism. These findings suggest that the period of pathological development is largely restricted to the first years of life in autism before the typical age of clinical diagnosis. Creative methods to research and identify autism during this process of pathological

development, in addition to the retrospective and prospective studies described above, will likely be critical to the advancement in the search for the cause of and treatment for autism.

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