There is increasing evidence that children with autism spectrum disorder (ASD) have age-related differences from controls in cortical volume (CV). It is less clear, however, if these persist in adulthood and whether these reflect alterations in cortical thickness (CT) or cortical surface area (SA). Hence, we used magnetic resonance imaging to investigate the relationship between age and CV, CT, and SA in 127 males aged 10 through 60 years (76 with ASD and 51 healthy controls). “Regional” analyses (using cortical parcellation) identified significant age-by-group interactions in both CV and CT (but not SA) in the temporal lobes and within these the fusiform and middle temporal gyri. Spatially nonbiased “vertex-based” analysis replicated these results and identified additional “age-by-group” interactions for CT within superior temporal, inferior and medial frontal, and inferior parietal cortices. Here, CV and CT were 1) significantly negatively correlated with age in controls, but not in ASD, and 2) smaller in ASD than controls in childhood but vice versa in adulthood. Our findings suggest that CV dysmaturation in ASD extends beyond childhood, affects brain regions crucial to social cognition and language, and is driven by CT dysmaturation. This may reflect primary abnormalities in cortical plasticity and/or be secondary to disturbed interactions between individuals with ASD and their environment.

Keywords: age, autism, brain, cortical thickness, MRI

Introduction
Autism spectrum disorder (ASD) is an increasingly recognized (Baird et al. 2006) group of life span persistent neurodevelopmental disorders of early onset that are characterized by abnormalities in language, social interaction, and a range of stereotyped and repetitive behaviors (WHO 1993).

The brain basis of ASD is poorly understood. However, longitudinal studies report that children with ASD have accelerated growth in head circumference as compared with controls (Hazlett et al. 2005; Dawson et al. 2007; Webb et al. 2007). In addition, many in vivo magnetic resonance imaging (MRI) studies have reported that young children with ASD have a significant increase in total brain volume (TBV) compared with typically developing controls (e.g., see Hazlett et al. 2005). In contrast, findings regarding differences in total brain volume (TBV) between individuals with ASD and controls during later childhood, adolescence, and adulthood have been less consistent. Some groups report no group difference in TBV (e.g., see Hallahan et al. 2008), and others find increased TBV in ASD (e.g., see Hazlett et al. 2008). Given that findings of altered TBV in ASD have been more consistently reported in pediatric compared with adult populations, some have suggested that people with ASD have differences in the trajectory of brain growth that are limited to early childhood (for a meta-analysis, see Redcay and Courchesne 2005).

Abnormal maturation of the cerebral cortex could contribute to age-related differences in brain volume between people with ASD and typically developing controls. For example, Courchesne et al. (2001) compared children with autism to typically developing controls aged between 2 and 16 years and reported age-related differences in total cortical gray matter volume. In a later study using the same sample, Carper et al. (2002) compared lobar cerebral gray matter volume in children with autism and controls. Their measure of cerebral gray matter volume excluded subcortical structures and therefore reflected cortical volume (CV). They found age-related differences in CV between children with autism and controls that varied by lobe. In the preschool years (2–4 years), children with autism had significantly increased CV in the frontal and temporal lobes as compared with controls. However, due to greater age-related CV increase in controls compared with children with autism, these differences were not apparent in older children. Also, there was a significant “age-by-group” interaction in the CV of these regions, and children with autism had a significantly smaller age-related increase in CV than controls. Thus, prior work suggests that in early childhood, people with ASD have significant differences from controls in the maturation of CV. However, it is unclear if these maturational differences normalize or persist into adolescence and adulthood and if they vary by brain region.

We previously reported that adults (aged 18–45 years) with ASD have significant age-related differences from controls in whole-brain gray matter volume (those with Asperger syndrome had a significantly smaller age-related reduction than controls) (McAlonan et al. 2002). Our work provides preliminary evidence that differences in brain maturation extend beyond childhood. However, we did not directly measure CV or include people from across the life span (i.e., children and older adults).

Furthermore, CV has 2 sole determinants—cortical thickness (CT) and surface area (SA). It is important to investigate how abnormalities in CV relate to CT and SA because these 2 measures have distinct genetic determinants (Panizzoni et al. 2007) contrasting phylogeny (Rakic 1995) and differing developmental trajectories (Armstrong et al. 1995; Sowell et al. 2007). CT has been hypothesized to reflect dendritic arborization/pruning within gray matter (Huttenlocher 1990) or changing myelination at the gray/white matter interface (Sowell et al. 2004), whereas SA is influenced by division of
progenitor cells in the embryological periventricular area (Chenn and Walsh 2002) and varies as a function of brain volume and cortical folding (gyrification). Establishing the relative contribution of CT and SA disturbances could therefore clarify the neurobiological mechanisms underlying CV abnormalities in people with ASD. New methods allow simultaneous measurement of CV, CT, and SA from MRI scans (Fischl and Dale 2000; MacDonald et al. 2000). These have not yet been applied to examine age-related differences in CV between people with ASD and controls or to establish the relative contribution of CT and SA alterations to these. Hence, it is unknown how abnormalities in CV relate to those in CT and SA, which may reflect different neurobiological processes.

The methods currently available for examining the relative contribution of CT and SA to alterations in CV require that these 3 measures are taken from a set of predefined cortical regions (that can be combined to give lobar estimates) (Fischl et al. 2004). However, such “lobar” approaches to the study of cortical maturation may be confounded because abnormalities in neurodevelopment may alter traditional lobar boundaries and/or extend across them. Therefore, a complementary strategy is to assess cortical anatomy in a spatially nonbiased manner by taking measures of CT at several thousand points across the cortical sheet. To date, however, this approach has never been applied to investigate cortical maturation in people with ASD.

In summary, it has been proposed that young children with ASD have age-related differences from controls in CV. However, it is unclear if these normalize or persist into adolescence and adulthood. Moreover, recent advances in MRI data analysis make it possible to measure differences in the 2 determinants of CV (CT and SA)—which reflect very different neurobiological processes. We therefore measured CV, CT, and SA in people with ASD (n = 76) and controls (n = 51) aged between 10 and 60 years. We tested the main hypothesis that age-related differences in CV between people with ASD and controls extend into adulthood. We also examined if matura
tional differences in CV related to those in CT, SA, or both. Finally, we carried out the first spatially nonbiased assessment of age-related differences in CT between people with ASD and controls in recognition of the fact that cortical abnormalities in ASD may not conform to traditional lobar boundaries.

Materials and Methods

Sample
We included 127 male volunteers aged between 10 and 60 years: 76 with ASD and 51 healthy controls. People with ASD were recruited through a hospital-based national clinic and a university department specializing in the assessment of ASD. The controls were drawn from the local community through advertisement. Of those with ASD, 62 (82%) had a diagnosis of Asperger syndrome, 10 (13%) autism, and 4 (5%) pervasive developmental disorder not otherwise specified (PDD-NOS) or PDD other. All were diagnosed clinically according to ICD-10 research criteria (WHO 1993) by a team of senior clinicians trained in the autism diagnostic interview revised (ADI-R) (Le Couteur et al. 1989) and the autism diagnostic observation schedule (ADOS-G) (Lord et al. 2000). ASD diagnoses were based on clinical interviews, collateral information from family members, and review of other information available, such as school reports. Forty-three (57%) of the participants, and/or their family members, also agreed to confirmation of clinical diagnosis using the ADI-R or ADOS. Thirty-three (43%) people were unable/unwilling to undergo the ADI or ADOS. There were no significant demographic (age and gender) or full-scale intelligence quotient (FSIQ) differences between those with and without ADI/ADOS confirmation of ASD diagnosis. Furthermore, there were no significant differences in mean age, FSIQ, gender, or the proportion of participants with ADI/ADOS confirmation of ASD diagnosis between ASD subgroups (i.e., Asperger vs. autism vs. PDD-NOS). Despite this, we checked the robustness of our findings to the exclusion of the 33 individuals with ASD who had been unable/unwilling to undergo the ADI/ADOS.

All participants had FSIQs greater than 70. Participants in the study underwent structured physical and psychiatric examination. No participants had a history of neurological disorder affecting brain function (e.g., epilepsy and stroke), major mental illness (e.g., psychosis, major affective episode, or substance abuse), genetic disorder associated with ASD (e.g., Fragile X syndrome), or a clinically abnormal finding on MRI. No participants were taking psychotropic medication at the time of the study. After complete description of the study to the subjects, written informed consent was obtained.

Image Acquisition and Analysis
Brain MRIs were acquired using a GE Signa 1.5-T neuro-optimized MR system (General Electric, Milwaukee, WI). ‘Freesurfer’ freeware (http://surfer.nmr.mgh.harvard.edu/fswiki) was used to derive models of the cortical sheet in each T1-weighted image and parcellate out the cortex into 35 regions. These well-validated (Fischl et al. 2004; Desikan et al. 2006) and fully automated procedures have been extensively described elsewhere (Fischl and Dale 2000; Fischl et al. 2004), and we will only provide a brief description here. First, a single filled white matter volume was generated for each cerebral hemisphere after intensity normalization, the removal of extracerebral tissues using a “skull stripping” algorithm, and image segmentation using a connected components algorithm (Dale et al. 1999). Then, a surface tessellation was generated for each white matter volume using a fitting a deformable template. The gray matter/cerebrospinal fluid (CSF) surface was also modeled using a similar process. Given explicit models for the white/gray and gray/CSF surfaces, the measure of absolute CT at any given point on the white-gray matter surface was then taken to be the shortest distance between that point and the gray/CSF surface. This measurement was made at approximately 150 000 points across each hemisphere for each scan.

Automated parcellation of each individual cortical hemispheric sheet into 35 regions (Fischl et al. 2004) was achieved by aligning each scan to a probabilistic atlas placed within a surface-based coordinate system. Total CV, total SA, and average CT measures for these 35 subregions were combined to generate lobar (frontal, temporal, parietal, and occipital) estimates of total CV, total SA, and average CT.

For all analyses, CV was expressed as a proportion of TBV—corrected cortical volume (cCV). Average TBV did not differ between cases and controls nor was there significant age-by-group interaction for TBV. We adjusted CV for TBV in order to remove variance in CV that was associated with global differences in brain size and thus increase statistical power to detect relationships between CV and our main variables of interest (i.e., age, group, and their interaction).

Data Analysis

Analysis 1
Regional measures from automated parcellation of the cortical sheet.

In our first set of analyses, we used regional measures of cCV, CT, and SA derived from automated parcellation of the cortical sheet. These allowed us to examine the lobar and sublobar regional distribution of age-related cCV difference in ASD and the interrelationship between cCV, CT, and SA. We initially used multivariate analysis of variance (MANOVA) to examine how variance in cCV, CT, and SA was explained by a model including 1 between-group (group) and 2 within-group (age and lobe) independent variables and their interaction terms. Next, for those measures (i.e., cCV, CT, or SA) where significant variance was explained by the “age-by-group-by-lobe” or age-by-group MANOVA terms, we carried out post hoc analyses of age-by-group effects for that measure within each lobe. Next, but only in those lobes where a significant age-by-group effect for a cortical measure was found, we examined age-by-group effects in each lobar subregion. Note that in all
these analyses, a significant main effect of "group" was not further explored if it was accompanied by a significant age-by-group interaction term. This is because the presence of a significant interaction indicates that the effect of each term in the interaction is dependent on the other and as such it is not coherent to consider the main effect of each term in isolation. Also—the sole purpose of our study was to investigate age-related group differences.

Analysis 2

A spatially nonbiased "vertex-based" approach. In our second set of analyses, we examined the regional distribution of age-related differences in CT in people with ASD in a spatially nonbiased manner. This additional analytic approach was adopted because cortical abnormalities in ASD may not conform to traditional lobar boundaries and in order to provide the most spatially fine-grained analysis of CT maturation in ASD available to date. At each of the approximately 150,000 points (vertices) in each hemisphere, the proportion of total variance in CT accounted for by 2 linear regression models was compared: One that did not include an age-by-group interaction term [CT = intercept + (group × b1) + (age × b2)] and one that did [CT = intercept + (group × b1) + (age × b2) + (group × age × b3)]. This resulted in an F ratio map for each hemisphere showing the degree to which the inclusion of an age-by-group term increased the proportion of CT variance that was accounted for.

The F ratio map was then thresholded using the false discovery rate (FDR) method to correct for multiple comparison (Genovese et al. 2002)—with q (the proportion of rejected null hypotheses that would be false rejections per family of tests) set at 0.05. We then examined within which temporal lobe subregion this effect was most pronounced. ANCOVAs for bilateral cCV and CT in each of the 9 temporal lobe subregions revealed (after correction for multiple comparisons) significant age-by-group-effects for middle temporal cCV (F = 12.6, P = 0.001, eta squared = 0.09) and CT (F = 16.3, P = 0.0005, eta squared = 0.12) and for CT of fusiform gyrus (F = 8.3, P = 0.005, eta squared = 0.06). Also, there was a trend toward significance for fusiform cCV (F = 6.4, P = 0.01, eta squared = 0.05). Scatter plots of cCV and CT against age for these temporal lobe subregions revealed an identical pattern to that seen for total temporal cCV and mean temporal CT. Controls showed age-related reductions in cCV and CT, whereas in ASD, cCV and CT were not significantly correlated with age. In younger participants, cCV and CT were less in ASD than in controls, but in older participants, this relationship was reversed. This pattern of CV and CT decreases in ASD followed by increases reflects the relative lack of age-related CT and cCV reduction in people with ASD compared with controls.

The same pattern of age-by-group interactions for cCV and CT being most marked within the temporal lobes held when we limited our analysis to controls and the 43 people with ASD in whom ADI-R or ADOS confirmation of diagnosis was available. Plots of CT and CV for each lobe against age within this subsample are available as supplementary material (Supplementary Figure 1). Furthermore, as in our larger sample, the temporal lobe subregional measures showing most marked age-by-group interactions were middle temporal cCV (F = 18.6, P = 0.0005) and CT (F = 18.5, P = 0.0005) and fusiform cCV (F = 9.4, P = 0.0005) and CT (F = 6.9, P = 0.01). Our findings also held when FSIQ was entered as a covariate. Age-related differences in lobar cCV and CT between people with ASD and controls in our data set do not reflect group differences in the variance of these measures as assessed by Levene’s test for equality of variances.

Results

Subject Characteristics

Subjects with ASD and controls did not differ in mean age. There was, however, a significant group difference in FSIQ (healthy controls had a significantly higher mean FSIQ than the ASD group: P < 0.005). Please see Table 1 for full details.

Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group</th>
<th>Cases (n = 76)</th>
<th>Controls (n = 51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td></td>
<td>76</td>
<td>51</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>31.7</td>
<td>28.6</td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td>10-60</td>
<td>11-59</td>
</tr>
<tr>
<td>Standard deviation</td>
<td></td>
<td>12.1</td>
<td>12.6</td>
</tr>
<tr>
<td>FSIQ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean*</td>
<td></td>
<td>105</td>
<td>122</td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td>73-145</td>
<td>83-155</td>
</tr>
<tr>
<td>Standard deviation</td>
<td></td>
<td>16.5</td>
<td>16.8</td>
</tr>
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<td>ASD diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asperger syndrome</td>
<td></td>
<td>62</td>
<td>—</td>
</tr>
<tr>
<td>Autism</td>
<td></td>
<td>10</td>
<td>—</td>
</tr>
<tr>
<td>PTSD other</td>
<td></td>
<td>4</td>
<td>—</td>
</tr>
<tr>
<td>ADI/ADOS available</td>
<td></td>
<td>43</td>
<td>—</td>
</tr>
</tbody>
</table>

*Significant difference P < 0.005.

Lobar and Sublobar Analyses of cCV, CT, and SA

MANOVA revealed a significant age-by-group-by-lobe interactions for cCV (F = 3.4, P = 0.03, partial eta squared = 0.08) and a significant age-by-group interaction for CT (F = 3.4, P = 0.03, partial eta squared = 0.03) but not SA (P = 0.8) (see Table 2). We therefore carried out post hoc lobar analysis of covariance (ANCOVAs) for cCV and CT only (see Fig. 1). Significant age-by-group effects were identified for temporal lobe cCV (F = 11.0, P = 0.001, eta squared = 0.08) and CT (F = 6.6, P = 0.01, eta squared = 0.05). We next examined within which temporal lobe subregion this effect was most pronounced. ANCOVAs for bilateral cCV and CT in each of the 9 temporal lobe subregions revealed (after correction for multiple comparisons) significant age-by-group effects for middle temporal cCV (F = 12.6, P = 0.001, eta squared = 0.09) and CT (F = 16.3, P = 0.0005, eta squared = 0.12) and for CT of fusiform gyrus (F = 8.3, P = 0.005, eta squared = 0.06). Also, there was a trend toward significance for fusiform cCV (F = 6.4, P = 0.01, eta squared = 0.05). Scatter plots of cCV and CT against age for these temporal lobe subregions revealed an identical pattern to that seen for total temporal cCV and mean temporal CT. Controls showed age-related reductions in cCV and CT, whereas in ASD, cCV and CT were not significantly correlated with age. In younger participants, cCV and CT were less in ASD than in controls, but in older participants, this relationship was reversed. This pattern of CV and CT decreases in ASD followed by increases reflects the relative lack of age-related CT and cCV reduction in people with ASD compared with controls.

Furthermore, as in our larger sample, the temporal lobe subregional measures showing most marked age-by-group interactions were middle temporal cCV (F = 18.6, P = 0.0005) and CT (F = 18.5, P = 0.0005) and fusiform cCV (F = 9.4, P = 0.0005) and CT (F = 6.9, P = 0.01). Our findings also held when FSIQ was entered as a covariate. Age-related differences in lobar cCV and CT between people with ASD and controls in our data set do not reflect group differences in the variance of these measures as assessed by Levene’s test for equality of variances.

Table 2

<table>
<thead>
<tr>
<th>Term</th>
<th>Measure</th>
<th>cCV</th>
<th>CT</th>
<th>SA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobe</td>
<td>F</td>
<td>1733.3</td>
<td>0.0005</td>
<td>208.3</td>
</tr>
<tr>
<td>Age</td>
<td>F</td>
<td>97.0</td>
<td>0.0005</td>
<td>63.4</td>
</tr>
<tr>
<td>Group</td>
<td>F</td>
<td>4.7</td>
<td>0.03</td>
<td>5.2</td>
</tr>
<tr>
<td>Age × lobe</td>
<td>F</td>
<td>49.3</td>
<td>0.0005</td>
<td>10.6</td>
</tr>
<tr>
<td>Group × lobe</td>
<td>F</td>
<td>3.0</td>
<td>0.04</td>
<td>2.4</td>
</tr>
<tr>
<td>Group × age</td>
<td>F</td>
<td>4.4</td>
<td>0.03</td>
<td>2.8</td>
</tr>
<tr>
<td>Group × age × lobe</td>
<td>F</td>
<td>3.4</td>
<td>0.03</td>
<td>3.4</td>
</tr>
</tbody>
</table>

Note: Significant test statistics are shown in bold. Note that SA across lobes does not vary as a function of group. Group differences exist for lobar cCV and CT, but these vary as a function of age and lobe.
Vertex-Based Analysis

Using this approach, we replicated the finding of the sublobar analysis within the temporal lobe reported above. In addition, highly significant age-related group differences in CT were identified within the right (medial frontal, superior frontal, inferior frontal, precentral, inferior temporal, parahippocampal...
gyri, fusiform and inferior parietal lobule) and the left (medial frontal, middle frontal, and superior temporal gyri) cortical sheet. In all these regions, CT reduced as a function of age among controls, but there was little or no relationship between age and CT within the ASD group (see Table 3 and Figure 2). Also, similar to the results from the "lobar analysis" above, in younger participants, CT was less in ASD than in controls but in older participants the relationship was reversed. These results were much the same when we only included controls and people with ASD in whom ADI-R or ADOS confirmation of diagnosis was available (see Supplementary Figure 3 and Supplementary Table 2). There remained regions of prominent age-by-group interaction for CT within lateral temporal, fusiform, and prefrontal cortices, and additionally peaks of significant age-by-group interaction were identified within right precuneus and superior temporal cortices. Also, age-by-group interactions for mean CT within the identified cortical regions remained highly significant with a model that included FSIQ as a covariate.

Discussion

We compared maturation of the cerebral cortex and its 2 determinants (CT and SA) between people with ASD and healthy controls aged from 10 to 60 years. We used 2 analytic approaches—one which examined lobar and sublobar measures of CV, CT, and SA derived from automated parcellation of the cortical sheet and another which examined CT at several thousand points across the cortical sheet in a spatially nonbiased manner.

Both analytic techniques revealed that people with ASD have significant age-related differences in cortical anatomy as compared with controls. Our "regional analysis" identified significant differences bilaterally in temporal lobe total cCV and mean CT. Also within temporal lobe, those subregional measures that differentiated ASD most from controls were middle temporal cCV and CT and fusiform cCV. This finding was replicated by the second spatially nonbiased analysis. However, this latter approach also revealed significant age-by-group interactions for CT in a number of other temporal, frontal, and parietal cortical areas. All these regions demonstrated the same phenomena: 1) in young people, cCV and CT were increased in controls relative to ASD but 2) in controls cCV and CT reduced significantly with increasing age, whereas it did not in ASD, so that 3) by middle age/late adulthood cCV and CT were greater in ASD compared with controls. In contrast, SA showed minimal age-related differences within either group, and this relationship did not differ across lobes or between people with ASD and controls.

Hence, our results suggest that cortical dysmaturation in ASD is not restricted to childhood but extends across the life span. It is likely therefore that age is a very important variable that may confound studies of brain anatomy (and particularly those investigating subtle differences in cortical architecture) in ASD. For example, our findings suggest that, a priori, studies of CT that include only school-aged children will have very different findings than those that include only adults (and vice versa). To date, 3 published studies have compared CT in ASD and controls—but without directly modeling the effects of age (Chung et al. 2005; Haddi khan i et al. 2006; Hardan et al. 2006). Two of these were carried out in youth, and the findings of one are in keeping with what would be predicted from our study (Chung et al. 2005), but the findings of the other (Hardan et al. 2006) are not. The third of these studies examined a relatively small number of adults (14 cases and 14 controls) falling within a wide age range (21–45 years) (Haddi khan i et al. 2006) and identified regional CT reductions in ASD compared with typically developing controls. Our data suggest that in the absence of longitudinally characterized samples extending across the life span, cross-sectional studies of CT in ASD will not only need to be much larger than most of those carried out to date but should also take into account the modulatory effect of age.

In our sample, CT dysmaturation in ASD appeared to drive age-related differences in CV between individuals with ASD and typically developing individuals. Although the statistical significance of group (i.e., ASD vs. controls) differences in CV within discreet age subgroups was not assessed, our data suggest that in late childhood, CV within frontal and temporal lobes is reduced in individuals with ASD compared with controls. This is in apparent conflict with existing reports of brain volumetric increases in ASD relative to controls in pediatric samples (Piven et al. 1995; Courchesne et al. 2001; Sparks et al. 2002; Wa iter et al. 2004; Palmen et al. 2005; Hazlett et al. 2006; Lenroot 2008). However, many of these reports relate to whole-brain volume (Piven et al. 1995; Sparks et al. 2002) or total gray matter volume (CV and subcortical gray combined) (Waiter et al. 2004; Palmen et al. 2005). It is possible for CV within a given lobe to be reduced in individuals with ASD relative to controls, whereas TBV or total gray matter volume shows no significant group differences or significant increases in ASD.

There are 3 available studies of lobar CV in ASD (Carper et al. 2002; Hazlett et al. 2006; Lenroot 2008). These report CV increases in preschool-aged children (Carper et al. 2002; Lenroot 2008) and adolescents/young adults (Hazlett et al. 2006) with autism (including comorbid learning disabilities)
Our data, however, suggest that CV is decreased in adolescents with ASD (all without learning disability and most with Asperger syndrome) compared with controls. Therefore, our findings might differ from those of others due to differences in the ASD subdiagnosis, cognitive profile, and/or age range of the samples studied. With regard to ASD subdiagnosis/cognitive profile, although it is clear that differing clinical presentations within the autism spectrum can be associated with common genetic risks (Bailey et al. 1995), IQ range and ASD subdiagnosis have been shown to influence reports of differences in cortical anatomy between people with ASD and controls (McAlonan et al. 2008). With regards to age range, CV increases in ASD relative to controls have been found in both studies that cover the preschool years (Carper et al. 2002; Lenroot 2008). Our study and that of Hazlett et al. (2006) both start in adolescence/early adulthood and generate contrasting findings regarding CV alterations in ASD relative to controls (globally increased CV and regionally decreased CV, respectively). These findings would be consistent with a model in which CV developmental trajectories in ASD and controls are furthest apart in the preschool years but then converge during childhood, making it harder to consistently identify group differences. Large longitudinal studies will be required to test this hypothesis.

Our study suggests a focal rather than global pattern of cortical dysmaturation in ASD that is most pronounced in regions that, within typically developing individuals, are involved in social cognition (e.g., medial prefrontal, lateral temporal, and lateral parietal cortices) (Lieberman 2007), language (inferior frontal gyrus) (Price 2000), and some aspects of executive function (dorsolateral prefrontal cortices) (Salmon and Collette 2005)—domains in which many subjects with ASD show impairments. Furthermore, in previous work, these same cortical areas have been reported to be functionally abnormal in children and adults with ASD during the performance of a range of cognitive tasks involving “theory of mind” processes (Castelli et al. 2002) (fusiform and superior temporal regions), irony comprehension (Wang et al. 2006) (medial prefrontal and lateral temporal regions), facial emotion perception (Critchley et al. 2000; Dalton et al. 2005) (fusiform region), set-shifting (Shafriz et al. 2008) (dorsolateral prefrontal cortex), and tests of “central coherence” (Lee et al. 2007) (dorsolateral prefrontal cortex). In addition to functional abnormalities, some of the cortical regions implicated in our investigation have also been reported by postmortem studies to show cellular abnormalities in ASD (e.g., in fusiform, middle temporal, and dorsolateral prefrontal cortices) (Casanova et al. 2002; van Kooten et al. 2008). These overlaps raise the

Figure 2. Results of vertex-based analysis of age-by-group interactions across both cerebral hemispheres. Color maps show F ratio statistic with “warmer” colors indicating a larger magnitude of age-by-group interaction. See Table 3 for details of those regions in which the F statistic exceeded the threshold imposed by FDR correction for multiple comparisons. Scatter plots of mean CT against age for controls (solid line) and cases (dashed line) are shown for 2 of these regions.
possibility that atypical cortical maturation in ASD may partially explain differences in cortical function (and/or vice versa).

Our combined analysis of CV, CT, and SA indicates that CV dysmaturation in ASD is probably driven by differences in CT rather than SA. Although relatively little is known of the factors that shape age-related changes in CT during typical development, interindividual differences in maturation of CT have been related to IQ (Shaw et al. 2006), rate of improvement in phonological processing (Lu et al. 2007), and single nucleotide genetic polymorphisms (Shaw et al. 2007). Twin studies suggest that at a group level, the relative role played by genetic and environmental factors in CT variance differs both by cortical region and age (Lenroot et al. 2009). The processes influencing cortical maturation in ASD may be very distinct from those that shape the typically developing cortex. Therefore, we can only speculate as to what might underlie atypical cortical maturation in ASD. One potential explanation is that structural dysmaturation represents the direct influence of genetic and environmental risk factors for ASD on cortical plasticity. For example, genetically mediated abnormalities of synaptic function in ASD (Garber 2007) could modulate dendritic development and hence CT. Alternatively, dysmaturation within a region could reflect the "secondary" impact that growing up with ASD has on the developing brain. For example, age-related reductions in CT may represent differences in "activity/experience-dependent" processes such as synaptic pruning. Dysmaturation could therefore reflect "underuse" of a cortical region that initially has normal developmental potential. Candidate mechanisms for regional abnormalities of cortical engagement in ASD include atypical patterns of eye gaze to faces (Dalton et al. 2005). These 2 proposed accounts for cortical dysmaturation in ASD raise distinct and testable hypotheses.

Our study has several limitations. First, our study was cross-sectional in design and thus susceptible to cohort effects in which apparently age-related phenomena are an artifact of age being nonrandomly distributed with respect to another variable (e.g., IQ) that is associated with the outcome of interest (e.g., brain size). Of such potential confounders that were measured in our study, age was not associated with FSIQ in our sample nor were people with different ASD subdiagnoses differentially distributed across the age range. Nevertheless, longitudinal studies are central in the study of brain development—as indicated by the dramatic interindividual variation and nonlinear growth trajectories identified by the few available large longitudinal projects examining typical and atypical brain maturation in humans (Giedd et al. 1999). Our pragmatic design did, however, allow us to examine a very wide age range (10–60 years) that would not be practically possible using longitudinal approaches and represents the largest age range studied to date in ASD using structural MRI. A second limitation of our study is that confirmation of ASD diagnosis in our clinician-based sample using ADI-R/ADOS was only possible in 57% of cases. The validity of the ASD diagnoses made in the remaining 43% of cases is supported by the fact that multiple sources of information were considered by a multidisciplinary team of clinicians trained in ADI/ADOS before reaching a consensus diagnosis. Moreover, our results did not change when we excluded people without ADI/ADOS confirmation of clinical ASD diagnosis. Finally, mean FSIQ in cases was significantly lower than in controls. This reflects the fact that FSIQ distribution within our controls was right-shifted relative to the samples upon which IQ tests were standardized. This phenomenon is also seen in some of the largest longitudinal MRI data sets used to compare typically and atypically developing populations (Shaw et al. 2006). Its potential impact on our findings is lessened by the fact that current mean population FSIQs are probably above 100 (Flynn 2000). Also, the reduction in FSIQ typically seen in ASD complicates the issue of group matching for FSIQ in ASD research (Szatmari et al. 2004). Further, the possibility that our results were driven by IQ differences between cases and controls rather than ASD status per se is limited by the fact that 1) our findings remained unaltered when we controlled for FSIQ and 2) the only available longitudinal study relating FSIQ to cortical anatomy in healthy controls (Shaw et al. 2006) found that maturational differences in the cortices of groups defined by IQ were largely restricted to frontal regions, whereas the age-related differences reported in our study are most marked in temporal regions. Finally, as noted above, there was no significant group difference in the relationship between age and IQ. Nevertheless, some cross-sectional studies (Narr et al. 2006) in healthy controls have found an association between IQ and cortical anatomy in regions that overlap with those identified in our study, and as such, it is still conceivable that group differences in IQ are a potential confound in our study. For the reasons outlined above, however, we do not think that they can fully explain the age-related differences in cortical anatomy that we identified between individuals with ASD and controls.

In summary, we found that people with ASD have focal rather than global age-related differences in cortical anatomy from controls that extend into adulthood. Also, these are mainly associated with variation in CT and not SA. This suggests that, within people with ASD, differences in specific neurobiological processes are not "fixed," rather they may continue to change across the life span.

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**Supplementary Material**

Supplementary material can be found at http://www.cercor.oxfordjournals.org/

**Notes**

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Address correspondence to Dr Armin Raznahan. Email: armin.raznah@iop.kcl.ac.uk.

**References**


WHO 1993. Mental disorders: a glossary and guide to their classification in accordance with the 10th revision of the international classification of diseases-research diagnostic criteria (ICD-10). Geneva (Switzerland): WHO.