

Cortical Thickness Change in Autism During Early Childhood

Elizabeth Smith,^{1*} Audrey Thurm,¹ Deanna Greenstein,² Cristan Farmer,¹ Susan Swedo,¹ Jay Giedd,³ and Armin Raznahan²

¹*Pediatrics and Developmental Neuroscience Branch, National Institute of Mental Health, Bethesda, Maryland*

²*Child Psychiatry Branch, National Institute of Mental Health, Bethesda, Maryland*

³*Department of Psychiatry at University of California, San Diego, California*

Abstract: Structural magnetic resonance imaging (MRI) scans at high spatial resolution can detect potential foci of early brain dysmaturation in children with autism spectrum disorders (ASD). In addition, comparison between MRI and behavior measures over time can identify patterns of brain change accompanying specific outcomes. We report structural MRI data from two time points for a total of 84 scans in children with ASD and 30 scans in typical controls (mean age time one = 4.1 years, mean age at time two = 6.6 years). Surface-based cortical morphometry and linear mixed effects models were used to link changes in cortical anatomy to both diagnostic status and individual differences in changes in language and autism severity. Compared with controls, children with ASD showed accelerated gray matter volume gain with age, which was driven by a lack of typical age-related cortical thickness (CT) decrease within 10 cortical regions involved in language, social cognition, and behavioral control. Greater expressive communication gains with age in children with ASD were associated with greater CT gains in a set of right hemisphere homologues to dominant language cortices, potentially identifying a compensatory system for closer translational study. *Hum Brain Mapp* 37:2616–2629, 2016. © 2016 Wiley Periodicals, Inc.

Key words: autism spectrum disorder; cortical thickness; surface based morphometry; expressive language; MRI

INTRODUCTION

Additional Supporting Information may be found in the online version of this article.

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*Correspondence to: Elizabeth Smith, National Institute of Mental Health, Pediatrics and Developmental Neuroscience Branch, 10 Center Drive MSC 1255, Building 10, Room 1C250, Bethesda, Maryland 20892-1255. E-mail: elizabeth.smith3@nih.gov

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Autism spectrum disorder (ASD) is a common neurodevelopmental disorder that is behaviorally defined, emerges early in life, encompasses a heterogeneous range of presentations, and is characterized by deficits in social communication and patterns of restrictive/repetitive behavior [American Psychiatric Association, 2013]. Genetically-driven disruptions of early brain development [Willsey et al., 2013], combined with environmental effects [Hallmayer et al., 2011] are thought to play an important role in ASD pathogenesis, but the growing neuroimaging literature in ASD has yet to identify neuroanatomical or functional markers that specifically and consistently accompany an ASD diagnosis [Philip et al., 2012; Stigler et al., 2011].

The majority of structural neuroimaging studies in ASD have included older children, adolescents, or adults, and have used cross-sectional study designs [Ecker et al., 2010; Hadjikhani et al., 2006; Hyde et al., 2010]. These studies hint at a potentially triphasic pattern of brain development in ASD, with increased brain growth in the very early years, normalization in late childhood, faster gray matter loss beginning in the teen years, and reduced gray matter loss with age in the adult years [Lange et al., 2015; Zielinski et al., 2014]. However, while these studies are useful for characterizing the brain in autism, understanding brain changes during the developmental window when ASD symptoms first emerge requires longitudinal measures of brain anatomy during early childhood. Neuroimaging research in young children with ASD has begun to incorporate longitudinal study designs [Courchesne et al., 2011; Hardan et al., 2009; Hazlett et al., 2011; Lange et al., 2015; Zielinski et al., 2014], but these approaches have yet to be combined with vertex-based image analysis methods that can map changes in cortical thickness (CT) and surface area (SA) across the cortical sheet. Integration of these two approaches is important for localizing early brain dysmaturation in ASD, as well as identifying patterns of neuroanatomical change that accompanying more desirable patterns of skill attainment.

In a recent cross-sectional neuroimaging study of preschool-aged children with ASD, we used surface-based methods for cortical morphometry to evaluate differences in CT and SA relative to typically developing controls [Raznahan et al., 2013]. This study showed that CT was greater in ASD than in controls in multiple cortical regions associated with social cognition and behavioral regulation, including the superior frontal gyrus, inferior frontal gyrus, medial temporal gyrus, superior temporal gyrus, and intraparietal sulcus [Raznahan et al., 2013]. In contrast to these CT differences, regional SA measures in ASD were not statistically distinguishable from those in typically developing controls. Regional CT variation has also been highlighted as a neuroanatomical phenotype of interest by several neuroimaging studies of ASD [Chung et al., 2005; Doyle-Thomas et al., 2013; Ecker et al., 2010, 2013, 2014; Hadjikhani et al., 2006; Hardan et al., 2006, 2009; Hyde et al., 2010; Jiao et al., 2010; Mak-Fan et al., 2012; Misaki et al., 2012; Raznahan et al., 2010, 2013; Scheel et al., 2011; Wallace et al., 2010, 2015; Zhou et al., 2013, 2014; Zielinski et al., 2014], and CT variation is associated with autistic traits both in typical individuals and those with ASD [Doyle-Thomas et al., 2013; Hadjikhani et al., 2006; Hardan et al., 2009; Richter et al., 2015; Wallace et al., 2015; Wallace et al., 2012]. However, only two studies of change over time have included very young children [Hazlett et al., 2011; Zielinski et al., 2014]. Further, studies have yet to investigate relations between CT change and changes in measures of autism symptoms in young children.

The current study extends our previous cross-sectional work by using neuroimaging over time and vertex-based

analyses to investigate neuroanatomical change in a sample of young children with ASD. We compare brain development between children with ASD and TD controls, and also investigate how brain development over time relates to specific areas of behavioral change within ASD. We focus on the following two questions: First, are differences in CT between ASD and TD developmentally dynamic within early childhood? Second, is change in CT related to clinically meaningful developmental changes in young children with ASD? Here, we specifically focus on changes in communication because of their importance in predicting adult outcomes in ASD [Magiati et al., 2014], and relationship to CT in both ASD [Balardin et al., 2015] and TD [Brouwer et al., 2014; Porter et al., 2011]. We also focus on symptom severity change in two domains of deficit in ASD (i.e., restrictive interests and repetitive behaviors, and social communication), which have been found to correlate with static neuroanatomical measures [Hadjikhani et al., 2006; Knaus et al., 2010; Rojas et al., 2006].

MATERIALS AND METHODS

This study was approved by an NIH Institutional Review Board and was performed in accordance with the guidelines and regulations thereof and in compliance with the Declaration of Helsinki. The nature of the experimental procedures was explained to parents/guardians of all participants, and written informed consent was obtained from all participants' parents/guardians.

Participants

Participants included 57 children (11 females) enrolled in a natural history study who were selected for the current analyses based on having two high-quality MRI scans (see Table I). The cohort was initially within the age range of 2 to 7 years, and the time between scans ranged from 0.86 to 3.57 years, with no difference in interscan interval between groups. Forty-two children were included in a group defined by diagnosis of DSM-IV defined autistic disorder (referred to here as ASD), while 15 children participated as typically developing controls (TDC). At each visit, all children completed the Autism Diagnostic Observation Schedule (ADOS) [Lord et al., 2000], the Vineland Adaptive Behavior Scales, 2nd Edition (VABS) [Sparrow et al., 2005], and either the Mullen Scales of Early Development (MSEL) [Mullen, 1995], the Differential Ability Scales-II (DAS-II) [Elliott, 2007], or the Wechsler Intelligence Scale for Children (WISC-IV) [Wechsler, 2004], depending on age and ability level. At both time points, there were no significant differences between groups on either age or time between scans, but the ASD group did have significantly more males and lower verbal and non-verbal DQ (see Table I).

To confirm diagnosis in the ASD group before the first scan, the Autism Diagnostic Interview-Revised (ADI-R)

TABLE I. Participant Characteristics

Characteristic	ASD mean (SD) [range]	TD mean (SD) [range]	Group difference
Number (scans)	42 (84)	15 (30)	
Sex (m:f)	38:4	8:7	$\chi^2 = 9.8, P = 0.004$
Time between scans (yr)	2.5 (0.67) [1.1–3.6]	2.4 (0.64) [0.86–3.2]	$F = 0.21, P = 0.7$
Age			
Time 1	4.0 (1.2) [2.2–7.5]	4.4 (1.3) [2.5–7.0]	$F = 1.6, P = 0.21$
Time 2	6.5 (1.2) [3.6–9.0]	6.8 (1.3) [4.4–8.8]	$F = 0.9, P = 0.35$
Verbal DQ ^a			
Time 1	41.7 (21.4) [11.7–96.4]	107.8 (15.2) [87.8–151.5]	$F = 120.6, P < 0.001$
Time 2	41.9 (28.7) [9.2–109.0]	120.8 (19.6) [89.0–147.1]	$F = 97.0, P < 0.001$
Nonverbal DQ ^a			
Time 1	60.4 (18.1) [20.1–109.2]	105.1 (11.7) [80.6–129.1]	$F = 78.8, P < 0.001$
Time 2	54.3 (26.2) [19.4–115.3]	116.9 (18.6) [82.1–140.8]	$F = 71.9, P < 0.001$
VABS expressive language AE			
Time 1	16.26 (8.77) [3–38]	67.2 (31.77) [25–147]	$F = 180.2, P < 0.001$
Time 2	26.98 (18.93) [8–90]	138.53 (78.50) [58–264]	$F = 147.8, P < 0.001$
VABS receptive language			
Time 1	18.50 (13.44) [1–78]	71.0 (49.02) [22–216]	$F = 80.57, P < 0.001$
Time 2	31.88 (25.37) [9–132]	112.33 (35.93) [59–216]	$F = 176.4, P < 0.001$
ADOS SOC severity ^b			
Time 1	6.83 (1.45) [3–10]		
Time 2	6.98 (2.08) [1–10]		
ADOS RRB severity ^c			
Time 1	8.57 (1.26) [5–10]		
Time 2	8.35 (1.51) [1–10]		
Percent minimally verbal ^d			
Time 1	67.4		
Time 2	46.5		

^aVerbal Developmental Quotient and Nonverbal Developmental Quotient were measured with the Mullen Scales of Early Learning ($n = 90$), the Differential Ability Scales ($n = 23$), and the Wechsler Intelligence Scales for Children ($n = 1$), depending on age and developmental level of each child. DQs were calculated for each child as Age Equivalent/Chronological Age \times 100 to reduce floor effects due to many participants scoring at the floor on standard scores.

^bADOS social communication severity score based on a scale of 1 to 10 with 10 being most severe symptoms (Gotham et al., 2009).

^cADOS restrictive and repetitive behaviors severity score, based on a scale of 1 to 10 with 10 being most severe symptoms (Gotham et al., 2009).

^dMinimally verbal status indicates communicative use of five or fewer words during ADOS administration (Thurm et al., 2015).

ASD = autism spectrum disorder; TD = typically developing controls.

[Rutter et al., 2003] was administered; parents of the TDC group completed the Social Communication Questionnaire [Rutter et al., 2004] to confirm lack of ASD symptoms. DSM-IV diagnoses of autistic disorder were confirmed by

doctoral-level clinicians based on the Autism Diagnostic Observation Schedule (ADOS), ADI-R, and clinical judgment; all children met ASD cutoffs on these measures [Risi et al., 2006]. Exclusion criteria for both groups included

impairing neurological disorder other than ASD that would have affected the validity of behavioral testing (e.g., cerebral palsy) and genetic abnormalities based on pathogenic findings from CGH microarray conducted on the ASD sample. All scans were reviewed by a board-certified radiologist and none were found to have clinically significant anatomical atypicalities. Additional exclusion criteria for the TDC group included having a first-degree relative with an ASD, a history of premature birth or extremely low birth weight, or history of special education services/early intervention before enrollment.

Neuroimaging

Children with ASD were scanned under sedation, administered by a board-certified anesthesiologist to minimize movement artifacts [Reuter et al., 2015], whereas the TDC group was scanned during natural night time sleep or while awake and watching a movie. All participants were scanned on the same 1.5 T General Electric Signa scanner (Milwaukee, WI) using a three-dimensional (3D) spoiled gradient recalled echo sequence with the following image acquisition parameters: Echo time, 5 ms; repetition time, 24 ms; flip angle 45°; acquisition matrix, 256 × 192; number of excitations, 1; and field of view, 24 cm.

Raw T1-weighted scans were first coded by two independent raters for degree of motion artifact using Blumenthal et al.'s 4-level coding system (i.e., 1 = none, 2 = mild, 3 = moderate, and 4 = severe) [Blumenthal et al., 2002]. Scans scoring a 1 or a 2 after consensus coding were then submitted to the CIVET pipeline for automated segmentation and modeling of cortical surfaces [Raznahan et al., 2013]. Only scans with accurate skull-stripping and segmentation at this level were analyzed further. The cortical surfaces from all individual scans were aligned at each of 80,000 vertices using curvature features via a 2D registration algorithm to align sulcal features [Lyttelton et al., 2007]. We focus here on the following CIVET-derived anatomical metrics of global brain anatomy: gray matter volume (GMV), white matter volume (WMV), cerebrospinal fluid volume (CSF), total tissue volume (TTV, GMV + WMV), total cortical volume (CV), total surface area (SA), and mean cortical thickness (CT). Spatially fine-grained analyses of cortical anatomy were based on measures of CT taken at ~80,000 points (vertices) on the modeled cortical surface of each scan [MacDonald et al., 2000]. This is in contrast to other studies of CT, which use parcellation schemes to examine anatomically-defined regions of interest a priori [e.g., Hazlett et al., 2011; Zielinski et al., 2014].

Statistical Analyses

We used linear mixed effects models to explore group differences in global measures of brain development, including GMV, WMV, CSF, TTV, CV, SA, and CT as well as in CT at the vertex level. In order to test our hypotheses we included main effects of group and age and a group ×

age interaction in our models [see Eq. (1)]: the interaction tests if there are group differences in brain development over time, and the main effect of group (in the absence of a significant interaction) measures differences in estimated means while controlling for age.

$$\begin{aligned} \text{Anatomy}_{ij} = & \beta_0 + \beta_1(\text{Age}_{ij}) + \beta_2(\text{Group}_i) \\ & + \beta_3(\text{Age}_{ij} \times \text{Group}_i) + d_i + e_{ij} \end{aligned} \quad (1)$$

We included a random intercept per person (d_i) to account for within-person dependence associated with multiple measures per person, and the residuals (e_{ij} s) were modeled with a Standard Normal distribution. For all analyses, we began with this parsimonious, simplified model. Then, in order to ensure our findings were not due to group differences in other variables in our sample known to be associated with cortical anatomy, including sex [Sowell et al., 2007], IQ [Misaki et al., 2012], or in global measures frequently found to differ in this population [Chen et al., 2011], we followed-up all significant findings by adding sex, nonverbal DQ, and TTV as covariates [see Eq. (2)].

$$\begin{aligned} \text{Anatomy}_{ij} = & \beta_0 + \beta_1(\text{Age}_{ij}) + \beta_2(\text{Group}_i) \\ & + \beta_3(\text{Age}_{ij} \times \text{Group}_i) + \beta_4(\text{Sex}_i) + \beta_5(\text{NVDQ}_{ij}) \\ & + \beta_6(\text{TTV}_{ij}) + d_i + e_{ij} \end{aligned}$$

To further assess potential effects of sex on group findings, we also tested the above model with males only [Eq. (3)]:

$$\begin{aligned} \text{Anatomy}_{ij} = & \beta_0 + \beta_1(\text{Age}_{ij}) + \beta_2(\text{Group}_i) \\ & + \beta_3(\text{Age}_{ij} \times \text{Group}_i) + \beta_4(\text{NVDQ}_{ij}) \\ & + \beta_5(\text{TTV}_{ij}) + d_i + e_{ij} \end{aligned}$$

Finally, for each anatomical metric of interest, we ran the above models after excluding subjects with anatomy scores more than two standard deviations from the sample mean. We used the nlme package (<http://CRAN.R-project.org/package=nlme>) in R to conduct all mixed model analyses [R Core Team, 2014].

The above approach was taken for both global and vertex-wise analyses. Vertex-wise analyses entailed running the models at each of 80,000 vertices across the cortical mantle. Vertex-wise effects were visualized after false detection rate (FDR) [Genovese et al., 2002] correction for multiple comparisons with q (the expected proportion of falsely rejected null hypotheses) set at 0.05. A separate FDR threshold was determined for each model and was calculated using all effects in the model except the intercept. We used Brain-view2 [Lerch, 2009] to identify MNI coordinates of the vertex with the highest t-value within a given area of significance and the Talairach Daemon [Lancaster et al., 1997] to label the location of these vertices for descriptive purposes.

In order to assess if changes in anatomy were associated with developmental changes in communication and

symptom severity within ASD, we focused on the receptive and expressive communication age equivalents from the VABS and the restrictive/repetitive behavior and social communication domain severity scores from the ADOS, respectively. These measures were chosen because they could be gathered over time across children with ranges of abilities, and would not artificially decrease with increasing age (i.e., due to varied rates of change at different ages as seen for DQ [Aiken, 1996]). For each participant with ASD, slopes for VABS scores were calculated as follows:

$$\text{Slope} = (\text{Age equivalent}_{\text{time2}} - \text{age equivalent}_{\text{time1}}) / (\text{age}_{\text{time2}} - \text{age}_{\text{time1}})$$

Slopes for ADOS severity scores were calculated as follows:

$$\text{Slope} = (\text{Calibrated severity score}_{\text{time2}} - \text{calibrated severity score}_{\text{time1}}) / (\text{age}_{\text{time2}} - \text{age}_{\text{time1}}) \quad (5)$$

Then, slopes were related to vertex-based measures of anatomy as follows:

$$\text{Anatomy}_{ij} = \beta_0 + \beta_1(\text{Age}_{ij}) + \beta_2(\text{Slope}_i) + \beta_3(\text{Age}_{ij} \times \text{Slope}_i) + d_i + e_{ij} \quad (6)$$

Age was centered at the sample mean (5.3 years) in all analyses, including interactions with age, so that the main effects of diagnosis [in Eq. (1)], and interindividual differences in symptom change [in Eq. (2)] could be interpreted at the mean age of our sample. Given our sample size and that we have two time points from each subject, we focus on linear effects in order to capitalize on within-subject and between-group effects of time.

RESULTS

Global Measures

Main effects of group membership (ASD, TDC) were not observed for any global anatomical measure (see Table II). Significant changes over time occurred on all anatomical measures in the TDC group except for GMV and CV. In ASD, significant changes over time occurred on all anatomical measures, with a marginal effect observed for CT. The interaction between diagnosis and age was significant in the GMV model, with a greater increase in volume over time in ASD versus TDC. This pattern was also observed in CV, which accounts for the bulk of total GMV in humans. The interaction between diagnosis and age was not significant in modeling SA, but was for CT. Specifically, individuals in the TDC group showed greater decrease of CT over time than individuals with ASD. Thus, differences in age-related CV change between

children with ASD and controls were underpinned by an attenuation of the typical pattern of age-related CT reduction in ASD. This, alongside similar rates of age-related SA increase in both groups, resulted in a greater rate of CV gain in children with ASD compared with the TDC group (see Fig. 1). These results remained significant in models accounting for sex, nonverbal DQ, and TTV, when modeled in males only, and when excluding data from participants with CT slopes over two SDs from the mean (for CT and SA analyses, see Supporting Information Table I).

Vertex-Level Cortical Thickness Measures

In order to further characterize group differences in CT change with age, we completed vertex-based CT analyses. Our vertex-based analyses for the group-by-age interaction revealed vertices within several regions where developmental patterns of CT change differed between groups. These differences were localized to vertices within left precentral gyrus, supramarginal gyrus, middle temporal gyrus, and cuneus, as well as within the right frontal pole, superior frontal gyrus, postcentral gyrus, inferior temporal gyrus, fusiform gyrus, and precuneus (see Fig. 2, Supporting Information Table I for coordinates of peak vertex). At each of these vertices, the TDC group showed significant CT decreases with time, while individuals with ASD showed less CT decrease (left supramarginal gyrus, right medial frontal gyrus), no change over time (left precentral gyrus, left middle temporal gyrus, right inferior temporal gyrus, right superior frontal gyrus, right fusiform gyrus, right precuneus, right postcentral gyrus), or even CT increases over time (left cuneus). Significant group-by-age interaction in these regions was confirmed by sensitivity analyses using a model accounting for sex, TTV, and nonverbal DQ, a model within males only, and after excluding data from participants with CT values over two SDs from the mean (see Supporting Information Fig. 3). Degree of motion (i.e., “none” or “mild”) did not predict CT in our sample ($t_{(1,73)} = -0.39, P = 0.70$).

These group differences in CT change occurred in the context of a widespread pattern of significant age-related CT decrease that was detected in both groups across large swaths of frontal, temporal, parietal, and occipital cortex (see Supporting Information Fig. 1). Notably, there were no areas of significant CT increase with age in TDC.

In addition to the aforementioned group differences in CT change, we also identified foci of developmentally static CT excess in ASD relative to controls in vertices located in the left superior temporal gyrus, inferior occipital gyrus, and a broad region over the superior frontal gyrus as well as within the right superior parietal lobule and a broad region overlapping the superior frontal gyrus and middle frontal gyrus (see Supporting Information Fig. 2). Developmentally static CT deficits in ASD relative

TABLE II. Main effects and group by age interaction for global anatomy

Main effect of group	ASD Mean (SE)	TDC Mean (SE)	β (SE)	<i>p</i>
Total tissue volume (cm ³)	1,322 (16.3)	1,285 (27.2)	-36.8 (31.7)	0.25
Cerebrospinal fluid volume (cm ³)	1,28.3 (3.0)	119.2 (5.0)	-9.1 (5.9)	0.13
White matter volume (cm ³)	419.2 (6.6)	410.9 (11.1)	-8.3 (12.9)	0.52
Grey matter volume (cm ³)	902.9 (10.5)	876.3 (17.6)	-28.4 (20.6)	0.20
Cortical volume (cm ³)	670.9 (8.6)	651.2 (14.4)	-21.1 (16.9)	0.24
Surface area (mm ²)	1,839.9 (19)	1,780.3 (32.2)	-59.7 (37.5)	0.12
Mean cortical thickness (mm)	3.83 (0.02)	3.82 (0.03)	-0.02 (0.04)	0.70

Main effect of age—ASD	ASD			
	β	SE	<i>t</i>	<i>p</i>
Total tissue volume (cm ³)	33.4	2.4	13.8	<0.001
Cerebrospinal fluid volume (cm ³)	3.7	0.97	3.8	<0.001
White matter volume (cm ³)	18.4	1.1	16.4	<0.001
Grey matter volume (cm ³)	14.8	1.8	8.4	<0.001
Cortical volume (cm ³)	10.6	1.3	7.9	<0.001
Surface area (mm ²)	46.3	3.0	15.5	<0.001
Mean cortical thickness (mm)	-0.01	0.006	-1.9	0.06

Main effect of age—TD	TD			
	β	SE	<i>t</i>	<i>p</i>
Total tissue volume (cm ³)	28.3	3.7	7.6	<0.001
Cerebrospinal fluid volume (cm ³)	6.7	1.6	4.1	<0.001
White matter volume (cm ³)	21.1	1.9	11.1	<0.001
Grey matter volume (cm ³)	6.8	3.7	1.9	0.08
Cortical volume (cm ³)	4.6	2.8	1.7	0.12
Surface area (mm ²)	44.8	5.3	8.5	<0.001
Mean cortical thickness (mm)	-0.04	0.01	-3.4	0.003

Interaction of group and age	ASD			
	β^a	SE	<i>t</i>	<i>p</i>
Total tissue volume (cm ³)	-5.3	4.7	-1.1	0.26
Cerebrospinal fluid volume (cm ³)	3.1	1.9	1.6	0.11
White matter volume (cm ³)	2.5	2.2	1.1	0.26
Grey matter volume (cm ³)	-7.9	3.7	-2.1	0.04
Cortical volume (cm ³)	-5.8	2.8	-2.1	0.04
Surface area (mm ²)	-1.3	6.0	-0.22	0.83
Mean cortical thickness (mm)	-0.03	0.01	-2.4	0.02

Main effect of group statistics reflects effect of group after accounting for the main effect of age.

^a β weights for interaction model with ASD as the reference group.

SE = standard error.

to controls were found in vertices within the left superior occipital gyrus, orbitofrontal gyrus, parahippocampal gyrus, and right orbitofrontal gyrus.

Next, we evaluated whether changes in cortical thickness within particular regions were associated with changes in communication and core autism symptoms in ASD. Within the ASD group, we identified four right hemisphere groups of vertices where the slope for expressive communication was associated with CT change with

age. These were within the pre/postcentral gyrus ($\beta = 0.01$, SE = 0.002, $t_{(40)} = 4.8$, $p < 0.001$), superior temporal gyrus ($\beta = 0.006$, SE = 0.002, $t_{(40)} = 3.7$, $p < 0.001$), inferior frontal gyrus ($\beta = 0.008$, SE = 0.002, $t_{(40)} = 4.9$, $p < 0.001$), and lingual gyrus ($\beta = 0.007$, SE = 0.002, $t_{(40)} = 3.3$, $p < 0.0001$, see Fig. 3.) Within these groups of vertices, greater rates of expressive communication gain in ASD were associated with increasing CT over time. These vertices continued to be significant after accounting for

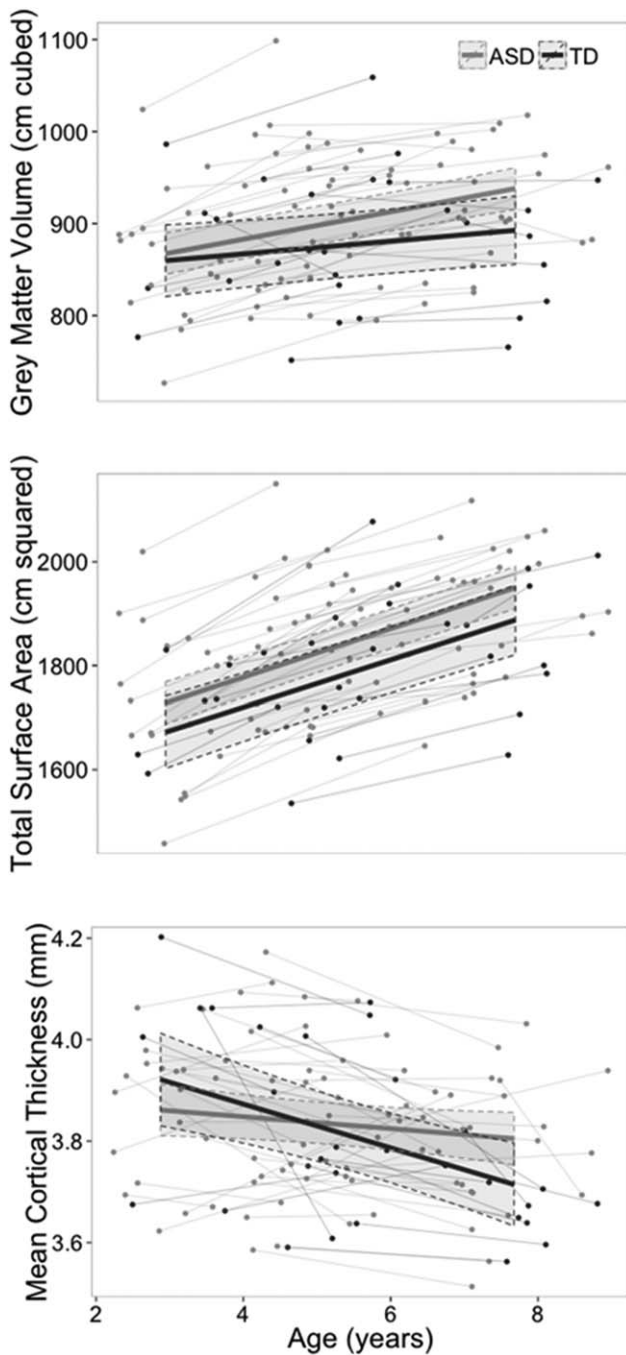


Figure 1.

Change in anatomy with age for grey matter volume, total surface area, and mean cortical thickness in autism spectrum disorder (ASD) and typically developing controls (TDC).

sex, TTV, and nonverbal DQ within the model, when modeled in males only, and excluding CT values over 2 SDs from the mean, for a total of six sensitivity models (see Supporting Information Table IV). Rate of change in

expressive communication did not significantly relate to rates of CT change within the left hemisphere. There were no brain regions where changes in CT were associated with changes in VABS Receptive Communication, ADOS SOC severity scores, or ADOS RRB severity scores.

DISCUSSION

Summary of Main Findings

Linear models with two time points of data for global measures indicated similar volumes and patterns of change over time in children with ASD and controls for TTV, WMV, CSF, and SA. GMV and CV showed different patterns of change over time by group, with greater increases in GMV and CV with time in the ASD group. In addition, the cerebral cortex of children with ASD showed less CT decrease with time compared with controls, particularly in vertices located in the left medial temporal gyrus, supramarginal gyrus, precentral gyrus, and cuneus and right postcentral gyrus, inferior temporal gyrus, superior frontal gyrus, precuneus, and fusiform gyrus. Relative to the decreases over time observed in the TDC group, CT in these groups of vertices decreased less, remained stable, or increased in children with ASD. Within the ASD group, greater expressive communication gains over time were associated with CT increase over time in vertices located in the right pre and postcentral gyrus, inferior frontal gyrus, superior temporal gyrus, and lingual gyrus.

Global Measures

We did not find statistically significant differences between children with ASD and TDC in rates of TBV, WM, or CSF change with development. This replicates the only other longitudinal study of brain anatomy in preschool aged children with ASD by Hazlett et al. [2011], which investigated linear changes in cortical anatomy in children with ASD and a heterogeneous control group at ages 2 and 4 to 5 years. Lack of difference between groups at this age fits with the triphasic model of brain development in ASD (i.e., that any early-emerging atypicalities in brain growth are stabilizing within this age range, Lange et al. [2015] and Zielinski et al. [2014]). We did, however, find evidence for altered GMV change with age in ASD such that total GMV, and its major subcomponent CV, increased more with age in ASD versus TDC. Moreover, within our sample, global CV dysmaturation in ASD was driven by aberrant global CT change with age (i.e., decreased age-related CT reduction) with no significant group differences in rates of total SA change with age. These findings contrast with those of Hazlett et al., who reported a developmentally stable CV excess in ASD, driven by larger total cortical SA rather than any alterations in CT. Methodological differences between studies

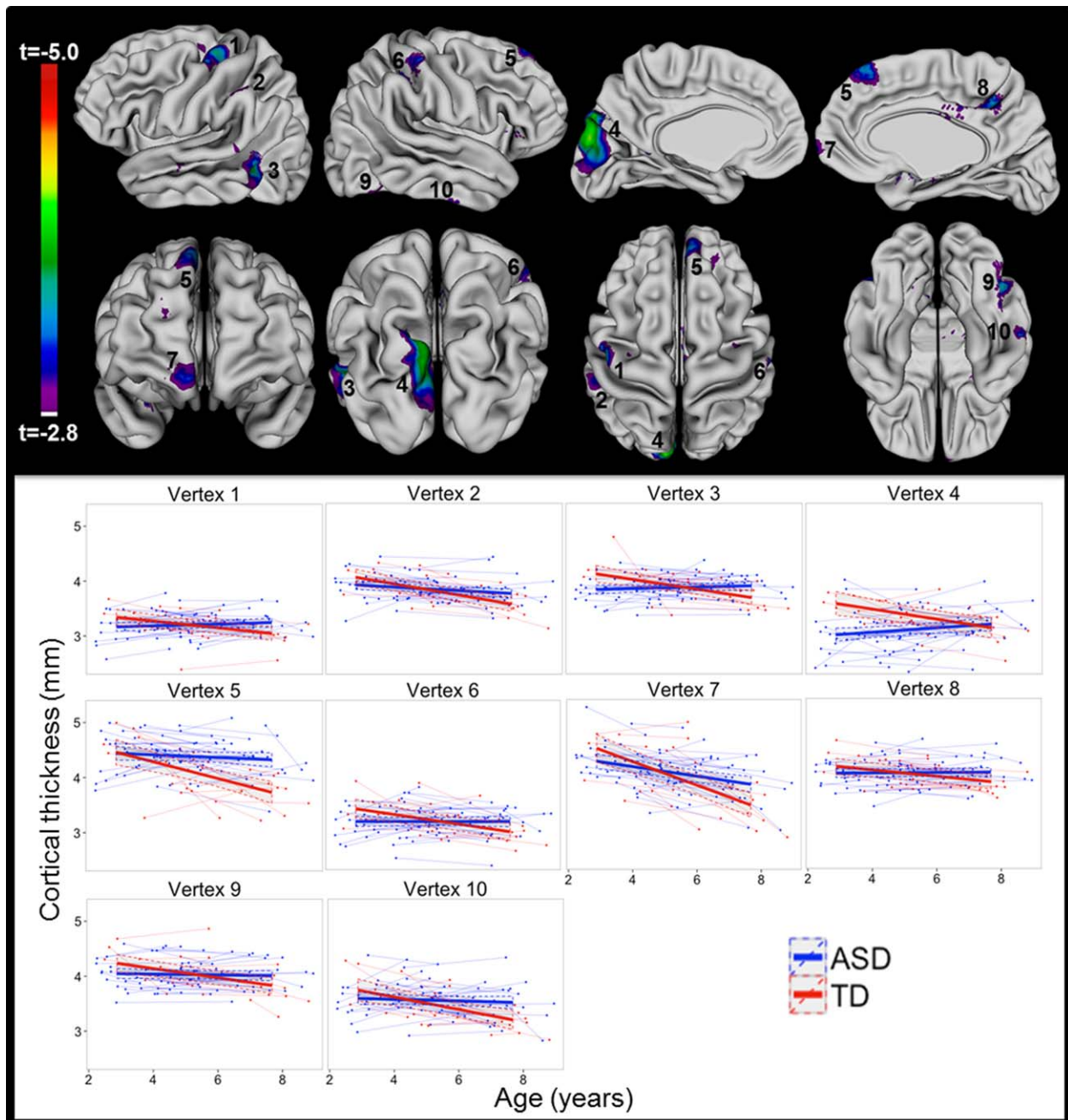


Figure 2.

Interaction of group and age. Highlighted regions represent areas where patterns of change in cortical thickness with age varied between autism spectrum disorder (ASD) and typically developing controls (TDC). Scatterplots for cortical thickness at the center of each numbered region are shown with separate lines for ASD and TDC.

that could potentially account for these conflicting findings include our use of a homogenous control group (the control group in Hazlett et al. comprised children with both typical and delayed development), and use of different methods for measuring cortical anatomy (i.e., no explicit

surface-based modeling of the cortical sheet or direct SA measurement in Hazlett et al.).

Of the nine studies in ASD that have used surface based methods to separately measure CT and SA, seven have found alterations of CT in ASD [Ecker et al., 2013, 2014;

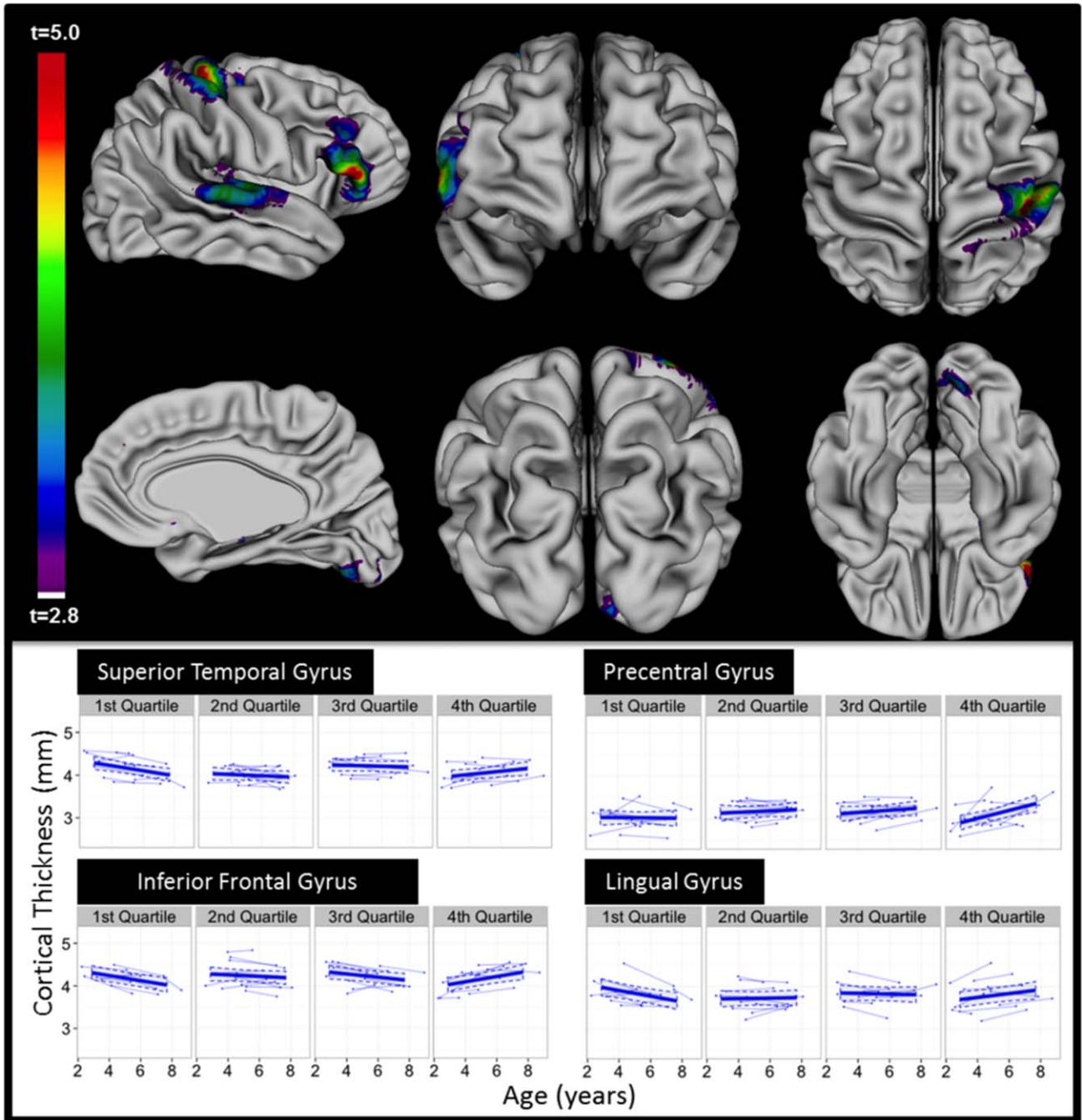


Figure 3.

Regions within ASD only where changes in CT were associated with changes in expressive language age equivalents as measured with VABS. (A) The regions highlighted represent regions where increases in CT with age were associated with increases in expressive language age-equivalents with age. (B) Scatterplots of

CT by age for 1st, 2nd, 3rd, and 4th quartiles for slope of expressive language scores within ASD. Although expressive language was measured continuously, mapping CT change with age within these categories allows for visualization of the significant interactions.

Libero et al., 2014; Mak-Fan et al., 2012; Raznahan et al., 2010, 2013; Wallace et al., 2015] while five have shown differences in SA [Ecker et al., 2014; Hazlett et al., 2011; Libero et al., 2014; Mak-Fan et al., 2012; Ohta et al., 2015]. Given extensive evidence that CT and SA are shaped by distinct genetic and environmental influences [Panizzon et al., 2009; Raznahan et al., 2012], emergence of more consistent differences in CT versus SA in ASD via replication would assist in translational efforts to identify molecular and cellular pathways underpinning aberrant cortical development in ASD.

Vertex-Level CT Findings in ASD Compared With TDC

As cortical changes in ASD may not conform to the traditional anatomical parcellations defined by gyral features, we used vertex-based analyses (versus a priori regions of interest from automated cortical parcellation) to characterize the spatial distribution of CT changes within our sample. Our vertex-level analyses of CT change in children with ASD and TDC yielded several findings of note. First, amongst our (albeit small) sample of TDCs, we identified vertices of significant CT decrease with age (see Supporting Information Fig. 1), which were most prominent in bilateral frontotemporal cortices. These findings represent the first vertex-level map of typical CT development within this age-range. Prior studies of CT development in typically developing children report a robust pattern of increasing CT over the first 2 years of life [Li et al., 2015; Lyall et al., 2014], and decreases in CT throughout much of the cortex during adolescence and into adulthood [Brown and Jernigan, 2012; Raznahan et al., 2011; Shaw et al., 2008; Tamnes et al., 2010; Thambisetty et al., 2010; Ziegler et al., 2010]. Data on CT change between 2 years of age and late childhood are sparse and less consistent, with evidence for both dominant patterns of CT reduction [Brown et al., 2012; Sowell et al., 2004] and CT increases [Raznahan et al., 2011; Shaw et al., 2008]. Further studies in this critical age-range will be required to reconcile these conflicting findings.

Second, our vertex-wise analyses produced evidence for differences between children with ASD and TDCs in rates of CT change over time. These differences generally involved an attenuation of typical age-related CT loss in ASD. This pattern of altered CT development in ASD differs from those of the four other longitudinal studies of regional CT change in ASD, each of which focused on a different age range [Hardan et al., 2009; Hazlett et al., 2011; Wallace et al., 2015; Zielinski et al., 2014]. Specifically, the prior reports found either no difference in CT change over time in toddlers and preschoolers with ASD [Hazlett et al., 2011] or greater age-related CT decreases over time in ASD relative to controls in school age children and in a broad sample of children and adults [Hardan et al., 2009; Wallace et al., 2015; Zielinski et al., 2014].

The difference between our results and these earlier reports could stem from (i) the methods used to measure CT, (ii) group characteristics, such as degree of intellectual disability, or (iii) varying patterns of cortical dysmaturation in ASD across different age-ranges (e.g., Supporting Information Fig. 3). Specifically, the triphasic developmental pattern seen across imaging studies in autism [e.g., Lange et al., 2015] posits that after the early increase in brain volume in the first 2 years in ASD, brain volume would at some point begin to decrease, eventually decreasing at a greater rate than in typical development. Therefore, whereas the first 2 years of life are characterized by brain overgrowth in autism, it is plausible that the present study captures the next developmental phase in ASD, when brain volume (and CT) have begun to decrease but are not changing at the same rate as in TD.

Third, our study adds to the converging evidence for CT alterations in ASD within a set of brain regions involved in language, social cognition and behavioral control. Collapsing across different classes of CT abnormality in ASD relative to controls (i.e., altered rates of change, static increases or static decreases), multiple independent studies localize CT alterations in ASD to rostral prefrontal cortices, the superior temporal sulcus and gyrus (STS/STG) and neighboring lateral temporal structures, inferior parietal lobule, and fusiform gyrus [e.g., Ecker et al., 2013; Hadjikhani et al., 2006; Jiao et al., 2010; Libero et al., 2014; Raznahan et al., 2013; Scheel et al., 2011; Zielinski et al., 2014]. Alterations of CT within the STS/STG have therefore been associated with ASD diagnosis and with degree of normative ASD traits in controls [Blanken et al., 2015; Wallace et al., 2012], highlighting the link between the STS/STG and social-communication development.

Finally, we identified foci where significant CT differences are found between ASD and TDC at mean age. These results echoed our earlier cross-sectional neuroimaging data within this cohort [Raznahan et al., 2013]. Specifically, the present study showed increased CT in ASD in vertices located within the bilateral superior frontal gyrus, left superior temporal gyrus, left lateral occipital gyrus, right middle frontal gyrus, and right intraparietal sulcus. In addition, the present study revealed regions of increased CT in TDC compared with ASD (see Supporting Information Fig. 2). Please see this prior publication [Raznahan et al., 2013] for a detailed systematic review of existing cross-sectional studies of specific brain anatomy differences in young children with ASD.

Vertex-Level Relationships Between Language and CT Development in ASD

In this study, we found an association between rates of expressive communication gains in ASD and rates of CT increase in vertices within a set of right hemisphere regions previously linked to development of language and communication. Specifically, we identified vertices within

the right somatomotor and somatosensory cortices where CT change with time was positively correlated with changes in expressive communication. These regions are primarily related to sensation and movement of the hand, but are also associated with gesture development and embodiment of language in typical development [Flöel et al., 2003; Hauk et al., 2004; Meister et al., 2003]. In addition, the pars triangularis of the inferior frontal gyrus is associated with gesture comprehension [Pazzaglia et al., 2008]. Two of the regions (IFG and somato-motor cortex) have also been identified as components of a CT covariance network that correlates with differences in expressive language in typically developing youth [Lee et al., 2014]. Links between language and CT development in ASD were also found in the STG at the primary auditory cortex [Lange et al., 2015].

The vertices within right IFG, STG, SSC/SMC, and LG where CT change and language development are correlated in ASD are nonoverlapping with those showing significant differences in CT change between ASD and TDC. This observation suggests that the positive correlation between CT increase and expressive communication gains in ASD at these vertices could potentially represent compensatory processes in ASD. For example, this lateralized relationship could potentially represent compensatory development in the right cortex in association with atypical left-hemisphere language specialization. In keeping with this hypothesis, several prior reports have found evidence for atypical lateralization in ASD [Cardinale et al., 2013; Eyster et al., 2012; Flagg et al., 2005; Floris et al., 2015; Herbert et al., 2002; Knaus et al., 2010; Lange et al., 2015], as well as evidence that atypical lateralization of language is specifically associated with language outcomes [De Fosse et al., 2004; Floris et al., 2015; Redcay and Courchesne, 2008]. That specialization of the right hemisphere for language could be compensatory rather than a primary neurological feature in ASD also fits with theories regarding right hemisphere compensation for early left hemisphere dysmaturation [Flagg et al., 2005].

Limitations and Future Directions

While the present study is the first to compare change over time in vertex-based neuroanatomical measures amongst young children with ASD versus typically developing controls, some limitations should be noted. First, while the groups did not vary on age or time between scans, which is important given rapid developmental change in this age group, the groups were not equally sized, or matched on DQ or sex. For this reason, statistical robustness of all group differences and the relation between language and CT in the ASD group were confirmed after accounting for TTV, nonverbal DQ, and sex within the model, in the sample of males only, and both including and excluding CT slopes more than two SDs from the mean, for a total of six sensitivity models per finding.

However, further work in larger samples is needed to better understand the role of these factors in brain dysmaturation in ASD. Therefore, important methodological priorities in follow-up work will include targeted recruitment of females with ASD, and control groups with idiopathic developmental delay/ID. In addition, ASD status was confounded with use of sedation in this study. Although we took great care to exclude any scans with significant motion artifact and found no difference in CT by degree of movement artifact (i.e., “none” vs. “mild”), it is theoretically possible that more subtle group differences in motion arising from group differences in sedation could have led to nonrandom biases in CT estimation between children with ASD and controls. In addition, the present study focuses on linear models due to sample size and having only two time points of data for each participant. While CT change is most likely linear after age 2 years [Brown et al., 2012], gathering three or more data points per subject in a larger longitudinal design would allow for testing of more complex models including those with nonlinear trends. Also, the sample size of the TDC group (30 scans, 15 participants) could lead to spurious differences between groups that would be driven by a small number of individual controls. While all distributions were subjected to outlier analyses and results were confirmed within a very stringently defined subset of data, the small size of this group necessitates replication of the present findings with a larger sample. Finally, the *in vivo* imaging methods employed in our study provide no information about the cellular and molecular underpinnings of detected CT alterations in ASD. Dominant theories for cellular underpinnings of cortical thinning in typical development include both dendritic pruning and myelination [Giedd et al., 2010; Kochunov et al., 2011], but data that can directly test these theories is lacking. Furthermore, mechanisms of developmental and disease-related CT variation need not overlap.

Notwithstanding these limitations, our study provides evidence of CT dysmaturation over time in ASD during early childhood, localized to vertices within several cortical regions reported in previous studies to show structural and functional alterations in older ASD cohorts. This finding attests to the early roots of altered brain development in ASD, and motivates longitudinal, vertex-based studies of even earlier brain development in typical development and ASD within prospective high-risk study designs [e.g., Wolff et al., 2012]. We also provide data on the relation between early changes in CT and language within ASD, with findings suggesting CT gains in language regions as a marker of compensatory processes supporting development of expressive communication within ASD. Exploration of this hypothesis using multimodal imaging data and finer-grained behavioral assessment may identify opportunities for targeted intervention to optimize earlier developmental trajectories in ASD. A critical component of this effort will be testing whether findings in idiopathic ASD cohorts like the current sample generalize to the growing number of genetically-defined ASD subgroups [Geschwind and State, 2015].

CONCLUSIONS

Study findings suggest that differences in cortical thickness between children with ASD and TDC change with age. This provides an important framework when considering cross-sectional differences between ASD and controls, and suggests that differences over time rather than static differences may serve as a more consistent neuroanatomical marker in ASD. These findings also suggest that within ASD, changes in brain anatomy are related to changes in expressive communication over time. Whether this relationship reflects compensatory processes or delayed maturation of brain regions related to skill development will be an essential next step for the field.

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