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Longitudinal Evaluation of Cerebral Growth Across Childhood in Boys and Girls with Autism Spectrum Disorder

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Abstract

Background: Cerebral overgrowth is frequently reported in children but not adults with autism spectrum disorder (ASD). This suggests that early cerebral over-growth is followed by normalization of cerebral volumes. However, this notion is predicated upon cross-sectional research that is vulnerable to sampling bias. For example, autistic individuals with disproportionate megalencephaly (ASD-DM), a subgroup with higher rates of intellectual disability and larger cerebral volumes, may be under-represented in studies of adolescents and adults. Furthermore, extant studies have cohorts that are predominately male thus limiting knowledge of cerebral growth in females with ASD.

Methods: Growth of total cerebral (TCV), gray (GM) and white (WM) matter volume, and GM proportion of TCV was examined in a longitudinal sample comprising 273 boys (199 ASD) scanned at up to four timepoints (Mean ages: 38, 50, 64, 137 months) and 156 girls (95 ASD) scanned at up to three timepoints (Mean ages: 39, 53, 65 months) using mixed effects modeling.

Results: In boys with ASD, cerebral overgrowth in the ASD-DM subgroup was predominately driven by increases in GM and persisted throughout childhood without evidence of volumetric regression or normalization. In girls with ASD, cerebral volumes were similar to TD girls, but growth trajectories of GM and WM were slower throughout early childhood. Proportion of GM to TCV declined with age a slower rate in autistic boys and girls relative to TD controls.

Conclusions: Longitudinal evidence does not support the notion that early brain overgrowth is followed by volumetric regression, at least from early to late childhood.

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Disclosures

Dr. Amaral is on the Scientific Advisory Boards of Stemina Biomarkers Discovery, Inc. and Axial Therapeutics. All other authors report no biomedical financial interests or potential conflicts of interest.

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Keywords

autism spectrum disorder; development; brain; disproportionate megalencephaly

INTRODUCTION

Autism Spectrum Disorder (ASD) is a neurodevelopmental diagnosis characterized by early impairments in social communication and interaction, as well as restricted, repetitive patterns of behaviors, interests or activities (1). Over the last 20 years, there have been over 2000 studies published in which magnetic resonance imaging (MRI) has been used to evaluate various aspects of brain structure or function in individuals with ASD. However, important issues related to the trajectory of brain development in autistic individuals have yet to be resolved. This is due, in part, to the lack of longitudinal studies that involve individuals at all levels of severity and cognitive ability from the time of diagnosis throughout middle childhood.

Previous head circumference and MRI studies have suggested that there is a period of early postnatal precocious brain growth in children with ASD (2–5). However, it is less common to observe enlarged brain size in adolescents and adults with ASD (6–11) although this is not true for all studies (5). These observations have prompted the suggestion that brain growth in ASD follows an altered developmental trajectory that is characterized by an early progressive phase followed by a volumetric regression that ultimately leads to normal brain size (12). We have suggested the alternative hypothesis that this picture of brain development may be an artifact due to the very different characteristics that are frequently exhibited between younger and older cross-sectional cohorts of individuals with ASD (13). In general, MRI studies of younger autistic individuals tend to have cohorts representing a broader range of autism severity and intellectual ability while studies of older individuals tend to recruit more compliant individuals with intellectual abilities within the typical range.

The current study utilizes data acquired through the MIND Institute Autism Phenome Project that began in 2006. Children are initially recruited between 2- and 3-½ years of age, shortly after initial ASD diagnosis, and undergo extensive longitudinal behavioral and MRI analyses. Data presented here are based on up to four longitudinal MRI acquisitions with the oldest obtained during middle childhood (8–13-years-old). Our targeted efforts to increase representation of females with ASD have resulted in the largest sample of females ever evaluated using MRI. The focus of this study is on the trajectory of postnatal brain growth in boys and girls with ASD.

In previous reports from the Autism Phenome Project, we have shown that not all children with ASD have precocious brain growth. Rather, approximately 15% of boys demonstrated disproportionate megalencephaly (DM) at their first MRI scan at age three (ASD-DM) (i.e. brain size disproportionate to height) (14,15). The remainder of boys and virtually all girls had brain sizes within 1.5 *SD* of the mean of typically developing (TD), sex-matched controls. We defined the subgroup with enlarged brains as ASD with disproportionate megalencephaly (ASD-DM) since their brain size was disproportionate to their height. The notion that only a subset of children with ASD have enlarged brains is consistent with

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the extensive literature of head circumference studies that indicate that approximately 20% of autistic individuals have enlarged heads (16). Children characterized as ASD-DM, in general, had the poorest prognosis for cognitive development from 3–6 years of age. This subset of autistic children had significantly less improvement in IQ scores and were more likely to have limited expressive language than autistic children with normal brain size (15).

We previously established that when evaluated at six years of age, those with ASD-DM still retained enlarged brains with no indication of a regressive phase in brain size (13). This was significant because the meta-analysis carried out by Redcay and Courchesne (12) indicated that the downward inflexion point for brain normalization should start prior to five years of age. Many of the previously studied children have now had a fourth MRI between 8–13-years of age. The current study continues to evaluate brain growth in children with ASD in comparison to ageand sex-matched TD children. We extend our previous investigations by also examining cerebral gray and white matter development. Finally, through targeted efforts to increase representation of females in our cohort, we can now, for the first time, reliably conduct evaluation of brain growth trajectories in girls with autism through early childhood.

METHODS

Participants

Participants were enrolled in the University of California (UC) Davis MIND Institute Autism Phenome Project or Girls with Autism Imaging of Neurodevelopment Study. All aspects of this study were approved by the UC Davis Institutional Review Board. Informed consent was obtained from each participant's parent or guardian.

A total of 1005 scans were acquired from 294 children with ASD (95 girls) and 135 TD controls (61 girls). Longitudinal, age-homogeneous cohort data were acquired over three yearly timepoints in early childhood (T1–T3) and a fourth in middle childhood (T4). As data collection in girls at T4 is just beginning, analysis of girls only included T1–T3 data. Nine scans were excluded for data quality (4 ASD, 5 TD). See Tables 1 and S1 for sample characteristics, and Figure S1 for a depiction of the longitudinal sampling. Further details on sample ascertainment and diagnostic assessments are reported in supplemental materials.

Neuroimaging

Images in early childhood (T1–T3) were acquired during natural nocturnal sleep (17). At T4, images were acquired while awake. Children at all developmental levels were imaged, including those with severe impairments, using behavioral analytic approaches (18). A quantitative assessment of motion artifact was conducted for each scan (18), and only images that passed quality assurance were included in the analyses.

Images were acquired at the UC Davis Imaging Research Center on a 3-Tesla Siemens Trio using an 8-channel head-coil. A three-dimensional T1-weighted MPRAGE sequence was acquired in early childhood (T1–T3: TR 2,170 ms, TE 4.86 ms, FOV 256, 192 sagittal slices, 1.0 mm slice thickness, 8:46 acquisition time), and in middle childhood using parameters adjusted to reduce acquisition time and increase compliance during awake scanning (T4: TR 2170 ms, TE 3.5 ms, FOV 256 mm, FA 7, 192 sagittal slices, 1.0 mm slice thickness;

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5:10 acquisition time). To control for changes in spatial distortion associated with hardware and software changes over time, a calibration phantom (ADNI MAGPHAM, The Phantom Laboratory) was utilized to perform distortion correction on each image (Image Owl, Inc., Greenwich, NY, USA, http://www.imageowl.com) (19).

Image Processing

Distortion-corrected images were bias-corrected and non-brain tissue was removed (BET) (20). Total cerebral volume (TCV) was calculated using template-based segmentation that removed brainstem and cerebellum (19). The resultant image was then segmented into gray matter (GM) and white matter (WM) using FAST tissue segmentation with partial volume estimation (21). Cerebral spinal fluid (CSF) was initially removed with the aid of CSF priors, and then the remaining image segmented into GM and WM volumes.

ASD Disproportionate Megalencephaly subgroup characterization

At T1, children with ASD-DM (22 boys, 5 girls) were classified using previously established criteria (13–15,22) of having a ratio of TCV-to-height greater than 1.5 *SD* above the mean of age- and sex-matched TD controls at T1. Children not exceeding 1.5 *SD* at T1 were characterized as ASD with normative brain size (ASD-N) (152 boys, 79 girls). Individuals without concurrent height and brain measurements at T1 had unconfirmed DM statuses (25 boys, 11 girls) and were excluded from subgroup analyses. Of these, eight ASD and two TD boys did not have imaging data at T1.

Analytic Plan

Overview—Trajectories of TCV, GM and WM growth were modeled separately. For each analysis, we first tested for group differences at the mean ages of each timepoint and then for group differences in the curvature of each trajectory. Analyses in girls were restricted to T1-T3 because T4 data collection is ongoing. Because of these sampling differences, primary analyses were conducted separately in boys and girls. Analysis of sex by diagnosis interactions was restricted to T1-T3. To evaluate diagnostic and developmental changes in the relative proportions of GM and WM, we computed the proportion of GM to TCV (i.e. GM/TCV). Since WM and GM proportions are mathematically complementary, analyses were only conducted on GM proportion.

We then conducted subgroup analyses (ASD-DM, ASD-N, TD) to examine potential ‘normalization’ of cerebral volumes. Due to the small number of girls with ASD-DM (n = 5), all subgroup analyses in girls were restricted to ASD-N. The primary hypotheses regard the curvature of trajectories after T1. For descriptive completeness we report the mean differences between subgroups, which by selection are expected to differ. Finally, we explored subsequent cerebral growth in ASD when TCV-to-height ratios at T1 are used as a dimensional predictor in the place of binary subgrouping.

Utilization of multiple fractional polynomials to model growth trajectories—Biological growth is rarely linear. The common solution to non-linearity is to introduce polynomial terms (i.e. linear, quadratic, cubic). While polynomials are theoretically capable of fitting most curves given adequate degrees of freedom, in most applications it is

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unfeasible to have more than two or three term polynomials. Unfortunately, such low degree polynomials have limited flexibility in which to model growth. Consequently, artifacts may be introduced, particularly if growth is asymptotic. Here we adopted multiple fractional polynomials (MFP) (23–25), a method that largely addresses the limitations of standard polynomials.

In MFP, we expand the list of available curvilinear functions to include fractional exponents (e.g., $\sqrt{age}$) and inverse relationships (e.g. $\frac{1}{age}$) and select function(s) that best fit the data using information criteria (23–25). The following set of candidate functions were evaluated: $\left[\frac{1}{age^2}, \frac{1}{age}, \frac{1}{\sqrt{age}}, \sqrt{age}, age, age^2\right]$. Prior research (23–25) indicates that most growth trajectories are well fit by either a 1st-order model that includes just one of these functions (e.g. $\sqrt{age}$) or by a 2nd-order model that includes a combination of two functions (e.g. $\sqrt{age} + age^2$). Selection of the optimal MFP model proceeds in two steps. First, all 1st and 2nd order mixed level models are estimated, then the best fitting model is identified using Bayesian Information Criteria, which penalizes against model complexity and is appropriate when models are not nested (26).

We separately selected best MFP models for TCV, GM, WM, and tissue proportion (GM/TCV). Each mixed effect model included a fixed effects model comprising diagnosis, MFP age term(s), and all interactions thereof, and a random effects models comprising a random intercept and slope(s) for each participant, where the slope was the corresponding MFP terms(s). Models were estimated using an unstructured matrix, so that each variance and covariance of the repeated measures were uniquely estimated from the data (26) using the nlme package (v. 3.1) in R (v. 3.5.1). Interaction effects were tested using likelihood ratio tests that contrasted models with and without the interaction. Group differences at the mean ages of T1 thru T4 were tested by re-centering age and inspecting parameters estimated using restricted maximum likelihood (26). False Discovery Rate (FDR) corrections were used for both mean difference and likelihood ratio tests (27).

RESULTS

Sample Characteristics

Age at each visit did not significantly differ by sex or diagnosis or interact (ps ≥.15). ADOS CSS was significantly lower at T3 than at T1 (p=.048) but did not significantly differ by sex, or interact (ps ≥.10). DQ was significantly lower in ASD (p<.0001) and lower at T1 than at T3 or T4 (ps ≤ .03), but DQ was otherwise similar across sex and timepoint (all interactions: ps ≥.41). The percentages of individuals at T3 and T4 with intellectual disability (i.e. DQs ≤ 70) were within the range seen in other reports (28) (See Table S1). Finally, no significant effects of attrition were observed; see supplemental materials for details.

Multiple Fractional Polynomial Selection

Table S2 describes each selected MFP model. Tables S3–S6 report the fits of competing MFP models for TCV, GM, WM, and proportion GM. To illustrate the value of the MFP

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method, Figure S2 provides visual comparison for TCV growth trajectory as predicted by a quadratic polynomial model versus the best five MFP models.

Cerebral Development in Boys

All tests of volume differences and age by group pair interactions in boys are reported in Table S7. Detailed R code and output parameters for each TCV, GM, WM, and proportion GM model are reported in the supplemental materials.

When all boys with ASD were compared to TD boys, TCV was significantly larger in boys with ASD at all timepoints (T1–T4). Growth trajectories were largely similar in TD and ASD boys, maintaining comparable differences in TCV, GM, and WM volume throughout childhood, with no significant age by diagnosis interactions evident (Figure 1A). As a percentage of TCV, the proportion of GM decreased (conversely, the proportion of WM increased) throughout childhood in both ASD and TD boys (See Figure 2A). The proportion of GM decline was more rapid in TD, as supported by a significant age by diagnosis interaction. However, this trajectory difference did not result in significant mean differences at any particular timepoint.

In the subgroup analysis, TCV, GM, and WM volumes were consistently greater in ASD-DM than in ASD-N and TD boys across all timepoints, while no significant volume differences were evident between ASD-N and TD boys at any timepoint. ASD-DM, ASD-N and TD boys exhibited similarly shaped trajectories of TCV, GM, and WM volume growth that maintained comparable group differences across timepoints (Figure 1B). The GM proportion of TCV decreased throughout early to middle childhood in both ASD-DM and ASD-N (see Figure 2B). Again, however, significant age by diagnosis pair interactions indicated a more rapid decline in GM proportion of TCV in TD, resulting in proportional GM differences that diminished with age between ASD-DM and TD boys, but increased with age between ASD-N and TD boys. Finally, the curvature of cerebral growth trajectories did not significantly differ as a function of TCV-to-height ratio at Time 1 in ASD when TCV-to-height ratio at T1 was used as a dimensional predictor, in place of the binary DM classification (ps ≥.08, see Figure S3)

Cerebral Development in Girls

All tests of volume differences and age by group pair interactions in girls are reported in Table S8. See supplemental materials for all model parameters. When comparing girls with ASD and TD, no significant mean differences in TCV, GM, or WM were observed at the mean ages of any timepoint (T1–T3). However, TCV, GM, and WM growth were slower in ASD (Figure 3A). The GM proportion of TCV decreased throughout early childhood in both ASD and TD girls (Figure 4A). However, those declines were more rapid in TD, as indicated by a significant age by diagnosis interaction and increasing differences over time.

We then evaluated differences between ASD-N and TD girls. No significant mean differences in TCV, GM, and WM were observed at any timepoint. However, the curvatures of TCV, GM, and WM trajectories significantly differed, such that growth rates were progressively slower in ASD-N (Figure 3B). The GM proportion of TCV decreased throughout early childhood in both ASD-N and TD girls (Figure 4B), but those declines

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were more rapid in TD, evidenced by the significant age by diagnosis interaction resulting in increasing differences over time. Finally, within girls with ASD-N, no significant differences in the curvatures of cerebral growth as a function of continuous TCV-to-height ratio at T1 were observed (*p*s ≥ .22; see Figure S4).

Sex Differences in Cerebral Development

Despite the apparent relative differences in cerebral development to sex-matched TD controls revealed in the analyses above, we did not observe age by sex by diagnosis interactions in analyses of T1–T3 data in early childhood for TCV, GM, WM, or GM-proportion (χ^2s≤.2.08, *df*s≥1, *p*s≥.14). To fully explore sex differences in cerebral development, future studies may require matched sample sizes between boys and girls in order to reliably detect three-way interactions with sex.

DISCUSSION

The primary goal of this study was to utilize longitudinal volumetric MRI to test the widespread notion that ASD is characterized by precocious cerebral over-growth in early childhood (2), followed by volumetric regression through the end of childhood (12). We evaluated the trajectory of cerebral growth, as well as the relative contributions from GM and WM, in a large cohort of children with ASD from 2–13 years of age. In boys, early cerebral enlargement in ASD was restricted to a subset with DM, and in this subset, cerebral enlargement was maintained into middle childhood without evidence of volumetric regression. I In girls, growth was slower in ASD, attenuating mean differences over time. Finally, in all children, GM proportion declined, but this decline was slower in boys and girls with ASD.

In boys, we found no evidence for volumetric regression of cerebral volume through early to middle childhood, either when all boys with ASD were evaluated together or when we sub-grouped by DM at T1. Indeed, in the majority of boys with ASD, i.e. ASD-N, volumetric trajectories were nearly identical to TD boys in both magnitude and curvature, exhibiting neither enlargement nor regression. In the subset of boys with ASD and DM at T1, we confirmed previous findings of early overgrowth (13,15,22). Extending these findings into middle childhood (11–13 years of age), we found that if brain enlargement was present during early childhood, it persisted throughout childhood.

Our findings in boys with ASD inform a recent meta-analysis of cross-sectional studies of brain volume in ASD (10) that reported age-related reductions in brain overgrowth in ASD, consistent with volumetric regression (12). This meta-analysis found that MRI studies exhibited systematic sampling biases against inclusion of older individuals with larger head and brain sizes—individuals who may have more impairments and are therefore less compliant with MRI protocols (10). During early childhood (2–5 years of age), scanning is often conducted during natural sleep, facilitating the inclusion of children across the full range of intellectual ability. In studies of older children and adolescents, when scanning during sleep is not feasible, individuals with intellectual disability are frequently under-represented. Our previous work has shown that the subset of boys with ASD and disproportionate brain enlargement at age 3 makes fewer gains in IQ over early childhood

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and are more likely to have scores in the range of intellectual disability by age 6 (15). Thus, previous cross-sectional studies of very young children with ASD likely included individuals with DM (or early brain overgrowth) that are under-sampled in studies of older children, adolescents and adults. In the current study, we utilized novel strategies to scan older children with more severe impairments (18), thus reducing the likelihood of under-sampling children with intellectual disability. Accordingly, we found no longitudinal evidence for regression of cerebral volumes in the ASD-DM subgroup or across all individuals with ASD through late childhood. These findings support the notion that individuals with larger brain volumes and higher rates of intellectual disability have been under-sampled in previous MRI studies of older autistic individuals. However, it remains to be seen whether volumetric regression will emerge in adolescence.

Another goal of this study was to investigate relative contributions of cerebral GM and WM to overall cerebral volume differences. While robust gains in WM volume were observed into middle childhood, GM volume gains tapered off after early childhood. This pattern of development is consistent with studies of normative development in which WM increases in volume into adulthood, while GM growth peaks before adolescence and then declines (29). When examining GM as a relative proportion of total cerebral volume, we observed decreases in the proportion of GM with age in all children, which is consistent with prior reports in TD (30), but we find that the rates of those decreases were slower in ASD, which widened differences over time. This pattern was observed in both ASD-DM and ASD-N subgroups. However, while slowed growth increased differences in GM proportion between ASD-N and TD boys, slowed growth diminished those differences between ASD-DM and TD boys, a pattern seemingly explained by initial differences present in early childhood.

The above findings may contrast with those from earlier reports of GM and WM development in ASD. A cross-sectional study of 17 boys with ASD, aged 84 to 132 months, reported absolute and proportional gains in ASD that were greater in WM than GM (31). A longitudinal study of 41 children with ASD (9 girls) aged 12 to 60 months reported smaller absolute but larger proportional gains in WM compared to GM volume in ASD (32). In contrast, an accelerated longitudinal study with 100 participants spanning childhood and adulthood reported overall *smaller* WM volumes in ASD (33). Discrepancies between studies might be explained by the smaller sample sizes of earlier studies, large inter-individual variability in cerebral volumes, and heterogeneity in the ages and IQs of participants examined. Earlier studies also relied on 1.5-Tesla magnets with offer poorer contrast than the 3-Tesla magnet used in this research (2,31,32). Aside from mean and proportional differences, previous studies also report contrasting developmental trajectories. For example, others have reported longitudinal *declines* in GM volume from early childhood well into adult life in both ASD and TD (33). However, this trajectory is in disagreement with both the current study and findings of an earlier longitudinal study in children with ASD (32), as well as studies of TD (34,35). The discrepancy with our results may arise from differences in study design, e.g. an accelerated longitudinal design with few measurements from early childhood and/or inflexible quadratic polynomial modeling which may have failed to capture changes in trajectory.

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Given evidence of sex differences in normative cerebral development (29,36), we evaluated girls separately from boys. When comparing girls with ASD to TD girls from 2–6 years of age, no significant differences in TCV, GM, or WM volumes were observed at any timepoint. This is consistent with our initial findings in a smaller subset of girls (n = 22) (37). The current data (95 girls) confirms that cerebral enlargement in ASD girls is, at most, very limited. Interestingly, although volumetric differences were small, trajectories differed in girls with ASD, exhibiting slower cerebral growth, particularly of WM, compared to TD. Consistently, GM proportion was increasingly larger in ASD than in TD. These developmental effects are less subtle than they might appear: Over two years' time between T1 and T3, the total cerebral volume difference between ASD and TD girls was reduced by approximately 10.6 cubic centimeters, which for context, is about six times the volume of the average adult amygdala.

It will be critical to continue following this cohort of females to determine whether this pattern of delayed growth persists and results in smaller WM volumes later in development. These results contribute to growing evidence of neurobiological sex differences in autism (38) and suggest that longitudinal evaluation is critical to identify sex differences in development that are not evident at cross-sectional points in time.

To our knowledge, this is the largest longitudinal study of cerebral development that spans 2–13 years of age and includes children with ASD with more severe cognitive impairments, even at older ages. MRI data were acquired at a single site, and a calibration phantom was employed to correct for hardware-induced distortion that may vary across time. In addition, targeted recruitment of females allowed for evaluation of cerebral growth trajectories in a much larger sample of females than any previous study (38). One potential issue to consider for future research is evidence that GM and WM tissue boundaries are less distinct in ASD, possibly resulting from altered neuronal migration during development (39,40). While this would not affect the accuracy of our TCV estimates, diffuse boundaries could conceivably affect GM/WM estimates. While we did not directly address this question, our use of partial volume estimation (21), to estimate tissue proportions within each voxel, partially ameliorates this concern. Nevertheless, the impact of graded WM/GM boundaries has not been examined systematically, and future research using new methodologies may qualify extant GM/WM findings in ASD.

In conclusion, we find that cerebral enlargement in ASD persists throughout childhood without evidence of normalization, and that enlargement is mostly limited to boys with ASD and disproportionate megalencephaly. In girls, ASD was associated with slowed cerebral growth throughout early childhood, particularly WM growth. In all children, the proportion of GM in the cerebrum declines over time, but those declines were slower and smaller in ASD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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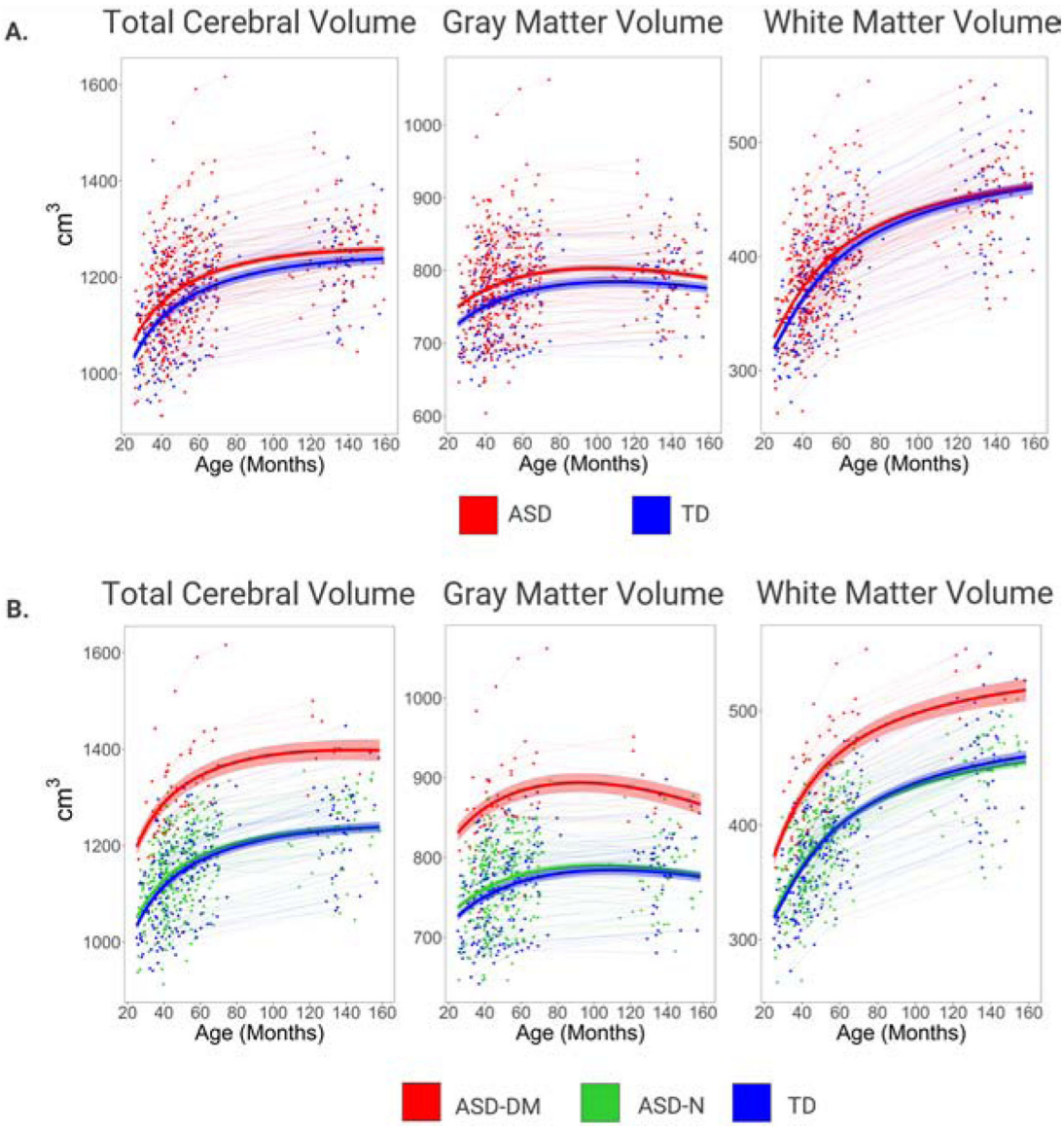

Figure 1.

Longitudinal trajectories of total cerebral volume (TCV), gray matter (GM), and white matter (WM) from early to middle childhood in **A)** boys with autism spectrum disorder (ASD) and typical development (TD), and in **B)** boys with ASD and disproportionate megalencephaly (ASD-DM), ASD with normative cerebral volume (ASD-N) and TD.

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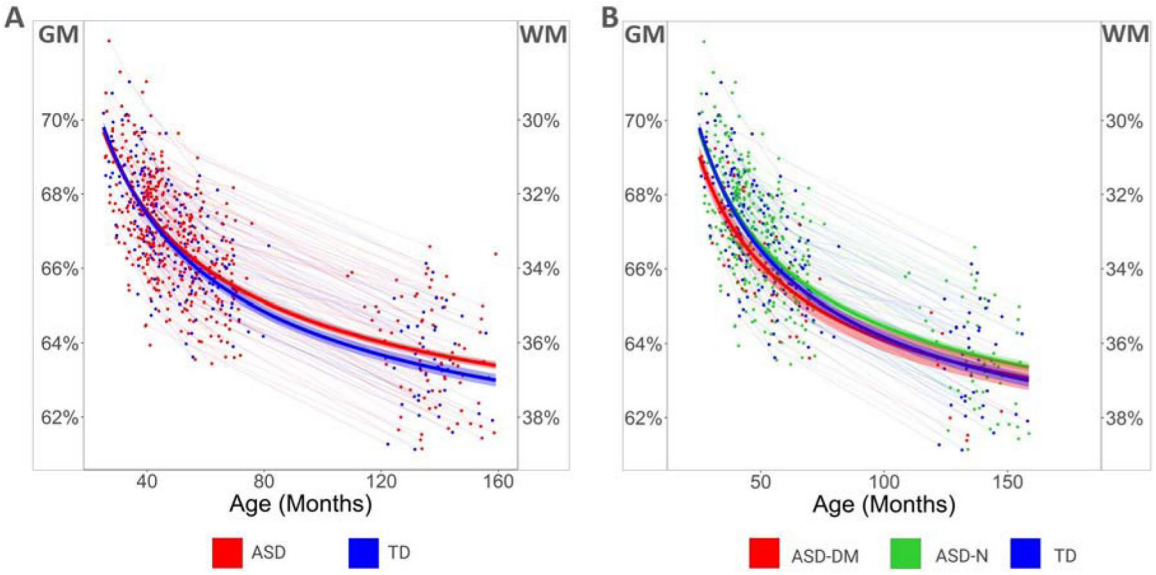

Figure 2.

Longitudinal trajectories of %GM and %WM from early to middle childhood in **A)** boys with autism spectrum disorder (ASD) and typical development (TD), and **B)** in boys with ASD and disproportionate megalencephaly (ASD-DM), ASD with normative cerebral volume (ASD-N), and TD.

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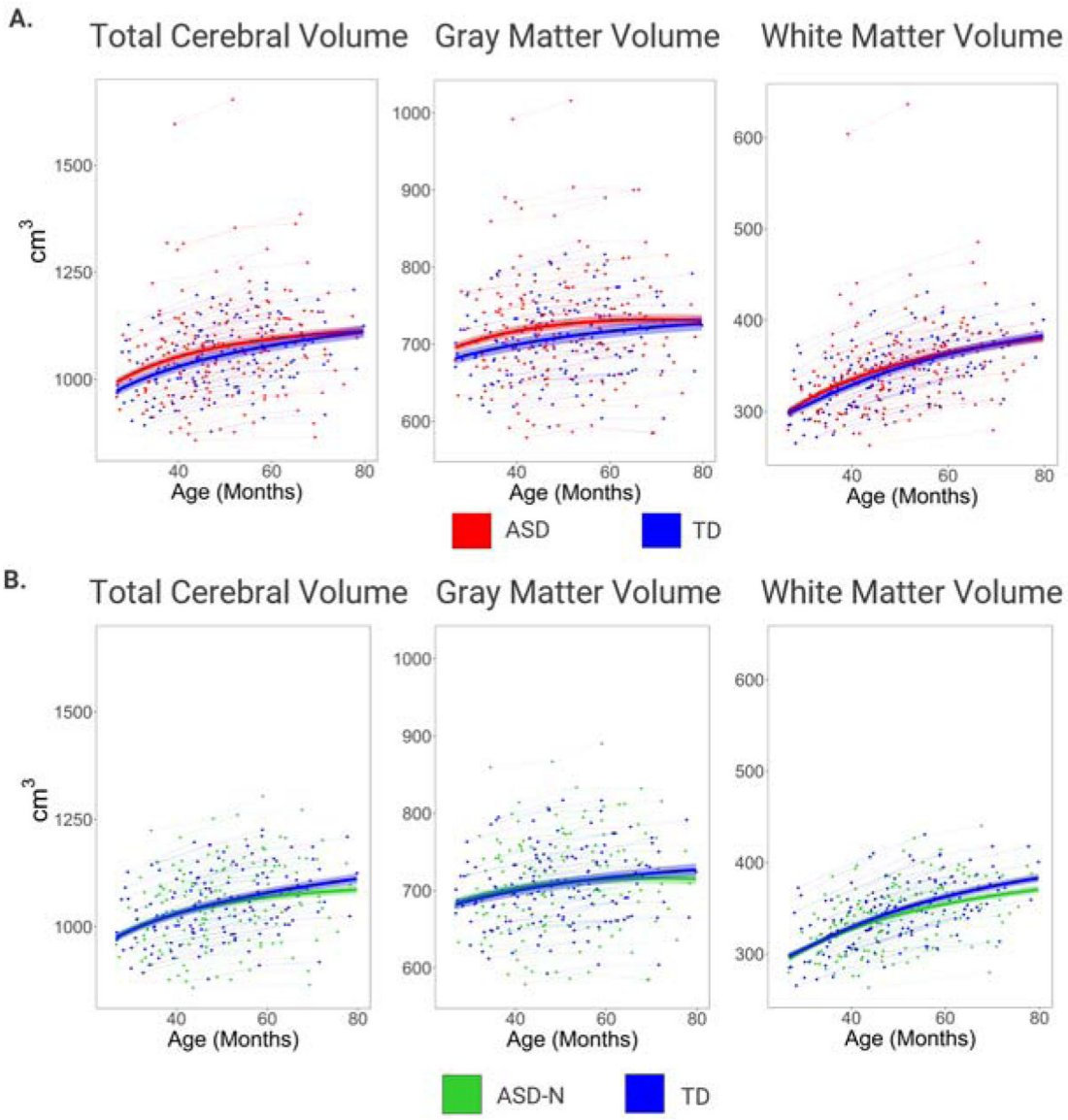

Figure 3.

Longitudinal trajectories of total cerebral volume (TCV), gray matter (GM), and white matter (WM) in early childhood in **A)** girls with autism spectrum disorder (ASD) and typical development (TD), and **B)** in girls with ASD with normative cerebral volume (ASD-N) and TD.

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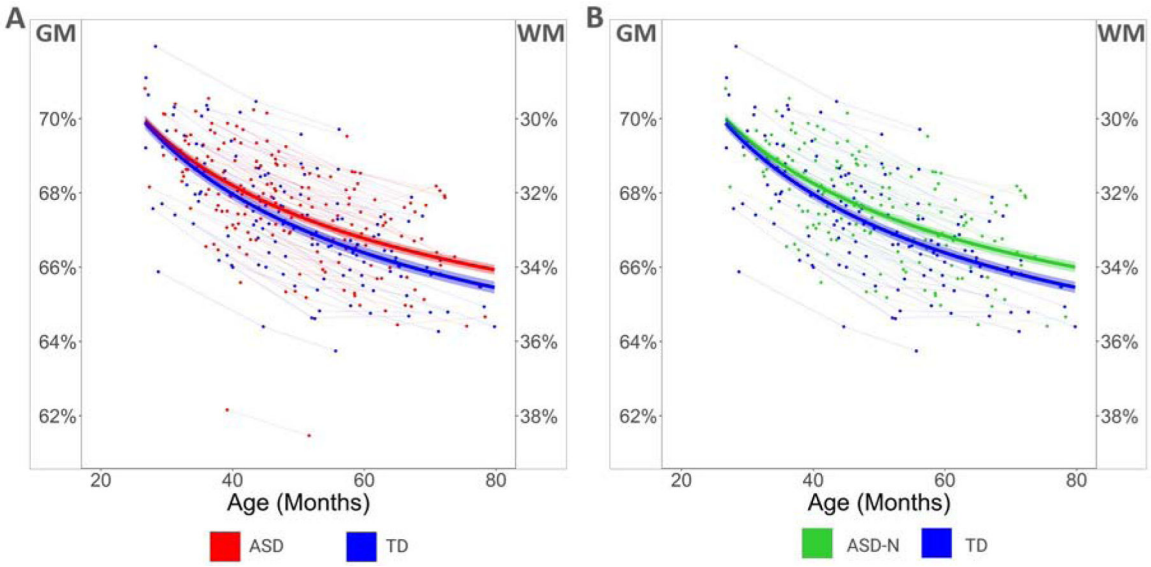

Figure 4.

Longitudinal trajectories of %GM / %WM in early childhood in **A)** girls with autism spectrum disorder (ASD) and typical development (TD), and **B)** in girls with ASD with normative cerebral volume (ASD-N) and TD.

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Table 1.

Sample Characteristics

		Boys		Girls	
Measure		**ASD**	**TD**	**ASD**	**TD**
Scans Included	Time 1	191	74	95	61
	Time 2	117	52	51	45
	Time 3	78	42	42	34
	Time 4	74	41	–	–
	Early + Time 4	67	41	–	–
Participants Included	1 scan	199	74	95	61
	≥ 2 scans	140	58	62	47
	≥ 3 scans	83	45	31	32
	≥ 4 scans	38	32	–	–
Age in Months, *Mean (SD)*	Time 1	38.1 (5.7)	36.7 (6.3)	39.3 (6.1)	38.4 (6.9)
	Time 2	50.7 (5.6)	50.2 (6.6)	53.5 (6.6)	52.6 (6.4)
	Time 3	64.0 (5.4)	63.4 (6.8)	64.7 (5.9)	65.2 (6.7)
	Time 4	136.8 (11.4)	137.5 (8.5)	–	–
ADOS CSS	Time 1	7.5 (1.7)	–	7.4 (1.7)	–
	Time 3	7.4 (2.1)	–	6.7 (2.4)	–
	Time 4	7.8 (1.8)	–	–	–
DQ/IQ	Time 1	70.0 (21.0)	103.3 (20.8)	72.2 (20.9)	108.5 (20.8)
	Time 3	79.9 (18.8)	110.6 (20.0)	80.3 (19.0)	115.4 (19.3)
	Time 4	82.2 (18.8)	113.6 (18.3)	–	–
ASD-DM Status at T1		22	–	5	–
ASD-N Status at T1		152	–	79	–
DM Status Unconfirmed		25	–	11	–

Notes: ASD = Autism Spectrum Disorder, TD = Typically Developing Controls; ASD-DM= Autism Spectrum Disorder with Disproportionate Megalencephaly; ASD-N= Autism Spectrum Disorder with normative brain to height ratio; Early refers to a Time 1, 2, or Tme 3 scan.

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KEY RESOURCES TABLE

Resource Type	Specific Reagent or Resource	Source or Reference	Identifiers	Additional Information
Add additional rows as needed for each resource type	Include species and sex when applicable.	Include name of manufacturer, company, repository, individual, or research lab. Include PMID or DOI for references; use “this paper” if new.	Include catalog numbers, stock numbers, database IDs or accession numbers, and/or RRIDs. RRIDs are highly encouraged; search for RRIDs at https://scicrunch.org/resources.	Include any additional information or notes if necessary.
Software; Algorithm	R-Studio	https://rstudio.com/	Version 1.2	Integrated Development Environment for R
Software; Algorithm	R Project for Statistical Computing	https://www.r-project.org/	v. 3.5.1	R statistical computing
Software; Algorithm	nlme R package	https://cran.r-project.org/web/packages/nlme	v. 3.1	Mixed Model Package in R
Software; Algorithm	FMRIB Software Library	https://fsl.fmrib.ox.ac.uk	v5.0	Image Segmentation

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