Published in final edited form as:

Autism Res. 2015 February ; 8(1): 82–93. doi:10.1002/aur.1427.

Longitudinal Volumetric Brain Changes in Autism Spectrum Disorder Ages 6–35 Years

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Abstract

LAY ABSTRACT—Since the impairments associated with autism spectrum disorder (ASD) tend to persist or worsen from childhood into adulthood, it is of critical importance to examine how the brain develops over this growth epoch. We report initial findings on whole and regional longitudinal brain development in 100 male participants with ASD (226 high-quality MRI scans) compared to 56 typically developing male controls (TDCs) (117 high-quality scans) from childhood into adulthood, for a total of 156 participants scanned over an eight-year period. We provide volumetric growth curves for the entire brain, total gray matter (GM), frontal GM,

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DATA ACCESS

We contributed some of the data from this project to the Autism Brain Imaging Data Exchange (ABIDE) and it is freely available (DiMartino et al., 2013). We have imported time 1 data and are in the process of contributing the rest of the data from this project to the National Institutes of Health National Database for Autism Research (NDAR; <http://ndar.nih.gov/>).

temporal GM, parietal GM, occipital GM, total cortical white matter (WM), corpus callosum, caudate, thalamus, total cerebellum, and total ventricles. Mean volume of cortical WM was reduced significantly. Decreases in regional mean volumes in the ASD sample were most often due to decreases during late adolescence and adulthood. The growth curve of whole-brain volume showed increased volumes in young children with autism and subsequently decreased during adolescence to meet the TDC curve between 10 and 15 years of age. The volume of many structures continued to decline atypically into adulthood in the ASD sample. The data suggest that ASD is a dynamic disorder with complex changes in whole and regional brain volumes that change over time from childhood into adulthood.

SCIENTIFIC ABSTRACT—Since the impairments associated with autism spectrum disorder (ASD) tend to persist or worsen from childhood into adulthood, it is of critical importance to examine how the brain develops over this growth epoch. We report initial findings on whole and regional longitudinal brain development in 100 male participants with ASD (226 high-quality MRI scans; mean inter-scan interval 2.7 years) compared to 56 typically developing male controls (TDCs) (117 high-quality scans; mean inter-scan interval 2.6 years) from childhood into adulthood, for a total of 156 participants scanned over an eight-year period. This initial analysis includes between one and three high-quality scans per participant that have been processed and segmented to date, with 21% having one scan, 27% with two scans and 52% with three scans in the ASD sample; corresponding percentages for the TDC sample are 30%, 30%, and 40%. The proportion of participants with multiple scans (79% of ASDs and 68% of TDCs) was high in comparison to that of large longitudinal neuroimaging studies of typical development. We provide volumetric growth curves for the entire brain, total gray matter (GM), frontal GM, temporal GM, parietal GM, occipital GM, total cortical white matter (WM), corpus callosum, caudate, thalamus, total cerebellum, and total ventricles. Mean volume of cortical WM was reduced significantly. Mean ventricular volume was increased in the ASD sample relative to the TDCs across the broad age range studied. Decreases in regional mean volumes in the ASD sample most often were due to decreases during late adolescence and adulthood. The growth curve of whole brain volume over time showed increased volumes in young children with autism, and subsequently decreased during adolescence to meet the TDC curve between 10 and 15 years of age. The volume of many structures continued to decline atypically into adulthood in the ASD sample. The data suggest that ASD is a dynamic disorder with complex changes in whole and regional brain volumes that change over time from childhood into adulthood.

Keywords

adolescents; adults; children; growth curve; mixed effects; MRI; variance

Introduction

Although it is often stated that brain development in autism spectrum disorder (ASD) is abnormal, there is little longitudinal evidence of this disorder in the published literature. This knowledge is critical for understanding the underlying neuropathology of ASD. Existing findings are based on inferences from age-related changes observed in cross-sectional studies and from studies of small samples with only two time points of data per subject. Cross-sectional studies have examined group differences in the development of

whole brain volume (WBV) in autism, and these studies have generally found evidence of its atypical growth trajectory (Carper et al., 2002; Courchesne et al., 2001, 2007, 2011; Hazlett et al., 2005; Nordahl et al., 2011; Schumann et al., 2010; Sparks et al., 2002; for a meta-analysis see Stanfield et al., 2008), with increases in some young children with the disorder (Nordahl et al., 2011; Schumann et al., 2010; Sparks et al., 2002) but decreases or no difference in volume in older individuals with ASD compared to typically developing controls (TDCs) (Carper et al., 2002). An age-related cross-sectional analysis identified a linear decrease in cortical GM volume with age (Giedd et al., 1996). As with WBV, there is evidence that compartmental volume of multiple brain subregions may follow an atypical developmental pattern in ASD (Ecker et al., 2012; Raznahan et al., 2010; Wallace et al., 2010).

At least three research groups have conducted two-timepoint longitudinal brain volume studies, with inter-scan intervals of 2–3.6 years (average 2.5 years), in older children with ASD compared to TDCs. Most of the studies have focused on specific brain structures and children initially 8–12 years of age. Slowed whole brain WM growth, especially noted in the temporal, parietal, and occipital lobes, was observed in 13 boys with ASD compared to 7 TDC (Hua et al., 2013). Increased rate of growth of the caudate was found in 49 children with autism compared to 37 controls in a study of striatal structures (Langen et al., 2013). A third research group reported results comparing samples ranging from 13–23 children with autism to 16–23 controls. Total GM volume and cortical thickness, especially in the occipital lobe, decreased with age at a greater rate, and whole brain stem volume increased at faster rates. Rate of growth in whole brain, corpus callosum (CC), amygdala, and hippocampal volume volumes did not differ significantly, with the CC showing persistently decreased volume in the ASD samples compared to TDCs (Barnea-Goraly et al., 2013; Frazier et al., 2012; Hardan et al., 2009; Jou et al., 2013).

Inferences about development from cross-sectional studies may be misleading. Large inter-individual differences in brain volumes (Brain Development Cooperative Group, Lange, 2012; Lange et al., 1997) and curvilinear arcs complicate efforts to describe expected developmental trajectories from cross-sectional data. Longitudinal studies have statistical capabilities beyond cross-sectional designs to characterize brain development trajectories critical for understanding individual development, simultaneously quantifying within-person and between-person variation (Snedecor & Cochran, 1989). Longitudinal studies of gray matter (GM) volumes in typically developing individuals have shown strikingly different developmental trajectories compared to the patterns suggested by age-related cross-sectional analysis (Giedd et al., 1999; Lenroot et al., 2010). While imaging studies of autism collecting only one or two timepoints of data per subject are an important first step toward understanding brain changes during late development, additional repeated measures per subject are needed to achieve reliable measures of individual change over time (Trefethen & Bau, 1997; Willett et al., 1998; Lenroot et al., 2010).

We compare longitudinal developmental trajectories of whole and regional brain volumes in individuals with ASD and TDCs from childhood into adulthood. The proportion of participants with multiple scans, 79% (79/100) of ASD and 68% (39/56) of TDC, is high in

comparison to that of large longitudinal neuroimaging studies of typical development (Giedd et al., 1999 (45%); Lenroot et al., 2007 (64%)).

The purpose of this study was to begin to map late brain development in autism at the group level, and determine if the trajectories were typical or atypical. Specifically, we asked the following questions: 1) Do brain volumes significantly change with age during late brain development in autism? 2) Are developmental trajectories in autism linear or quadratic? 3) Is there regional specificity? 4) Do developmental curves differ in autism compared to typical development? Morphometric brain development is protracted in humans, extending well into the third decade in some regions (Giedd & Rapoport, 2010; Brain Development Cooperative Group, Lange, 2012; Kuzawa et al., 2014). For that reason, we used a cohort sequential (accelerated longitudinal) sampling plan (Harezlak et al., 2005; Willett et al., 1998) to begin to obtain information about changes in brain volume across the entire period of late brain development from childhood into adulthood. We purposely examined a wide age range using this sampling design because it is important to gain some understanding of brain changes in ASD across this age interval without waiting 30 years for results. We focused on global and regional volumes that have been most extensively examined in large volumetric studies of typical brain development including whole brain, total gray matter (GM), frontal GM, temporal GM, parietal GM, occipital GM, total cortical white matter (WM), corpus callosum (CC), caudate, thalamus, total cerebellum, and total ventricles (Brain Development Cooperative Group, Lange, 2012; Giedd et al., 1999; Lenroot et al., 2007; Tiemeier et al., 2010).

MATERIALS AND METHODS

Participants

ASD and age-matched TDC participants ranging in age from 3 to 35 years were actively recruited from community and clinical sources (i.e., parent support groups, youth groups, schools, clinical social skills groups) as part of an ongoing study. All participants in this study were males; other groups are focusing exclusively on females with ASD. We achieved the necessary statistical power by excluding heterogeneity in brain volumes associated with sexual dimorphism. Participant retention was 84.5% for ASD and 70.4% for TDC. At least one high quality MRI scan was available from 94% of ASD and 95% of TDC individuals resulting in data from 156 individuals (100 ASD; 56 TDC) for analysis. Multiple high-quality scans were available from the majority of participants, and only high-quality scans were included.

Longitudinal data collection occurred at up to three separate times over the course of 8 years for each subject. 21% having one scan, 27% with two scans and 52% with three scans in the ASD sample; corresponding percentages for the TDC sample are 30%, 30%, and 40%. There were few controls in the 3–5 year age range; we can make longitudinal comparisons beginning at 6 years of age (not affecting total number of scans).

ASD was diagnosed using the Autism Diagnostic Interview-Revised (ADI-R) (Lord et al., 1994), the Autism Diagnostic Observation Scale-Generic (ADOS-G) (Lord et al., 2000) and the DSM-IV-TR (American Psychiatric Association, 1994) criteria. Eighty-six percent of

participants met full criteria for autism based on the ADI-R and ADOS criteria, 10% of participants met criteria for PDD-NOS (clinical phenotype, ASD criteria on the ADOS and meeting at least one ASD cutoff in the ADI-R social or communication domains, and scoring within two points in the other domain), 4% of participants met criteria for the broad autism phenotype (meeting ASD criteria on either the ADOS or the ADI-R); Lainhart et al. (2006). The ADOS was administered at study entry only. Exclusion criteria were clinical indications of medical causes of ASD (i.e., patient history, fragile-X, karyotype, or clinical examination), history of severe head injury, prematurity, neonatal hypoxia-ischemia, seizure disorder, other neurological and genetic conditions, severe intellectual developmental disability, and any contraindication to scanning at 3T. Participants with seizure disorder were excluded because their brain images could have shown volumetric and other changes that were not due to autism, and because those with seizures may represent a subgroup with a distinct mechanism that results in seizures and thus different from the majority who do not have seizures. TDCs were confirmed as having typical development through the ADOS-G, IQ testing, neuropsychological testing, and standardized psychiatric measures collected at the first time point (Leyfer et al., 2006). Family history information was collected from all subjects at the time of entry. Lack of deviation from typical development and family history over time was confirmed by an updated history and further testing at subsequent time points. The data from several individuals who failed to continue to meet our criteria for typical development over time were excluded. After initially meeting inclusion criteria at time 1 four TDCs developed mild depression, one TDC reported a sibling newly diagnosed with ASD, and one TDC was later diagnosed with ADHD and had a new sibling with an ASD diagnosis. We had a few participants who were unable to be scanned due to service related obligations during young adulthood or attrition (moving out of the area), but the main cause of inability to be scanned at a certain time was having braces in between scans. Informed consent was obtained from parents or guardians and participants of adult age; assent was obtained from participants unable to provide consent. A combination of remifentanyl and propofol for deep sedation was administered to 26 ASD participants (age range 3.08–8.16 years) at time 1, and 16 ASD participants at time 2 (age range 3.08–8.16 years); all of these 16 participants also had deep sedation at time 1. An on-site faculty anesthesiologist administered the medications and continuously monitored the participants; there were no complications. The study was fully IRB approved with signed parental approval, following the Declaration of Helsinki for human experimentation.

Table 1 is a description of the ASD and TDC samples with respect to number and inter-scan interval of scans, family income, age, body mass index (BMI), and performance IQ (PIQ) as measured by the Wechsler Intelligence Scale for Children-3rd Edition (WISC-III; Wechsler, 1991) or Wechsler Adult Intelligence Scale (WAIS-III; Wechsler, 1997); we administered the DAS and DAS-Pre for the 3–5 year olds. We included PIQ to control for general intellectual ability. We included BMI because height and weight can be represented in a single covariate and because it has been shown that WBV does not depend on height in typical development (Lange et al., 2010).

The younger and older individuals with autism did not significantly differ in severity of behavioral measures of autism when they were 4–5 years old, as indexed by the total ADI-R algorithm items scored at that age. Family income served as a surrogate for “socioeconomic

status.” Handedness was determined through the Edinburgh Handedness Inventory (Oldfield, 1971).

MRI protocols

Whole-brain T1-weighted images were acquired on a Siemens Trio 3.0T scanners using a 3D sagittal MP-RAGE sequence. At time 1, an 8-channel, receive-only array coil was used with the following protocol parameters: TI=1100ms, TR=1800ms, TE=2.93ms, flip angle=12 degrees, 210 Hz/pixel bandwidth, 6.7ms echo spacing, a 256×256×160 acquisition matrix (A/P phase-encode, R/L slice encode) over a 256×256×160 mm field-of-view to generate 1 mm isotropic resolution in 7:41 minutes. At times 2 and 3, a 12-channel, receive-only array coil was used with the following protocol: TI=900ms, TR=2200ms, TE=2.91ms, flip angle=9 degrees, 240 Hz/pixel bandwidth, 6.8ms echo spacing, a 256×240×160 acquisition matrix (A/P phase-encode, R/L slice encode) over a 256×240×192mm field of view to generate voxels with 1×1×1.2 mm resolution in 9:14 minutes. To account for any systematic differences in the imaging hardware (coil) and protocol at time 1 versus times 2 and 3, a linear regression ‘protocol’ variable (which also accommodated for pulse sequence differences) was included in all statistical models. We found that gradients were stable across repeated scans by fitting a regression line to seven repeated measurements of total intracranial volume (TICV) for a 40 year old adult over a period of ~4.5 years; the estimated slope was not significantly different from zero. Rehearsal was used for the younger children to practice lying in the scanner.

MRI analysis

All volumetric analyses were computed using FreeSurfer® software (version 5.1, <http://surfer.nmr.mgh.harvard.edu/>; Fischl et al, 2002, Fischl et al., 2004) and followed the steps for longitudinal processing (Reuter et al., 2012). All structures were large enough to obtain reliable segmentations given our volume/sample size ratios (except perhaps for caudate and thalamus). All post-processing was performed on identical nodes of a supercomputer using CentOS 5.4, eliminating potential for operating system bias in computed volumes (Gronenschild et al., 2012). Segmentation and classification errors were screened by examination of scatter-plots for each region of interest and outliers identified. All outliers were visually inspected and if significant tissue classification error was present it was removed from the analysis. WBV was derived as the sum of supratentorial GM and supratentorial WM, excluding posterior fossa and ventricles. Total supratentorial GM included all cortical GM and subcortical GM. Total ventricular volume was derived as the sum of all ventricular volumes.

Biostatistical analysis

Figure 1 depicts our sampling result over time for all participants. Descriptive statistics by diagnostic group were generated based on unadjusted native space brain volumes. Longitudinal mixed-effects analysis of covariance models (Laird & Ware, 1982; Lange & Laird, 1989; Lange & Ryan, 1989; Venables & Ripley, 2002) were applied to evaluate the combined effects of diagnostic group, age, PIQ, and BMI on brain volume. Age at scan was treated as the within-subject repeated measure. Mean and variance-covariance functions for the mixed models were chosen by uniform application of the Akaike Information Criterion

(Akaike, 1974) to yield the best-fitting yet simplest growth curve models for each brain structure. A test-wise false-positive error rate was set at 0.05, thus controlling for potential structure-wise errors. Based on reported effect sizes of covariates on regional human brain volumes (Lange et al. 1997), our sample size (N=156) had probative power of at least 80% to detect regional age- and group-related variation in all measured structures at all ages at a false-positive error rate of 5%. Missing data were assumed to be missing at random; no multiple imputations were performed. Computations for all data analysis were conducted in R version 2.12.1 (64-bit Leopard build, 12/16/10) (R Core Team, <http://www.r-project.org>), the results of which are, in this case, equivalent to those produced by SAS.

RESULTS

Descriptive statistics

Table 1 is a summary of sample characteristics by diagnostic group. The ASD and TDC groups showed no significant differences by mean family income, age, inter-scan intervals, BMI, or handedness, although there was a significant difference in mean PIQ, verbal IQ (VIQ) and full-scale IQ (FIQ) (as anticipated). Mean family income was higher than that of a national normative sample of healthy children (Lange et al., 2010; Brain Development Cooperative Group, Lange, 2012) and higher than the mean household income in Salt Lake County, but was similar in the ASD and TDC groups.

Unadjusted Mean Brain Volumes and Variances

Table 2 is a summary of group means and standard deviations of all measured whole and regional brain volumes. Mean volumes of total cortical WM were significantly reduced in the ASD sample. Region-specific F-tests for variance differences between groups indicated that total GM and all lobar GM volumes had greater relative variance in the ASD sample except in the occipital lobe. Thalamic variance was decreased in the ASD sample.

Trajectories of Volumetric Development

Figure 2 is a plot of raw WBVs and Figure 3 contains the best-fitting growth curves for each of the structures for ASD and TDC separately by group for each region with 95% least squares confidence envelopes.

Table 3 is a summary of best-fitting mixed-effects growth curve models for each global and regional brain volume accounting for the effects of age, diagnostic group, and age by group interactions on linear and curvilinear (quadratic) scales. No volumes were affected significantly by individual differences in either PIQ or BMI. WBV curves for ASD and TDC were of inverted-U shape. The ASD curve was flatter and tilted downward relative to the TDC curve. Mean WBV appeared increased in ASD relative to TDC during earlier childhood. The ASD curve met the TDC curve in early adolescence, but instead of joining with the TDC curve and continuing to follow it, WBV in the ASD group continued to decrease into adulthood. The overall decrease in mean ASD WBV occurred during late adolescence and adulthood. We examined changes in WBV relative to TICV. TICV developmental trajectories (not shown) differed in the two groups. Similar to the WBV curve, average TICV was greater in the ASD group in childhood, but continued virtually

identical to that of the TDC group after 10 years of age. In contrast, ASD WBV decreased slightly but steadily during the pre-pubertal, pubertal, and post-pubertal age ranges into adulthood, increasingly diverging from the TICV curve relative to the TDCs. The volumes of all structures changed significantly with age in both groups. The type of best-fit developmental change (linear or quadratic) varied by region, yet was similar in the two groups for any given region. The developmental trajectories of ASD and TDC were, however, significantly different for half of the regions (6 out of 12).

The mixed-effects models showed a case-control group difference in total cortical WM ($p = 0.005$) consistent with the previous two-sample t-test. ASD differences in slopes showed steeper declines in WBV ($p < 0.001$) and occipital GM ($p < 0.01$), and a reduced age-related increase in total cortical WM ($p = 0.002$). The ASD WBV, temporal GM, parietal GM, occipital lobe GM, and total ventricular volumes trajectories had different quadratic shape relative to TDCs. Although thalamic volume curves appeared to differ between groups (Figure 3), increased variance and the best model prevented the difference from reaching statistical significance. The age trajectories of total cerebellum volume did not differ between groups. Table 4 is an interpretive summary of the results presented in Table 3.

DISCUSSION

The proportion of participants in our study with multiple scans (79% of ASDs and 70% of TDCs) is high in comparison to that of large longitudinal neuroimaging studies of typical development (Giedd et al., 1999 (45%); Lenroot et al., 2007 (64%)). Our findings converge with the results of past studies to suggest that ASD is a dynamic disorder with atypical differences in whole and regional brain volumes that change over time from early childhood into adulthood. Our results show atypical processes continuing far beyond the differences in early childhood reported by other autism research studies; our longitudinal findings to date support the hypothesis that late neurodevelopment is atypical in autism. The period of late development, from three years of age into adulthood, is characterized by complex interactions among a host of factors. Instead of following the typical brain volume curves during this period, individuals with ASD as a group appear to continue to lose brain volume, so that by 30 years of age the volumetric capacity of the brain is reduced. Half of ASD growth curves were characterized by abnormally high volumes in early childhood, typical values between 10 and 15 years of age, and then abnormal further decline into adulthood.

Developmental trends in our TDC group were generally similar to those found in large studies of typical male brain development (Brain Development Cooperative Group, Lange, 2012; Giedd et al., 1999; Lenroot et al., 2007; Tiemeier et al., 2010). Volumetric trajectories of our TDC whole brain, total cortical WM, CC, thalamus, caudate, and total cerebellar volumes were inverted-U curves. CC size continued to increase with age until the mid-20's and total ventricular volume increased linearly from early childhood through adulthood. In contrast to previous studies of typical development, TDC trajectories of total GM, frontal GM, parietal GM, and occipital volumes were linear, rather than inverted-U in shape, although consistent with a recent nationwide representative study (Brain Development Cooperative Group, Lange, 2012). Net developmental decreases were observed in GM volumes, as seen in large TDC studies.

The atypical decline in brain volume during adolescence in autism occurs before the plateau in improvement in ASD symptoms (Taylor & Seltzer, 2010) and before poor outcome occurs in many ASD adults (Howlin et al., 2013). The transition to adulthood is associated with loss of the structure previously provided in school and home settings where roles are set and demands on independent and adaptive skills are limited. The transition to adulthood brings many individuals face to face with new demands. If the atypical decline in brain volume is found to be pathological, the timing of onset decline raises the possibility that biological mechanisms increase the vulnerability of the young to the stress associated with the major changes in life and increased demands for adaptation that lie ahead. The timing of the onset of atypical decline in brain volume also raises the hope that additional research will elucidate the mechanisms involved and this knowledge will inform the development of specific and improved treatments and preventive interventions to increase resilience and improve quality of life in affected individuals.

Because it is not possible for every participant in a longitudinal study to be scanned at each timepoint for a variety of reasons, longitudinal studies usually include some cross-sectional data (Giedd et al., 1999; Lenroot et al., 2007; Brain Development Cooperative Group, Lange, 2012). As in these studies, the statistical methods we used are able to combine single- and multi-timepoint data to estimate group trajectories in a joint cross-sectional and longitudinal study.

We had sufficient power to estimate the longitudinal trajectories of brain volumes in ASD relative to typical development. It will be extremely important to add more timepoints for increasingly reliable estimates of longitudinal changes of brain volume at the individual level. A minimum of three scans per participant is required for reliable linear trajectories, and a minimum of four timepoints for reliable quadratic trajectories at the individual level (Trefethen & Bau, 1997; Willett et al., 1998) when employing a cohort sequential sampling design. Clearly, as more participants and more timepoints are added, the precision of estimated group and individual trajectories increases. It is thus anticipated that as more participants and imaging timepoints are added to the present study, group-level longitudinal trajectories of brain volumes in ASD and how they differ from typical development will be refined. These more informative curves will identify disturbances in developmental neurobiological processes shared by affected individuals driven by subgroups, including those defined by medication usage and comorbidity.

Identification of brain growth and maturation trajectories for individuals will allow the more definitive study of variation across individuals and relationships to important dimensional features in ASD such as IQ. In typical development, behavioral and cognitive development are known to be linked to volumetric total and regional brain development into young adulthood (Luders et al., 2009; Shaw et al., 2006). We do not yet know if increased brain volume in young children with ASD leads to the decreased volume at older ages, i.e., whether the two phenomena are developmentally continuous. Establishing brain development trajectories of individuals with ASD will enable studies of biological continuity and discontinuity (Rutter et al., 2006)..

The regional volume trajectories studied here likely reflect distinct but interdependent neurodevelopmental processes. For example, CC is increasing while cortical gray matter is overall decreasing and total ventricular volume increasing during typical late neurodevelopment. Brain structure is dynamic throughout this age range, both in terms of gross morphology (Giedd et al., 1999; Sowell et al., 2002; Paus, 2005) and network-level architecture (Zielinski et al., 2010). The specific process (or processes) driving these changes remains unknown, but one might speculate that early ‘pluripotency’ of functional brain systems leading to distinct consolidated network organization is one plausible explanation. For instance, through a process classically described as ‘pruning’, preexisting neuronal populations are lost as they fail to become integrated into a functional domain, developmental skill, or cognitive process. Throughout neurodevelopment, as brain networks become integrated within networks, they also become segregated from other networks, resulting in domain specificity. Integration very likely results in more local and long-range interconnectivity between nodes of a given network, whereas segregation likely involves neuronal populations not yet assimilated into a network being lost. This process would lead to increasing CC volume, as more spatially discrete cortical nodes are ‘brought online’ through long-range (and interhemispheric) WM tract modification (e.g., myelination), as well as decreasing GM as fewer cellular populations ‘make the cut’. This decrease in GM volume is reflected in increasing ventricular volume. (Clinically, neurodegenerative diseases often produce profound ventriculomegaly as a consequence of GM atrophy, even as WM volume is preserved.) Further examination of our data in this context supports this concept. Both total GM and ASD WBV decrease continuously throughout our age range. Further, Figure 3 shows that ventricular volume steadily increases, coincident with steadily declining temporal lobe GM (the temporal lobe surrounds and defines a large portion of the lateral ventricles). In addition, total WM volume increases continuously throughout our age range, likely reflecting both local and long-range connectivity, and shares very similar trajectory with CC volume. CC volume may be directly proportional to total WM volume, which seems intuitive under this model of network development. Admittedly, our present data are insufficient to resolve this question directly, but our group remains in active pursuit.

Our study will help us to determine the clinical correlates of inter-subject brain differences brought on by increased brain volume in early childhood and reduced brain volume during adolescence and adulthood in ASD. Sampling individual trajectories more densely will also assist in the study of causal pathways to determine if different trajectories are associated with different levels of functioning and risk genes and contextual factors. Postmortem brain tissue studies of small samples of individuals with autism have begun to discover genetic disruptions in the frontal cortex and reduced minicolumns that may lead to widespread disruptions in volumetric brain growth (Casanova et al., 2002; Buxhoeveden et al., 2006; Stoner et al., 2014). Development of reliable predictive models of treatment response and outcome *in vivo* will identify mechanisms important for understanding secondary, and tertiary preventive interventions.

Limitations and Future Considerations

Although their ASD diagnoses were confirmed, the majority of individuals with ASD and all TDCs were recruited from community sources, not clinical sources. ASD and TDC

groups were not matched on IQ; we found no IQ effect on brain volumes in the mixed-effects analysis (although there are effects of regional brain volumes on IQ (Lange et al., 2010). The wide age range of participants at study entry raises the possibility of an ASD cohort effect, i.e., factors that affect brain volumes related to autism severity may have differed in participants who entered the study when they were younger compared to those who were older. We found, however, no difference between younger and older participants on the total of ADI-R algorithm items that are scored for when participants were 4–5 years of age. Finally, the T1 relaxation times of brain tissues vary through the lifespan (Saito et al., 2009; Westlye et al., 2010), which will influence MR signal intensities that are used by the FreeSurfer® segmentation tools. This may affect the likelihood of a voxel being classified as GM or WM, which is a problem in any other similar MRI study. Immature WM could plausibly have a signal intensity that increases the likelihood of its classification as GM such that a reported decrease in GM volume may reflect a change in the size of an immature WM compartment that has been misclassified as GM. The use of the labels “GM” and “WM” volumes in this article thus refers to the above operational definitions, while acknowledging that immaturities of WM development may have affected our tissue classifications. We also acknowledge critical distinctions between brain tissue volumes and developmental maturation.

CONCLUSIONS

It has been known for decades that clinical change in affected individuals between childhood and adulthood is highly variable. In a 1971 follow up study, Leo Kanner observed that adults with autism who had appeared so alike as children in their “startling unique” pattern of shared behavior, appeared strikingly different from each other 30 years later (Kanner, 1971). We now report evidence of atypical brain development from six years of age into adulthood, and posit that autism and its increased clinical variability with age will be better understood by longitudinal change over time rather than by cross-sectional features at any single period of development. Our cohort sequential design and the maximum of three scans per participant analyzed to date have provided novel, unique and critical insights into developmental trends in the autism community. We are currently working to enrich our data set for further understanding patterns of pathology, disease mechanisms, brain health, and predictors of future course.

Acknowledgments

FUNDING

The project described was supported by Grant Numbers RO1 MH080826 (JEL, EDB, ALA, NL), RO1 MH084795 (JEL, PTF, NL), RO1 MH097464 (JEL, NL, ML), KO8 MH092697 (JSA), and KO8 MH100609 (BAZ) from the National Institute Of Mental Health; Grant Numbers T32 HD07489 (BGT) and P30 HD003352-45 (Waisman Center Core Grant) from the Eunice Kennedy Shriver NICHD, the Hartwell Foundation (BGT), the Primary Children’s Foundation Early Career Development Award (BAZ) and the Poelman Foundation (EDB). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Mental Health, the National Institute of Child Health & Development, or the National Institutes of Health. We thank Tracy Abildskov, Dr. Jeffrey Lu, Henry Buswell, the Utah Center for Advanced Imaging Research (UCAIR), and former members of the Utah Autism CPEA for their assistance during the early stages of this project. We sincerely thank the children, adolescents, and adults with autism and the individuals with typical development, who participated in this study, and their families.

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Figure 1.

Figure 2.

Figure 3.

Table 1

Characteristics of the longitudinal sample.

	ASD	TDC	Total
Number of subjects	100	56	156
Scans per subject, <i>Mean (SD)</i>	2.3(0.8)	2.1(0.8)	2.2(0.8)
# Subjects with 1 scan	21	17	38
# Subjects with 2 scans	27	17	44
# Subjects with 3 scans	52	22	74
Total Scans	226	117	343
Family Income	97,178(1062)	107,767(2498)	100,872(1563)
Age (years)	16.4(7.7)	18.0(7.1)	17.0(7.5)
Age range	3.1–34.5	4.1–34.1	3.1–34.5
Inter-scan Interval	2.7(0.5)	2.6(0.6)	2.6(0.5)
Inter-scan Interval Range	1.7–3.9	1.6–4.5	1.6–4.5
FIQ	99.9(18.9)	119.0(13.9)	107.1(19.5)
FIQ range	49–137	89–153	49–153
PIQ	100.7(18.4)	116.9(15.5)	106.2(19.1)
PIQ range	50–138	90–155	50–155
VIQ	94.9(20.4)	115.3(13.9)	101.9(20.8)
VIQ range	51–145	87–151	51–151
BMI ^a	22.7(6.6)	22.1(4.5)	22.5(5.9)
BMI range	13.1–46.3	14.5–32.7	13.1–46.3
Right Handedness (%) <i>Mean (SD)</i>	85.3(35.4)	96.4(18.6)	89.4(30.8)

^aBody Mass Index = Mass (kg)/Height (m)².

Table 2

Group mean differences in mean and variance across brain regions.

Structure	Mean Volume (cc)			Group Difference t-test p-value	SD			Heterogeneity of Variance F-test p-value
	TDC	ASD	Direction		TDC	ASD	Direction	
Whole Brain	1325.8	1303.6	ASD < TDC	n.s.	105.6	123.9	TDC < ASD	n.s.
Total GM	773.7	772.8	ASD = TDC	n.s.	61.1	83.1	TDC < ASD	< 0.001
Frontal GM	223.1	223.4	ASD = TDC	n.s.	25.8	32.2	TDC < ASD	0.008
Temporal GM	131.7	128.4	ASD < TDC	n.s.	6.8	8.3	TDC < ASD	< 0.001
Parietal GM	154.3	157.7	TDC < ASD	n.s.	16.4	23.0	TDC < ASD	< 0.001
Occipital GM	57.2	57.3	ASD = TDC	n.s.	5.5	8.9	TDC < ASD	n.s.
Total Cortical WM	522.3	501.9	ASD < TDC	0.005	62.3	65.9	TDC < ASD	< 0.001
Corpus Callosum	3.30	3.10	ASD = TDC	n.s.	0.64	0.56	ASD < TDC	n.s.
Caudate	8.5	8.4	ASD = TDC	n.s.	1.20	1.28	TDC < ASD	n.s.
Thalamus	16.2	15.9	ASD = TDC	n.s.	1.71	1.81	ASD < TDC	0.007
Total Cerebellum	29.8	29.9	ASD = TDC	n.s.	4.04	4.17	TDC < ASD	n.s.
Total Ventricles	14.8	15.9	TDC < ASD	n.s.	7.45	7.36	ASD < TDC	n.s.

SD, standard deviation

n.s., not significant at alpha = 0.05

Table 3

Percent changes in group mean growth curves between groups from best-fitting mixed-effects models.

Structure	Longitudinal Age and Group Differences (%)									
	Group (ASD-TDC)	p-value	Age	p-value	Age X Group	p-value	Age ²	p-value	Age ² X Group	p-value
Whole Brain	<i>n.s.</i>	-	2.25	<0.001	-1.66	<0.001	-0.06	<0.001	0.04	0.005
Total GM	<i>n.s.</i>	-	-0.61	<0.001	<i>n.s.</i>	-	<i>n.s.</i>	-	<i>n.s.</i>	-
Frontal GM	<i>n.s.</i>	-	-0.98	<0.001	<i>n.s.</i>	-	<i>n.s.</i>	-	<i>n.s.</i>	-
Temporal GM	<i>n.s.</i>	-	-0.55	<0.001	<i>n.s.</i>	-	-0.03	<0.05	0.02	<0.05
Parietal GM	<i>n.s.</i>	-	-0.32	<0.021	<i>n.s.</i>	-	<i>n.s.</i>	-	-0.01	<0.05
Occipital GM	<i>n.s.</i>	-	-0.44	0.002	-0.15	<0.01	<i>n.s.</i>	-	0.02	0.002
Total Cortical WM	-3.91	0.005	3.90	<0.001	-0.53	0.002	-0.07	<0.001	<i>n.s.</i>	-
Corpus Callosum	<i>n.s.</i>	-	3.42	<0.001	<i>n.s.</i>	-	-0.07	<0.001	<i>n.s.</i>	-
Caudate	<i>n.s.</i>	-	1.15	<0.001	<i>n.s.</i>	-	-0.03	<0.001	<i>n.s.</i>	-
Thalamus	<i>n.s.</i>	-	3.15	<0.001	<i>n.s.</i>	-	-0.08	0.001	<i>n.s.</i>	-
Total Cerebellum	<i>n.s.</i>	-	3.25	<0.001	<i>n.s.</i>	-	-0.06	<0.001	<i>n.s.</i>	-
Total Ventricles	<i>n.s.</i>	-	1.33	<0.001	<i>n.s.</i>	-	<i>n.s.</i>	-	-0.01	<0.05

n.s., not significant at $\alpha = 0.05$.

Table 4

Interpretive summary of numerical findings in Table 3.

Brain Region Volume	Significant Group Differences in Mean Volume	Tendency for larger volumes in younger ASD and smaller volumes in older ASD	Significant Trajectory Differences	Linear differences	Quadratic differences
Whole Brain	No	Yes	Yes	Yes, ASD decrease	Yes, ASD flattened
Total GM	No	No	No	No	No
Frontal GM	No	Yes	No	No	No
Temporal GM	No	No	Yes	No	Yes, ASD slight U shape *
Parietal GM	No	Yes	Yes	No	Yes, ASD some U shape *
Occipital GM	No	Yes	Yes	Yes, ASD greater decrease	Yes, ASD some U shape *
Total Cortical WM	ASD decreased	Yes	Yes	Yes, ASD lesser increase	No
Corpus Callosum	No	No	Yes	No	No
Caudate	No	No	No	No	No
Thalamus	No	Yes	No	No	No
Total Cerebellum	No	Yes	No	No	No
Total Ventricles	No	No	Yes	No	Yes, ASD slight inverted-U shape *

* At older ages only