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Longitudinal changes in cortical thickness in autism and typical development

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The natural history of brain growth in autism spectrum disorders remains unclear. Cross-sectional studies have identified regional abnormalities in brain volume and cortical thickness in autism, although substantial discrepancies have been reported. Preliminary longitudinal studies using two time points and small samples have identified specific regional differences in cortical thickness in the disorder. To clarify age-related trajectories of cortical development, we examined longitudinal changes in cortical thickness within a large mixed cross-sectional and longitudinal sample of autistic subjects and age- and gender-matched typically developing controls. Three hundred and forty-five magnetic resonance imaging scans were examined from 97 males with autism (mean age = 16.8 years; range 3–36 years) and 60 males with typical development (mean age = 18 years; range 4–39 years), with an average interscan interval of 2.6 years. FreeSurfer image analysis software was used to parcellate the cortex into 34 regions of interest per hemisphere and to calculate mean cortical thickness for each region. Longitudinal linear mixed effects models were used to further characterize these findings and identify regions with between-group differences in longitudinal age-related trajectories. Using mean age at time of first scan as a reference (15 years), differences were observed in bilateral inferior frontal gyrus, pars opercularis and pars triangularis, right caudal middle frontal and left rostral middle frontal regions, and left frontal pole. However, group differences in cortical thickness varied by developmental stage, and were influenced by IQ. Differences in age-related trajectories emerged in bilateral parietal and occipital regions (postcentral gyrus, cuneus, lingual gyrus, pericalcarine cortex), left frontal regions (pars opercularis, rostral middle frontal and frontal pole), left

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supramarginal gyrus, and right transverse temporal gyrus, superior parietal lobule, and paracentral, lateral orbitofrontal, and lateral occipital regions. We suggest that abnormal cortical development in autism spectrum disorders undergoes three distinct phases: accelerated expansion in early childhood, accelerated thinning in later childhood and adolescence, and decelerated thinning in early adulthood. Moreover, cortical thickness abnormalities in autism spectrum disorders are region-specific, vary with age, and may remain dynamic well into adulthood.

Keywords: autism; brain development; developmental neuroimaging; human brain mapping; MRI

Abbreviations: ADOS = Autism Diagnostic Observation Schedule; ASD = autism spectrum disorder

Introduction

The relationship between brain structure and the autistic phenotype has been an active area of research for nearly three decades. Early studies of total brain volume in young children at the time of autism spectrum disorder (ASD) diagnosis, in combination with retrospective head circumference data, have established that the rate of head and brain growth is abnormally rapid during the first few years of life in some but not all children with autism (Lainhart *et al.*, 1997; Courchesne *et al.*, 2003; Lainhart, 2003; Hazlett *et al.*, 2005). A robust early literature based largely on cross-sectional studies characterized gross morphological features and growth trends of autistic brains, and detailed differential compartmental volumes of white matter, grey matter, and total brain volume. For example, most children with ASD are normocephalic at birth, and 15–20% will develop macrocephaly during the first years of life (Lainhart *et al.*, 2006). Autistic children between 2–4 years old have increased total cerebral grey matter and white matter (Courchesne *et al.*, 2001; Schumann *et al.*, 2010; Hazlett *et al.*, 2011), and the most consistent findings related to compartmental volumes in early autism are increased mean frontal and temporal lobe grey and white matter volumes (Carper *et al.*, 2002; Schumann *et al.*, 2010; Hazlett *et al.*, 2011). The parietal lobe is less consistently affected, whereas the occipital lobe is usually spared (Carper *et al.*, 2002; Hazlett *et al.*, 2011). From ~2 years of age, the autism brain on average enters a phase of plateaued growth. When viewed against the backdrop of persistent growth in normal children, this phase can be interpreted as a relative decline in the growth rate to below normal. Around mid-childhood (5–10 years of age), the average autism brain is no longer much larger than normal controls (Herbert *et al.*, 2003; Kates *et al.*, 2004). Both white matter and grey matter exhibit markedly slowed rates of growth during this stage (Courchesne *et al.*, 2001). By late childhood, adolescence, or young adulthood, depending on the study, mean brain volumes in autism and normal control samples do not differ, even though mean head circumference and rates of macrocephaly remain increased in the autism groups (Lainhart *et al.*, 1997; Courchesne *et al.*, 2001; Hardan *et al.*, 2001; Aylward *et al.*, 2002). In contrast with typical development, however, adolescence and young adulthood in autism are often periods when cognitive and behavioural functioning plateaus or deteriorates. Individuals with autism who do not decline during adolescence and young adulthood for the most part remain significantly impaired. Thus, the brain changes associated with 'normalization' of brain volume in autism are likely inherently pathological or a complex mixture of pathology, compensatory mechanisms, relatively normal processes, and silent sculpting of the brain by the often atypical life experiences of individuals with autism. These reports suggest that the trajectory of early brain overgrowth, followed by plateau and later decline, is a consistent trend in the disorder (Courchesne *et al.*, 2004, 2011). However, most studies to date are cross-sectional rather than longitudinal, and these trends remain to be clarified with individual brain development data and particularly in later childhood. Furthermore, specific regional abnormalities beyond gross morphological changes remain understudied.

Recent advances in MRI technology, statistical methodology, and analytical techniques have added new insights to these early findings related to relative contributions of regional brain volumes, thickness of the cortical mantle, cortical gyrification and surface area, and morphology of subcortical structures. Significant discrepancies in the literature suggest that brain regions demonstrating macroscopic structural abnormalities in autism may be different at different ages, and undergo differential rates of growth and decline, giving rise to independent trajectories of abnormalities over time. Further, affected brain substrates may vary by severity, IQ, gender and developmental stage. For example, in a preliminary analysis based on two scan time points, Hardan *et al.* (2009) described changes in thickness and volume between subjects aged 8–12 years at baseline, who were subsequently rescanned ~2 years later. The ASD group had accelerated decreases in grey matter volume and cortical thickness in the temporal and occipital lobe, and decreases in occipital cortical thickness were most robust. Greater thinning was associated with greater symptom severity on social scales (frontal) and motor stereotypies (temporal regions). Notably, subjects were not matched on IQ, and intergroup differences did not withstand correction for IQ. A second preliminary longitudinal study of 13 boys with autism and seven typically developing boys scanned 3 years apart found robust whole brain white matter growth in the typically developing boys but slowed growth in the boys with autism in bilateral temporal, and left parietal and occipital lobes (Hua *et al.*, 2013).

Cortical thickness analyses provide a method of interrogating brain regional structure at high spatial resolution. Two basic types of cortical thickness abnormalities are described most commonly in the literature. The first is a difference in cortical thickness at any age, i.e. either thicker or thinner in ASD (Chung *et al.*, 2005; Hadjikhani *et al.*, 2006; Hardan *et al.*, 2006; Dziobek *et al.*, 2010; Hyde *et al.*, 2010; Wallace *et al.*, 2010; Scheel

et al., 2011; Misaki *et al.*, 2012). The second is a difference in age-related change in cortical thickness, represented by age × diagnosis interactions (Chung *et al.*, 2005; Hardan *et al.*, 2009; Raznahan *et al.*, 2010; Wallace *et al.*, 2010; Scheel *et al.*, 2011; Mak-Fan *et al.*, 2012; Misaki *et al.*, 2012). However, age-related changes in cortical thickness in ASD are predominantly drawn from cross-sectional data, which can only infer developmental trends from changes across individuals (Kraemer *et al.*, 2000). Longitudinal studies with multiple time points and larger sample sizes are necessary to disentangle these characteristics, to clarify reported developmental trajectories, and ultimately to determine whether distinct early developmental trajectories can predict autistic phenotypic features later in life. Here we report the first large-sample multi-time point longitudinal assessment of cortical thickness in autism.

Materials and methods

Subjects

Participants included 97 male individuals with ASD and 60 typically developing male control subjects aged 3–39 years at the date of scan (ASD mean 16.8, range 3–36 years; control mean 18.0, range 3–39 years; overall mean 15.07 years at enrolment). A total of 345 scans were included in the analysis following an accelerated longitudinal design. Three scans were available on 48 ASD and 24 typically developing control subjects, two scans on 27 ASD and 17 typically developing control subjects, and one scan on 22 ASD and 19 typically developing control subjects (Fig. 1). For subjects with a single time point, follow-up data are currently unavailable for a variety of reasons, including technical (e.g. orthodontic braces), educational (e.g. out-of-state college), and social (e.g. long-term family or community obligations). For participants with multiple scans, the average interscan interval was 2.6 years. Participants were unrelated, and were recruited and scanned at the University of Utah as part of a longitudinal imaging study of brain development in autism and typical development. Extensive 'rehearsal' procedures, including mock scanning, were used to optimize data yield. Young participants with ASD were offered sedation if needed to improve MRI data quality, and 49 scans (of 345) were acquired under standard sedation administered and monitored by an on-site faculty anaesthesiologist. Further details regarding study design, community-sample recruitment, and consent and enrolment procedures have been previously published (Alexander *et al.*, 2007; Prigge *et al.*, 2013). Autism diagnosis was based on the Autism Diagnostic Observation Schedule-Generic (ADOS-G; Lord *et al.*, 2000), Autism Diagnostic Interview-Revised (ADI-R; Lord *et al.*, 1994), DSM-IV (American Psychiatric Association, 1994), and ICD-10 criteria. Seventy-eight per cent of the autism sample met full criteria for autism (clinical phenotype plus formal ADOS and ADI-R criteria), 14% met criteria for pervasive developmental disorder not otherwise specified (PDD-NOS) (clinical phenotype plus PDD-NOS ADOS criteria and narrowly missing autism ADI-R criteria), and 8% met criteria for broad autism spectrum disorder (clinical phenotype plus meeting autism criteria on ADOS total or two ADI-R subdomains) as defined by Lainhart *et al.* (2006). Participants with ASD were excluded if medical causes of autism were implicated from participant history, Fragile-X gene testing, karyotype and observation. Control participants also received the ADOS-G (Lord *et al.*, 2000) and standardized psychiatric assessments. Participants with history of medical conditions that could affect brain development or morphometry were excluded (severe head injury, neonatal hypoxia-ischaemia, seizures). Psychiatric comorbidity was assessed in all subjects using the Autism Comorbidity Interview (Leyfer *et al.*, 2006) and diagnosis-specific questionnaires. Although there is some degree of symptomatic overlap with autism diagnosis, 50.7% of our ASD sample had features of psychiatric comorbidity (obsessive-compulsive disorder 36%, ADHD 25%, depression 12%, anxiety 7%, multiple/other 20%). Thirty-eight per cent of our subjects with ASD were taking psychotropic medications (40% stimulants, 17% selective serotonin reuptake inhibitors, 10% antipsychotics, 5% antidepressants, 1% anxiolytics, 27% multiple/other). Neurological or psychiatric comorbidity and psychotropic medication use were exclusion criteria for the control group.

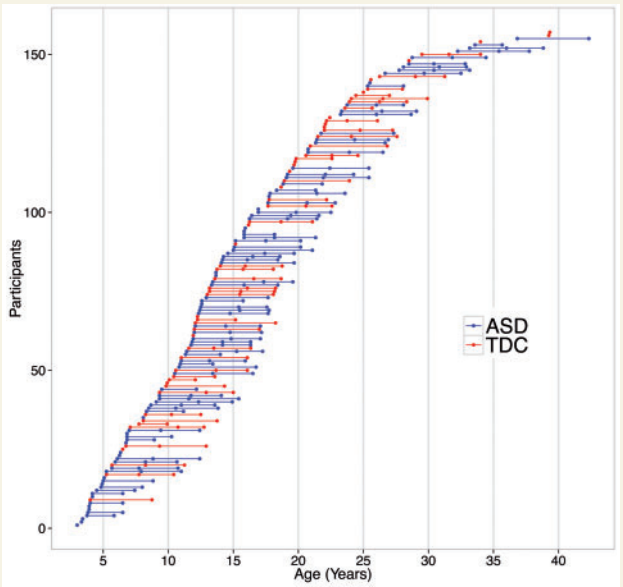

Figure 1 Participant age at scan. Each dot represents a participant scan. Each line represents a participant with repeated scans. ASD = blue; typically developing control (TDC) subjects = red.

From this data set, four scans were excluded due to motion, and four scans failed automated FreeSurfer segmentation. Both right and left handed individuals were included, with a non-significant tendency toward less right handedness in ASD (Edinburgh Handedness Score (Oldfield, 1971): ASD = 59, range −100 to 100; typically developing control subjects = 72, range −80 to +100; group comparison: $t = 1.8$, $P = 0.07$).

Intelligence quotient

At the initial study visit, IQ was assessed using the Differential Abilities Scale (Elliott, 1990), Wechsler Intelligence Scales for Children- Third Edition (Wechsler, 1991), or Wechsler Adult Intelligence Scale - Third Edition (Wechsler, 1997), providing indices of verbal, non-verbal and full-scale IQ. Of 97 children with ASD, 15 had full-scale IQ < 70. These data are representative of a community sample of ASD.

Imaging protocol

Magnetic resonance images were acquired on a Siemens Trio 3.0 T scanner. At time point 1, an 8-channel, receive-only RF head coil was used to acquire sagittal 3D MPRAGE T_1-weighted images (inversion time = 1100 ms, echo time = 2.93 ms, repetition time = 1800 ms, flip angle = 12°, field of view = 56 mm, slice thickness = 1.0 mm, 160 slices). At time points 2 and 3, a 12-channel, receive-only RF head coil was used to acquire 3D MPRAGE T_1-weighted images (inversion time = 900 ms, echo time = 2.91 ms, repetition time = 2300 ms, flip angle = 9°, field of view = 256 mm, slice thickness = 1.2 mm, 160 slices). Because of an MRI headcoil upgrade between time points 1 and 2, a 'time point' covariate was included in our analyses. Changes in magnetic resonance sequence parameters were co-incident with headcoil upgrade and are captured by the 'time point' covariate.

Cortical thickness estimation

All MRI scans were processed on the same workstation using FreeSurfer image analysis suite v5.1.0 (http://surfer.nmr.mgh.harvard.edu/). Technical details are described previously (Fischl and Dale, 2000; Fischl *et al.*, 2002, 2004). To extract reliable volume and thickness estimates, images were automatically processed within a customized analysis stream adapted from the standard longitudinal pipeline included in FreeSurfer (Reuter *et al.*, 2012). Specifically, a sample-specific group average template was created using robust, inverse consistent registration (Reuter *et al.*, 2010). Several processing steps, including skull stripping, spatial transforms, atlas registration, spherical surface maps, and atlas-based regional parcellations were then initialized with common information from the within-subject template, to substantially improve reliability and statistical power (Reuter *et al.*, 2012). Automated cortical parcellation and region of interest definition was performed using the Desikan-Killiany Atlas (Desikan *et al.*, 2006), resulting in mean cortical thickness estimations calculated from all vertices within 34 cortical parcellations per hemisphere. Average lobar cortical thickness values were also calculated.

Statistical analyses

To determine longitudinal age-related changes in cortical thickness, we used linear mixed-effects models to examine cortical thickness as a function of diagnostic group and age at scan. This study was designed to describe longitudinal cortical thickness growth in ASD, and the ASD group was thus the reference group for all analyses. The following covariates were also examined: age^2, group × age, group × age^2, time point, group × time point. Group differences were first examined with age centred at Time 1 mean age (15 years). The lowest Akaike Information Criterion (AIC; Akaike, 1974) determined the best-fitting model for each region. False discovery rate (FDR; Benjamini and Hochberg, 1995) correction for multiple-comparisons testing was applied. Mean group differences were also examined with age re-centred in childhood (7 years) and adulthood (23 years). Because of the IQ differences between our ASD and typically developing control subject groups, analyses were rerun with full-scale IQ, group × full-scale IQ and group × age × full-scale IQ as covariates. Between-group differences in intelligence measures, handedness, and interscan interval were examined using *t*-tests. R version 3.0.1 (R Core Team, 2013; URL http://www.R-project.org/) and RStudio (Rstudio, 2012; URL http://www.rstudio.org/) were used for the analysis and R package FindMinIC (Lange *et al.*, 2013, http://CRAN.R-project.org/package=FindMinIC) for mixed-effects model selection.

Results

Subject characteristics

Participants with ASD and typically developing control subjects did not differ in mean age or interscan interval. There was a significant group difference in all IQ measures, with lower IQ in the ASD group ($P < 0.001$; Table 1).

Longitudinal changes and mean differences in cortical thickness

In both groups, age-related cortical thinning was found across the entire cortex. Table 2 displays the mixed effects model estimates for each region of interest with the ASD group as the reference group and differences from typically developing control subjects described by the group effect and interactions. Figure 2 displays age-related changes by lobe. Regions of interest with significant group differences in age-related changes are displayed in Fig. 3. Regions of non-significant group differences in age-related changes are displayed by lobe in Supplementary Figs 1–4.

Table 1 Demographics

	ASD, *n* = 97		TDC, *n* = 60		Group comparison	
	Mean (SD)	Range	Mean (SD)	Range	*t*	*P*
Age (years)	16.8 (8)	3.0–42.3	18.0 (7.4)	4.0–39.3	1.39	0.164
Interscan interval (years)	2.85 (0.8)	1.9–6.0	2.88 (1.0)	1.5–6.1	0.25	0.801
Performance IQ[a]	96.97 (18)	50–133	115.3 (16)	88–155	6.25	<0.001
Verbal IQ[b]	96.05 (23)	51–145	114.9 (14)	89–151	6.06	<0.001
Full-scale IQ[c]	94.34 (22)	49–137	117.8 (15)	89–153	7.77	<0.001
ADOS communication	4.9 (1.5)	1–8	0.4 (0.6)	0–2	25.6	<0.001
ADOS social	9.4 (2.5)	4–14	0.6 (0.9)	0–4	30.3	<0.001
ADOS total	14.5 (3.6)	6–22	1.0 (1.3)	0–5	32.4	<0.001

[a]Performance IQ: ASD *n* = 91, typically developing controls *n* = 59.
[b]Verbal IQ: ASD *n* = 85, typically developing controls *n* = 59.
[c]Full-scale IQ: ASD *n* = 96, typically developing controls *n* = 60.
TDC = Typically developing controls.

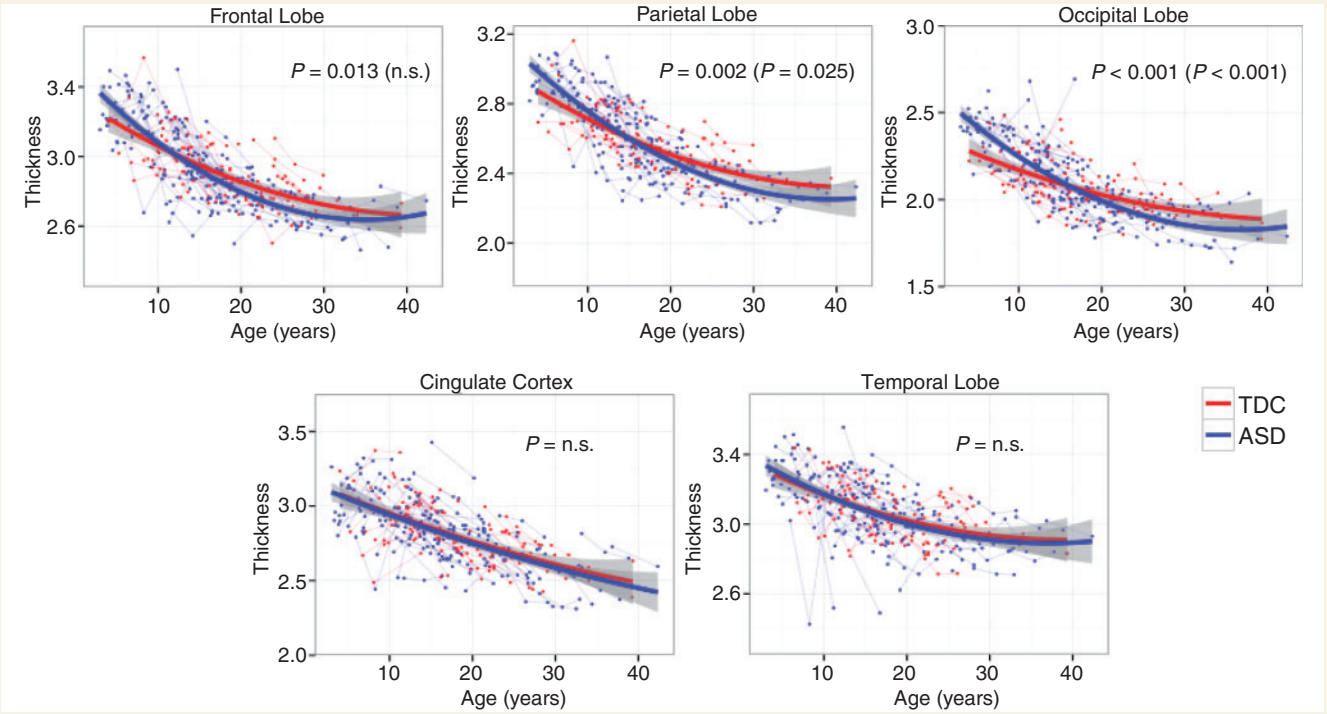

Figure 2 Lobar cortical thickness trajectories. Longitudinal cortical thickness trajectories in frontal, temporal, parietal, and occipital lobes and cingulate cortex. Age by group interactions reveal increased cortical thinning in ASD in frontal, parietal, and occipital lobes centred at age 15 years. *P*-values are before (and after) controlling for full-scale IQ. Each scan is represented by a dot and repeated scans are connected by lines. ASD = blue; typically developing control (TDC) subjects = red; n.s. = not significant.

Frontal lobe

Increased cortical thinning in ASD was found in the total average frontal lobe and both frontal hemispheres (group by age interactions: left $P = 0.014$, right $P = 0.021$, total $P = 0.013$; Fig. 2). After controlling for full-scale IQ, only the left frontal lobe demonstrated increased cortical thinning in ASD (data not shown). Average frontal lobe thickness was decreased in ASD and was significantly thinner by adulthood ($P = 0.009$; Table 3).

Region of interest analyses both with and without controlling for full-scale IQ revealed significant group × age interactions, indicating increased age-related cortical thinning in ASD compared to typically developing control subjects, in right paracentral cortex and left pars opercularis, rostral middle frontal gyrus and frontal pole (Fig. 3). Before controlling for multiple comparisons, the left pars orbitalis and left pars triangularis were also significant. Increased cortical thinning in ASD was also found in the left precentral gyrus while controlling for full-scale IQ ($P = 0.027$) but did not survive correction for multiple comparisons (Supplementary Fig. 1). Reduced thickness during childhood and adolescence was found in the left pars opercularis, rostral middle frontal cortex and frontal pole, whereas in adulthood, thinner cortex was found only in the right paracentral cortex (Table 3). Bilateral pars triangularis (adolescence and adulthood) and right pars opercularis (adulthood) were thinner in ASD, but did not show significant group × age interactions. Reduced thickness in bilateral caudal middle frontal and precentral gyrus regions of interest was found in ASD only after controlling for full-scale IQ.

Temporal lobe

No group differences in average thickness or age-related changes were found in the total temporal lobe or either temporal hemisphere even after controlling for full-scale IQ (Fig. 2). Region of interest analysis showed increased age-related cortical thinning, and decreased overall thickness in adulthood in the right transverse temporal gyrus in ASD (Fig. 3 and Tables 2 and 3). Transverse temporal gyrus was also thicker in ASD in childhood, although this did not survive full-scale IQ correction. In ASD, the left temporal pole was thicker during childhood and adulthood, and the right temporal pole thinner in childhood, after controlling for full-scale IQ.

Parietal lobe

Lobar analysis revealed increased age-related cortical thinning in ASD in the average left, right and total parietal lobe (group × age interactions: left $P = 0.002$, right $P = 0.004$, total $P = 0.002$; controlling for full-scale IQ: left $P = 0.032$, right $P = 0.012$, total $P = 0.025$; Fig. 2). Controlling for full-scale IQ, average parietal thickness in ASD was significantly lower than typically developing control subjects in adulthood ($P = 0.009$; Table 3). Increased age-related cortical thinning in ASD was found bilaterally in the postcentral gyrus, inferior and superior parietal lobules, left supramarginal gyrus, and right precuneus (Table 2). After controlling for full-scale IQ, bilateral postcentral, left supramarginal and right superior parietal regions remained significant (Fig. 3 and Table 2).

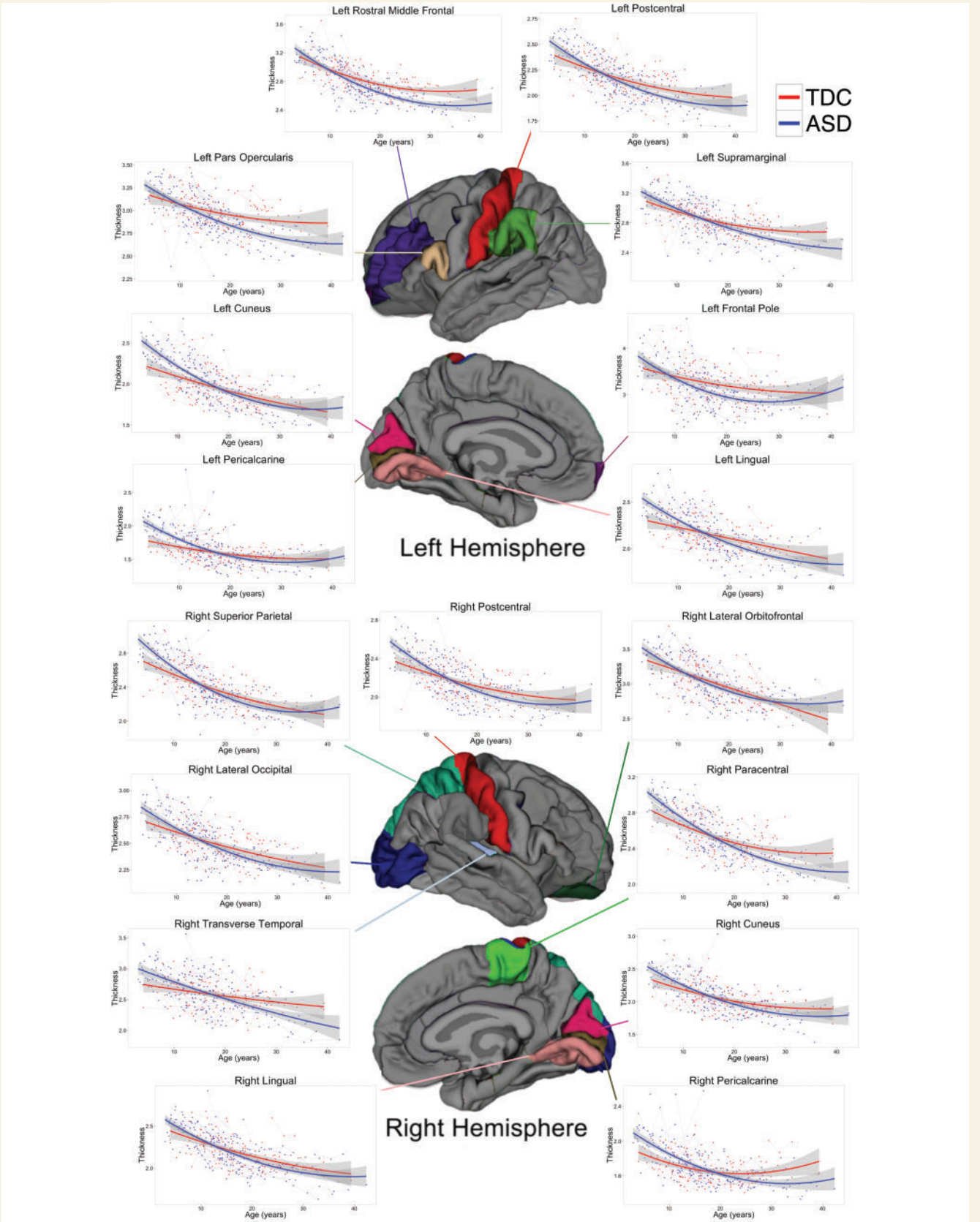

Figure 3 Abnormal age-related cortical thickness trajectories in ASD. Coloured brain regions identify significant group differences in age-related cortical thickness changes. Each scan is represented by a dot and repeated scans are connected by lines. Regions depicted were significant both before and after controlling for full-scale IQ at $P < 0.05$ (FDR). ASD = blue; typically developing control (TDC) subjects = red.

Also controlling for full-scale IQ, decreased thickness in adulthood was found in the bilateral inferior parietal, right postcentral, and left lateralized superior parietal and supramarginal gyrus (Table 3). Right superior parietal thickness was increased in childhood only.

Occipital lobe

Total occipital lobe and each occipital hemisphere showed increased cortical thinning in ASD, both with and without controlling for full-scale IQ (group × age interaction $P < 0.001$; Fig. 2). In the total average occipital lobe, increased thickness in ASD was found during childhood ($P < 0.001$, controlling for full-scale IQ $P = 0.032$), but no group differences remained by adolescence (Table 3).

All occipital regions showed greater age-related cortical thinning in ASD and all remained significant after controlling for full-scale IQ except for left lateral occipital gyrus (Fig. 3 and Table 2). This was associated with thicker cortex during childhood in ASD in bilateral cuneus and right pericalcarine (Table 3). The left lingual gyrus was thicker during childhood and the right lingual gyrus thinner by adulthood.

Cingulate and insula

No group differences in average thickness or age-related changes of the total cingulate, subregional cingulate, or insula were observed between ASD and typically developing control subjects (Fig. 2 and Tables 2 and 3, and Supplementary Fig. 4).

Discussion

We report here longitudinal neurodevelopmental trends of cortical thickness in ASD and compare those to a typically developing sample. Our study clarifies preliminary reports of structural brain development in ASD by establishing age-based thickness trajectories of individual subjects. In addition, we used a higher resolution parcellation scheme than most previous studies, enabling sub-lobar and regional structural assessment. Moreover, we used a whole-brain approach in contrast with previous studies limiting analysis to one or a small number of regions of *a priori* interest. Our findings contribute improved temporal and spatial resolution of cortical developmental trends in ASD, and are largely consistent with previous work.

Although our data do not represent subjects younger than 3 years, we evidenced accelerated cortical thinning predominantly in frontal, parietal and occipital regions in early childhood. This is consistent with previous findings describing macrocephaly and volumetric overgrowth in very young children, with a trend toward pseudonormalization beyond the age of 4 years (Courchesne *et al.*, 2001, 2004, 2011; Hardan *et al.*, 2001; Schumann *et al.*, 2010; Hazlett *et al.*, 2011). Further, our data reveal accelerated cortical thinning in autism throughout mid-childhood, reflecting pseudonormalization of thickness between the ages of 8–18 years, depending on brain region. It is important to note, however, that thickness pseudonormalization may not reflect broader structural or functional pseudonormalization. Our main findings of reduced cortical thickness and atypical cortical thinning agree with previous studies of ASD (Hadjikhani *et al.*, 2006; Hyde *et al.*, 2010; Jiao *et al.*, 2010; Scheel *et al.*, 2011; Mak-Fan *et al.*, 2012; Ecker *et al.*, 2013). By re-centring our models at age 7 and 23, we demonstrate regions of increased cortical thickness in childhood and decreased cortical thickness in adulthood, supporting previous cross-sectional studies (Mak-Fan *et al.*, 2012).

Our findings of thinner cortex by adolescence in predominantly frontal regions suggest that pseudonormalization occurs earlier in these areas, whereas posterior regions demonstrate a more protracted decline. This finding is supported by Courchesne *et al*. (2011), who investigated brain volume in 259 autistic subjects aged 2–50 years and 327 controls. Their mixed cross-sectional and longitudinal data provide additional evidence that autistic total brain volume is already enlarged versus controls at the age of 2–3 years, plateaus in later childhood reaching an inflection point around age 8–9 years (though somewhat earlier for females), and shows persistent decline beyond early adulthood. Part of their data set included scans from Schumann *et al*. (2010) who performed a mixed cross-sectional and longitudinal volumetric study in autistic children between 2–5 years of age and normal controls. They determined in a relatively robust sample size that autistic children between the ages of 2 and 3.5 years (mean 32 months) had larger total brain (7%), white matter (10%), and grey matter (5%) volumes versus controls (mean 30 months, range 1.6 to 3.5 years). Frontal (6%) and temporal (9%) grey matter volumes were also larger. Mixed-effect regression models revealed that all regions except occipital cortex showed increases of volume, or growth trajectory, or both, in autism. Temporal, frontal, and cingulate cortex showed the greatest increases in grey matter volume and growth trajectory. These results and ours converge to suggest that the trajectory of early brain overgrowth, followed by accelerated decline, is a consistent trend in the disorder both in terms of regional volume (Courchesne *et al.*, 2004, 2011) and thickness of the cortical mantle.

Our data suggest that regional cortical thickness is already greater in ASD than typically developing control subjects at age 3–4 years, consistent with this concept. Lack of data below this age could have biased our model fit, leading to spuriously steep slopes at our young age extreme. However, no differences in cortical thickness have been found in very young children with ASD (Hazlett *et al.*, 2011), whereas differences have been observed in older children. Several excellent cross-sectional studies show trends between older childhood and adulthood in cortical thickness in ASD, although results are somewhat inconsistent. Raznahan *et al*. (2010) studied a wide age range of individuals with autism and control subjects (age 10–60 years) to clarify differential contributions to structural changes in thickness, volume, and surface area. They report age by diagnosis interactions of volume and thickness (but not surface area) in fusiform and middle temporal gyrus. In these regions, there was an age-related decrease in volume and thickness in typically developing control subjects, but not in ASD, likely reflecting their extended age range. Using a parallel 'shotgun' approach analysing multiple brain surface points, widespread (but focal) age × group interactions were found in temporal, parietal, and frontal cortices, reflecting decreased volume and thickness in ASD subjects that remained

Table 2 Cortical thickness variation with age and diagnosis

Frontal lobe		**Intercept[a]**	**Effect**	**Age**	**Age^2**	**Group × Age**	**Group × Age^2**
Caudal middle frontal	L	2.914	0.0347	−**0.0214*****	**0.0004*****	0.0043	–
	R	2.914	**0.0417**	−**0.0239*****	**0.0005*****	–	–
Lateral orbitofrontal	L	3.002	0.0414	−**0.0299*****	**0.0008*****	0.0059	−0.0006
	R	3.037	0.0346	−**0.0309*****	**0.0006****	0.0074	−**0.0008***
Medial orbitofrontal	L	2.816	−0.0066	−**0.0286*****	**0.0006*****	–	–
	R	2.834	−0.0249	−**0.0360*****	**0.0006****	–	–
Paracentral	L	2.559	−0.0055	−**0.0324*****	**0.0007*****	0.0052	–
	R	2.577	−0.0113	−**0.0321*****	**0.0006*****	**0.0106*****	–
Pars opercularis	L	2.937	**0.0787***	−**0.0234*****	**0.0005****	**0.0124****	−0.0004
	R	2.976	**0.0540**	−**0.0234*****	0.0003$^+$	0.0072$^+$	–
Pars orbitalis	L	3.180	0.0288	−**0.0306*****	**0.0009*****	0.0136$^+$	−0.0008$^+$
	R	3.242	0.0203	−**0.0310*****	**0.0009*****	–	–
Pars triangularis	L	2.827	**0.0834***	−**0.0281*****	**0.0006*****	0.0082$^+$	–
	R	2.883	**0.1198****	−**0.0251*****	**0.0007*****	0.0054	−0.0006
Precentral	L	2.662	0.0032	−**0.0193*****	**0.0004*****	0.0048	–
	R	2.667	0.0041	−**0.0189*****	**0.0003****	0.0045	–
Rostral middle frontal	L	2.782	**0.0609**$^+$	−**0.0309*****	**0.0007*****	**0.0080****	–
	R	2.800	0.0327	−**0.0315*****	**0.0008*****	0.0048	–
Superior frontal	L	3.191	−0.0048	−**0.0233*****	0.0002$^+$	–	–
	R	3.172	0.0351	−**0.0256*****	**0.0004****	–	–
Frontal pole	L	3.123	**0.1699***	−**0.0410*****	**0.0014*****	**0.0234****	−**0.0014***
	R	3.207	−0.0803	−**0.0299*****	**0.0008****	–	–
Temporal lobe		Intercept[a]	Group	Age	Age^2	Group*Age	Group*Age^2
Bank superior sulcus	L	2.890	0.0308	−**0.0188*****	0.0004**	–	–
	R	2.783	−0.0066	−**0.0199*****	**0.0003**$^+$	0.0066	–
Entorhinal	L	3.369	−0.0166	−0.0112**	0.0004	–	–
	R	3.466	−0.0009	−**0.0149****	0.0007*	–	–
Fusiform	L	2.900	−0.0109	−**0.0178*****	**0.0005*****	–	–
	R	2.871	0.0111	−**0.0186*****	**0.0005*****	–	–
Inferior temporal	L	3.142	−0.0023	−**0.0160*****	0.0003$^+$	–	–
	R	3.194	0.0264	−**0.0221*****	**0.0005*****	–	–
Middle temporal	L	3.196	−0.0093	−**0.0126*****	–	0.0064	–
	R	3.296	0.0210	−**0.0167*****	0.0003$^+$	–	–
Parahippocampal	L	2.809	0.0831	−**0.0091****	–	–	–
	R	2.631	0.0697	−0.0088**	–	–	–
Superior temporal	L	3.071	−0.0048	−**0.0140*****	–	–	–
	R	3.121	0.0292	−**0.0160*****	0.0002	–	–
Temporal pole	L	3.675	−0.0931	−**0.0208*****	**0.0012*****	0.0063	−0.0009
	R	3.740	0.0350	−0.0169***	0.0009**	0.0119	−0.0012*
Transverse temporal	L	2.594	−0.0232	−**0.0238*****	0.0004*	–	–
	R	2.635	−0.0305	−**0.0286*****	**0.0005****	**0.0121****	–
Parietal lobe		Intercept[a]	Group	Age	Age^2	Group*Age	Group*Age^2
Inferior parietal	L	2.836	0.0199	−**0.0342*****	**0.0007*****	0.0107**	−0.0004
	R	2.850	0.0388	−**0.0305*****	**0.0007*****	0.0103**	−0.0005$^+$
Postcentral	L	2.173	0.0275	−**0.0229*****	**0.0005*****	**0.0098****	−0.0004$^+$
	R	2.168	0.0134	−**0.0254*****	**0.0007*****	**0.0118*****	−0.0006*
Precuneus	L	2.657	0.0080	−**0.0283*****	**0.0005*****	–	–
	R	2.648	−0.0133	−**0.0271*****	**0.0003****	0.0058$^+$	–
Superior parietal	L	2.438	0.0084	−**0.0331*****	**0.0009*****	0.0116**	−0.0006*
	R	2.432	0.0054	−**0.0345*****	**0.0010*****	**0.0126****	−**0.0007***
Supramarginal	L	2.853	0.0158	−**0.0250*****	**0.0004*****	**0.0073***	–
	R	2.913	0.0039	−**0.0226*****	**0.0003****	–	–

(continued)

Table 2 Continued

Occipital lobe		Intercept[a]	Group	Age	Age^2	Group*Age	Group*Age^2
Cuneus	L	2.036	−0.0424	**−0.0321*****	**0.0007*****	**0.0131****	−0.0005
	R	2.089	−0.0011	**−0.0289*****	**0.0007*****	**0.0119****	−0.0004
Lateral occipital	L	2.435	−0.0191	**−0.0214*****	**0.0003****	0.0059*	–
	R	2.510	0.0189	**−0.0227*****	**0.0005*****	**0.0085****	−0.0004$^+$
Lingual	L	2.162	0.0082	**−0.0248*****	**0.0005*****	**0.0115*****	−0.0005$^+$
	R	2.207	0.0249	**−0.0251*****	**0.0005*****	**0.0094****	−0.0005$^+$
Pericalcarine	L	1.668	−0.0406	**−0.0243*****	**0.0007*****	**0.0120****	−0.0004
	R	1.731	−0.0567*	**−0.0228*****	**0.0006*****	**0.0116*****	–
Other		Intercept[a]	Group	Age	Age^2	Group*Age	Group*Age^2
Insula	L	3.369	0.0416	**−0.0173*****	–	–	–
	R	3.409	0.0316	**−0.0179*****	–	–	–
Rostral anterior cingulate	L	3.069	0.0078	**−0.0230*****	–	–	–
	R	3.280	−0.0439	**−0.0224*****	–	–	–
Caudal anterior cingulate	L	2.711	0.0601	**−0.0198*****	–	–	–
	R	2.804	0.0099	**−0.0218*****	–	–	–
Isthmus cingulate	L	2.789	0.0156	**−0.0126*****	−0.0002	–	–
	R	2.698	0.0218	**−0.0084****	**−0.0004****	–	–
Posterior cingulate	L	2.761	−0.0070	**−0.0165*****	–	–	–
	R	2.770	−0.0255	**−0.0187*****	–	0.0051	–

[a]All Intercepts significant at $P < 0.001$ (FDR).

***$P < 0.001$ FDR; **$P < 0.01$ FDR; *$P < 0.05$ FDR; $^+P < 0.05$ uncorrected (did not survive FDR correction).

Bold indicates significant effects ($P < 0.05$ FDR) after controlling for FSIQ.

Estimates from best-fitting mixed-effects models of cortical thickness changes in autism. The autism group is the reference group, with age centred at 15 years. Age-related changes in the ASD group are described in the Age and Age^2 effects. The group effect and group × age interaction terms describe how the typically developing control group differs relative to ASD.

stable through adulthood but continued to normally decline in control subjects. This led to a tendency toward no difference from controls (or at times increased thickness) in older adults with ASD. Focusing on adolescence and young adulthood (mean age 17 years), Wallace *et al*. (2010) found thinner cortex overall in ASD as well as age-related changes in thickness in ASD but not in typically developing control subjects in a small number of regions, with thinner cortex in older (17–24 years) compared to younger (12–17 years) subjects with ASD. In a study of young adults, Ecker *et al*. (2013) found decreased thickness in the anterior temporal lobe and increased thickness in left lateral prefrontal cortex in ASD relative to typically developing control subjects. Apparent lack of consistency between age-related results in these cross-sectional studies underscores the importance of examining longitudinal changes of cortical thickness within individuals, rather than age-related changes across individuals, to determine case-control differences in developmental trajectories. Our results suggest dynamic rates of change in cortical thickness during each of these age ranges, providing a plausible resolution to the above discrepancies. Moreover, our data are consistent with decelerated thinning in older ASD subjects relative to typically developing control subjects in some regions (e.g. bilateral lingual gyrus and right lateral orbitofrontal cortex), but not in others (e.g. left pars opercularis and right transverse temporal gyrus), further underscoring regional specificity of longitudinal age-related trajectories.

We compare reports from very young and older individuals with ASD with caution, as the respective study samples differ from ours in several important ways in addition to the stage of brain development. Hazlett *et al*. (2011) studied a very young ASD sample that included mostly boys (86%) but also examined girls. In contrast, most studies of older individuals focused exclusively on males to decrease heterogeneity. In addition, Hazlett *et al*. (2011) included cognitively high-functioning and low-functioning children with ASD. To date, studies of cortical thickness in older individuals have been limited to cognitively high-functioning individuals with ASD (full-scale IQ $\geqslant$ 70, often average and above-average IQ), once again to decrease heterogeneity in the ASD sample, which may be greater at older than at younger ages. More generally, ASD samples in studies of cortical thickness differ considerably in severity and inclusion/exclusion criteria.

In the context of existing literature, we interpret our findings to support an expanded framework for understanding the dynamic natural history of autistic brain anatomy. The combined results of studies of cortical thickness in individuals with ASD between 2 to 60 years of age suggest dynamic cortical dysmaturation according to three major phases of cortical development. First, the lack of any difference in cortical thickness in very young children with ASD and increased cortical thickness by age 3–4 years suggests that cortical thickness increases at an abnormally rapid rate throughout very early childhood. This first phase may also involve a region-specific lack of normal cortical thinning in early childhood (i.e. lack of thinning in areas that are thinning in typical development). The first major transition in cortical development in ASD appears to occur rather abruptly in early childhood as cortical expansion gives way to region-specific cortical thinning. During the second phase of cortical development in ASD, accelerated thinning (more thinning than typical for age) occurs, resulting in thickness trajectories that pseudonormalize, or begin to merge with those of

Table 3 Group changes in cortical thickness by developmental stage

		Not controlling for full-scale IQ			Controlling for full-scale IQ		
		Childhood	Adolescence	Adulthood	Childhood	Adolescence	Adulthood
Frontal lobe							
Lobar frontal		–	–	−2.9*	–	–	−3.2**
Caudal middle frontal	L	–	–	–	–	−2.3^{+}	−3.9**
	R	–	–	–	−3**	−3.2**	−3.4**
Paracentral	R	3.3*	–	−3.1*	–	–	−3.7**
Pars opercularis	L	–	−2.7*	−5.3***	–	−2.6*	−3.9**
	R	–	–	−4.0**	–	−2.7*	−4.5**
Pars triangularis	L	–	−2.9*	−5.6**	–	−5.0**	−7.6***
	R	–	−4.2**	−4.5*	−3.8**	−4.9**	−4.3**
Precentral	L	–	–	–	–	–	−3.0**
	R	–	–	–	–	–	−3.4**
Rostral middle frontal	L	–	−2.2^{+}	−4.8**	–	−3.8**	−6.4***
	R	–	–	–	−2.2^{+}	−2.4^{+}	−2.6^{+}
Frontal pole	L	–	−5.4*	−9.1**	–	−5.2*	−8.9**
Temporal lobe							
Temporal pole	L	5.1*	–	–	3.5*	–	3.9*
	R	–	–	–	−6.2*	–	–
Transverse temporal	R	4.4*	–	–	–	–	−5.1*
Parietal lobe							
Lobar parietal		2.7*	–	−2.2^{+}	–	–	−2.7**
Inferior parietal	L	2.8^{+}	–	−3.1**	–	–	−3.5**
	R	–	–	−3.4*	–	–	−2.6*
Postcentral	L	3.2^{+}	–	−4**	–	−2.8^{+}	–
	R	4.8**	–	−3.5*	–	–	−4.7**
Superior parietal	L	4.4**	–	–	–	–	−3.4*
	R	5.0**	–	–	4.8**	–	–
Supramarginal	L	–	–	−2.8*	–	–	−2.8*
Occipital lobe							
Lobar occipital		5.4***	–	−2.6^{+}	4.2^{+}	–	–
Cuneus	L	7.6***	–	–	7.6***	–	–
	R	5.2*	–	–	5.1*	–	–
Lateral occipital	L	–	–	−2.3^{+}	4.3^{+}	–	–
	R	–	2.8^{+}	−2.4^{+}	–	–	−2.4^{+}
Lingual	L	4.7**	–	−3.5*	4.3*	–	−3.0^{+}
	R	–	–	−3.4*	–	–	−3.8*
Pericalcarine	L	8.5**	–	–	–	–	–
	R	7.6***	3.3*	–	6.3**	–	–
Other							
Insula	R	–	–	–	−1.4^{+}	−1.5^{+}	−1.6^{+}

Regional differences in group mean cortical thickness during childhood, adolescence, and adulthood. Values are percentage differences in ASD relative to typically developing control subjects. R = right; L = left.
***$P < 0.001$, **$P < 0.01$, *$P < 0.05$ FDR, $^{+}P < 0.05$ uncorrected (did not survive FDR correction).

typically developing control subjects. Our data suggest that pseudonormalization of cortical thickness may follow a spatial progression from frontal to occipital regions between ~8–18 years. By the end of adolescence, cortical thickness in ASD is reduced or no different than typically developing control subjects in all brain regions (Fig. 2). The third phase represents a gradual region-specific deceleration of normal cortical thinning in early adulthood in ASD, which may persist well into middle age. However, this phase of less thinning than typical does not appear to occur in all brain regions.

Two important methodological considerations may be drawn from this work. First, as suggested by Raznahan *et al*. (2010) and others, cortical thickness abnormalities in ASD are region-specific. Studies that use gross anatomic parcellation schemes (e.g. lobar analyses or large-volume averaging) may have insufficient sensitivity to detect critical structural brain changes. Second, cortical dysmaturation in ASD may extend throughout adulthood and in some regions may be progressive.

Hazlett *et al*. (2011) and Winkler *et al*. (2010) argue that cortical thickness may derive from distinct neuro-embryological processes with spatial specificity, and may provide clues to the early cellular or molecular foci of abnormalities. Although the histological determinants of macroscopic cortical thickness remain undetermined, it is intriguing to speculate that brain regions with similar trajectory abnormalities in ASD may share conserved embryologic, genetic, molecular, or cellular, or network

connectivity characteristics. Indeed, pseudonormalization of total brain volume and cortical thickness between early childhood and young adulthood may reflect abnormal underlying cellular/molecular processes, synaptic pruning, and aberrant network consolidation. In typically developing individuals, dynamic changes in circuitry and regional and subregional brain morphometry occur during later childhood, adolescence, and young adulthood despite little change in total brain volume (Caviness *et al.*, 1996; Sowell *et al.*, 2002; Giedd, 2004), setting the stage for mature cognitive functioning. These changes reflect the emergence of consolidated large-scale structural brain networks during this developmental period (Zielinski *et al.*, 2010).

Characterizing autistic subtypes using structural neuroimaging techniques remains a major goal in the field. Two studies of autism-related traits in typically developing individuals identified informative regions at predicting ADOS scores (left pars triangularis, frontal pole, temporal pole, postcentral gyrus; Sato *et al.*, 2013) and Social Responsiveness Scale (SRS) scores (right precentral, left superior parietal; Wallace *et al.*, 2012) that overlap with those that were atypically developing or thinner than typically developing control subjects in our sample. Jiao *et al*. (2010) recognized the wide phenotypic range in ASD, and used both volumetric and thickness-based analyses to construct predictive models in a small number of subjects aged 6–15 years. They describe decreased cortical thickness in ASD within bilateral inferior frontal gyrus (pars triangularis), and left medial orbitofrontal gyrus, parahippocampal gyrus, and frontal pole, and increased thickness in left caudal anterior cingulate and precuneus, largely consistent with our findings. Misaki *et al*. (2012) used a canonical correlation model and concluded that IQ is positively correlated with cortical thickness in orbitofrontal, postcentral, and superior temporal regions in normal adolescents. Further, greater thinning with age was seen in dorsal frontal regions in those with 'superior IQ' (>120), replicating earlier work in normal controls (Shaw *et al.*, 2006). However, neither of these associations were seen in the ASD group. This suggests that the structural correlates of similar IQ scores are altogether different in autism versus normal adolescents.

The relationship of cortical thickness within specific regions of interest to network-level structural architecture is unclear. Previous work in our laboratory used structural covariance of grey matter density to evaluate network-level abnormalities in ASD and typically developing control subjects matched on age and IQ (Zielinski *et al.*, 2012). Despite similar IQ, we determined that the socioemotional salience network is markedly underdeveloped in ASD, whereas default mode network topology is both under-represented frontally and over-represented posteriorly. This default mode network uncoupling may represent a primary abnormality, a compensatory aberration, or both. Notably, ADOS-Social Impairment scores correlated with structural coupling between frontal regions in typically developing control subjects, and posterior regions in ASD. Similarly, the cellular and molecular bases for regional cortical thickening as well as thinning remain unclear. Independent genetic influences for thickness and related measures such as surface area have been reported (Panizzon *et al*., 2009; Winkler *et al*., 2010; Chen *et al*., 2013), but how these influences translate to neural packing density, dendritic arborization, support cell morphology, neuropil composition, and other factors, is incompletely understood.

In the present study, many regions reflecting abnormal thickness or growth trajectory represent major nodes within large-scale, domain-specific brain networks including sensorimotor, visual, speech and language, default mode, socioemotional salience, and executive-control networks. Cortical hubs of primary sensorimotor domains exhibited atypical growth and thickness, consistent with previous studies (Hyde *et al.*, 2010; Scheel *et al.*, 2011). Primary motor cortex was thinner in adulthood in ASD. Primary somatosensory cortex showed increased cortical thinning in ASD, with the right hemisphere thinner by adulthood. Right transverse temporal (Heschl's) gyrus, encompassing primary auditory cortex, demonstrated accelerated thinning in ASD, consistent with a recent study by our group demonstrating reduced growth in right Heschl's gyrus grey matter volume during childhood and adolescence in ASD (Prigge *et al.*, 2013). Increased thickness in visual regions during childhood, as well as increased age-related cortical thinning, was found in our sample. Differences in frontal regions important for speech and language were also found. Robust increased cortical thinning in ASD was found in left pars opercularis, and left pars triangularis and pars orbitalis showed similar trajectories but did not survive multiple comparisons correction (Supplementary Fig. 1). Lateral frontal, orbitofrontal, and temporoparietal regions, representing major hubs of executive-control, socioemotional salience, and default mode networks, respectively, also demonstrated abnormal age-dependent trajectories.

We further characterized structural coupling in our data set by performing preliminary analyses of 'regional cortical thickness covariance' using an adaptation of the MACACC method (Mapping Anatomical Correlations Across Cerebral Cortex; Lerch *et al*., 2006), as well as correlated rate of change within each group. Using subjects with multiple time points, we first characterized difference scores between the two earliest time points, and performed cross-correlations across regions which demonstrated group $\times$ age interactions in our primary analysis (Supplementary Fig. 5A). We then analysed correlations of rate of change (i.e. linear slope) between these regions within each group (Supplementary Fig. 5B). Although preliminary, these data suggest abnormal interhemispheric as well as network-level cortical thickness coupling in ASD.

How abnormal regional changes in cortical thickness are related to abnormal structural or functional changes in other parts of the brain remains to be determined. Network-level approaches, including more fine-grained assessment of cortical thickness using multivariate methods will provide much insight into specific anatomic changes related to autism across the lifespan. Our results provide evidence of cortical dysmaturation extending through adolescence and into adulthood in at least some brain regions, in at least some individuals with the disorder. Beyond mid-adulthood, imaging data of the ageing brain in autism are sparse. Understanding ageing in autism will become increasingly important as the disorder is more frequently recognized and diagnosed in individuals of all ages, and as therapeutic interventions continue to expand the functional lives of autistic patients.

Limitations

Our study was designed to provide an overview of cortical thickness growth and decline in a community sample of ASD. There are several limitations, both technical and practical, that should be further clarified by subsequent studies. First, our incomplete longitudinal data do not yet permit construction of individual-level growth trajectories. More longitudinal data points, particularly in younger subjects, are required to model growth curves of appropriate complexity at the single-subject level. Second, the reciprocal developmental trophisms of grey matter and white matter maturation remain unknown. For example, the impact of white matter maturation on MRI signal characteristics of grey matter (and thus semi-automated tissue class boundary definitions) is unclear. Although our age range lies outside of the most robust period of white matter maturation, future studies will clarify whether related systematic bias should be considered in the study of very early autism, and consider this potential confound more broadly. Third, our data span an MRI scanner upgrade consisting of a new headcoil and magnetic resonance pulse sequence adjustments. Although limited living phantom data were acquired to ensure pre- and post-upgrade consistency, our study lacks a thorough complement of phantom data to directly quantify the effect of these changes. Fourth, cortical thickness in isolation may not turn out to be the best indicator of developmental abnormalities in ASD. Work is underway in our laboratory to characterize the interrelationships of thickness and other structural measures across the lifespan in ASD, and some combination of these metrics may produce optimal prediction models. Lastly, our sample includes a broad age range and excludes females, limiting the generalizability of these data. Future studies will clarify how our results relate to specific periods of human development, and to gender differences in autism.

Conclusion

In summary, an abnormal trajectory of brain development in ASD appears to be conserved across assessment modality, characterized by accelerated growth earlier than age 2.5 years, accelerated decline throughout much of later childhood, and decelerated decline during early adulthood and beyond. Our results demonstrate that distinct contributions to these trends may be made from region-specific developmental influences and growth characteristics. Our work supports and clarifies earlier reported heterogeneity of cortical thickness, brain volume, and rate of brain growth in children with autism, based largely on cross-sectional studies. Moreover, our results underscore the importance of understanding regional variability and incorporating regional selectivity in models of neurobiological subtypes of autism defined by anatomic features and rate of growth. Further, IQ substantially influences brain anatomy and growth trends, and should be carefully considered in such models. There remains a lack of data in much of childhood, particularly in longitudinal studies, and specific regional abnormalities remain understudied. More comprehensive longitudinal MRI studies of cortical thickness and other anatomic measures across the lifespan are needed to confirm results found to date, and to clarify structural changes in the context of cognitive function during critical periods of brain development in ASD.

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Supplementary material

Supplementary material is available at *Brain* online.

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