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Increased Surface Area, but not Cortical Thickness, in a Subset of Young Boys With Autism Spectrum Disorder

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Abstract

The Autism Phenome Project is the largest, single site, longitudinal magnetic resonance imaging (MRI) study of young children with autism spectrum disorder (ASD). Previous analyses from this cohort have shown that the children with autism have a total brain volume at time 1 (~3 years of age) that is 6% larger than typically developing (TD) children. This finding is driven primarily by 15% of the boys with ASD that have disproportionate megalencephaly (ASD-DM) or brain size that is 1.5 standard deviations above what would be expected for the child's height. In the current study, cerebral cortical grey matter volume, thickness, and surface area were assayed from MRI scans of 112, 3-year-old boys with ASD and 50 age-matched TD boys. The boys with ASD-DM (n = 17) were analyzed separately from the boys with normal brain size (ASD-N, n = 95). Previous studies of cortical thickness and surface area for ASD children in this age range have come to diametrically different conclusions concerning the significance of cortical thickness vs. surface area. Current analyses indicate that cortical thickness was comparable across the ASD and TD groups. However, surface area was significantly greater in the ASD group compared to the TD group. This result was driven largely by the children with ASD-DM. Even in the ASD-DM group, not all cortical regions demonstrated increased surface area. These results provide strong evidence that the early cortical overgrowth associated with ASD is due primarily to increased surface area and not to increased cortical thickness.

Keywords

cortical thickness; surface area; gray matter volume; megalencephaly; autism spectrum disorder; FreeSurfer

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Introduction

Autism spectrum disorder is characterized by impairments in social communication and repetitive behavior [American Psychiatric Association, 2013]. ASD is an incredibly heterogeneous disorder that has both a complex genetic architecture [Devlin & Scherer, 2012; Geschwind & Levitt, 2007; State & Levitt, 2011] and substantial individual differences in the severity of core and co-morbid symptoms. This heterogeneity has complicated attempts to characterize many of the biological features of ASD including the underlying neuroanatomy. Retrospective head circumference studies suggest that children with ASD are born with normal or slightly smaller brain size but the trajectory of growth accelerates abnormally during the first year of life [Courchesne, Carper, & Akshoomoff, 2003; Dawson et al., 2007]. Recently, a prospective study of sibling infants at risk for ASD reported that infants who later developed ASD had enlarged total cerebral volume as early as 12 months of age [Shen et al., 2013]. This is consistent with many other studies indicating that young children with ASD have brain overgrowth [Amaral, Schumann, & Nordahl, 2008; Courchesne et al., 2001; Hazlett et al., 2005, 2011; Nordahl et al., 2011; Schumann et al., 2010]. The cellular underpinnings of the brain overgrowth during early childhood, however, remain unclear.

The size of the human brain is largely determined by the size of the cerebral cortex and the subjacent white matter. The volume of the cerebral cortex is determined by cortical thickness (CT) and cortical surface area (SA). Surface area and cortical thickness are thought to be genetically independent [Panizzon et al., 2009; Winkler et al., 2010] and modulated by different neurobiological mechanisms. The enlarged brain in ASD could result either from an expansion of cortical thickness or of cortical surface area or of both. Several magnetic resonance imaging (MRI) studies have examined CT in ASD with inconsistent results. Some studies have reported increased CT in frontal and temporal regions [Hardan, Muddasani, Vemulapalli, Keshavan, & Minshew, 2006; Hyde, Samson, Evans, & Mottron, 2010], while others reported cortical thinning in temporal and parietal regions [Hadjikhani, Joseph, Snyder, & Tager-Flusberg, 2006; Wallace, Dankner, Kenworthy, Giedd, & Martin, 2010]. Six studies [Ecker et al., 2013; Mak-Fan, Taylor, Roberts, & Lerch, 2012; Raznahan et al., 2009, 2010, 2013; Wallace et al., 2013] have directly quantified SA in older individuals with ASD. These studies have generally concluded that SA in ASD is comparable to typically developing subjects. To our knowledge, only two studies have examined CT and SA in young children with ASD [Hazlett et al., 2011; Raznahan et al., 2013]. Hazlett et al. [2011] found no significant differences in CT but observed increased SA and overall brain volume in 2-year-old children with ASD (51 males and 8 females) compared to age matched controls (28 males and 10 females). Raznahan et al. [2013], in contrast, did find significant regional increases in cortical thickness in 2-to-5-year-old boys ($n = 66$) with ASD although the overall brain volume and SA in their cohort of ASD subjects was not greater than the age matched typically developing boys ($n = 29$). Raznahan et al. [2013] used surface-based morphometry to measure CT and SA, while Hazlett et al. [2011] employed voxel-based morphometry. Surface-based morphometry takes into account the intrinsic two-dimensional structure and highly folded geometry of the neocortex [Dale, Fischl, & Sereno, 1999; Fischl, Sereno, & Dale, 1999] and is considered to be a more accurate technique for measuring CT

and SA compared to classical voxel-based morphometry. It is well-known that a subset of young children with ASD have megalencephaly [Chawarska et al., 2011; Courchesne et al., 2001, 2003; Davidovitch, Patterson, & Gartside, 1996; Fombonne, Roge, Claverie, Courty, & Fremolle, 1999; Kanner, 1968; Klein, Sharifi- Hannauer, & Martinez-Agosto, 2013; Lainhart et al., 2006; Miles, Hadden, Takahashi, & Hillman, 2000; Sacco et al., 2007; Woodhouse et al., 1996], however, neither of the two previous studies separately investigated CT and SA in the children with large brains. The present study utilized FreeSurfer, which is the most commonly used software for surface-based morphometry, to explore cortical surface anatomy in children with ASD who were previously determined to have brain size disproportionately larger than body size in comparison to children with ASD who have normal brain size. In the Autism Phenome Project, only a subset of 15% of the boys with ASD demonstrate brain overgrowth (ie. megalencephaly) during early childhood that is disproportionate to height (ASD-DM). This is in contrast to the much larger subset of boys with ASD that have normal brain volume (ASD-N). This is the first study to investigate cortical surface anatomy in the subset of children with ASD-DM. Brain overgrowth is less apparent in girls with ASD in this cohort, and thus our current investigation is focused on boys. The aim of the study was to investigate cerebral cortical gray matter volume (GV), CT, and SA in this large and well-characterized sample of young boys with ASD compared to age matched TD boys.

Methods

Participants

Participants for this study (112 boys with ASD and 50 age-matched, TD boys) were recruited through the MIND (Medical Investigation of Neurodevelopmental Disorders) Institute of the University of California, Davis (UCD), as part of the Autism Phenome Project. This study was approved by the UCD institutional review board, and informed consent was obtained from the parent or guardian of each participant. Demographic features for the participants are provided in Table 1.

Diagnostic assessments of the participants were conducted by research reliable licensed clinical psychologists using the Autism Diagnostic Observation Schedule-Generic (ADOS-G) and the Autism Diagnostic Interview-Revised (ADI-R). Diagnostic criteria for ASD were derived from the Collaborative Programs of Excellence in Autism network. Participants met ADOS-G cutoff scores for autism or ASD, were above the cutoff score for autism on either the social or communication sub-scale of the ADI-R and were within two points of the autism cutoff for all other subscales on the ADI-R. An ADOS severity score was calculated [Gotham, Pickles, & Lord, 2009], to allow for comparison of autism severity across participants tested with different ADOS-G modules. Developmental ability was determined for all participants using the Mullen Scales of Early Development (MSEL). A Developmental Quotient (DQ) was calculated as the average of the age equivalent scores on the Visual Reception, Fine Motor, Receptive Language, and Expressive Language scales, divided by chronological age, multiplied by 100. Inclusion criteria for typically developing controls included scores within 2 standard deviations of the mean on all subscales of the MSEL. In addition, TD children were screened and excluded for autism using the Social

Communication Questionnaire (scores > 11) (SCQ, Lifetime Edition). All TD and ASD children were native English speakers and had no suspected vision or hearing problems or known genetic disorders and/or other neurological conditions. Additional exclusion criteria were limited to physical contraindications for MRI.

Identification of Disproportionate Megalencephaly

A subset of boys with ASD have been identified that have total cerebral volume (TCV) disproportionately larger than height. Height was measured and recorded using a medical scale at the time of the clinical visit. Total cerebral volume, which comprised total gray and white matter volumes and excluded the volume of the brainstem, cerebellum, and ventricles, was measured as described in Nordahl et al. [2011]. MRI data were typically obtained less than 2 months apart from height data and any participant with height and TCV measurements greater than 6 months apart was excluded from this analysis. Individuals with disproportionate megalencephaly were identified as having a ratio of TCV to height greater than 1.5 standard deviations above mean TCV to height ratio for TD males (6% of TD boys would meet this definition). Using this definition, 15% of male subjects with ASD were classified in the ASD-DM subgroup and the remaining males with ASD were classified as ASD-N.

MRI Data Acquisition

All participants underwent MRI scans on a 3T Siemens TIM Trio MRI system (Siemens Medical Solutions, Erlangen, Germany) with an 8-channel head coil at the UCD Imaging Research Center. All scanning for participants was performed during natural sleep [Nordahl et al., 2008]. For each participant, a 3D T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) scan (TR 2170 ms; TE 4.86 ms; matrix 256 × 256; 192 sagittal slices, 1-mm isotropic voxels) was obtained. A T2-weighted scan was also obtained for clinical evaluation when possible (i.e., when the child remained asleep). All MPRAGE and available T2 scans were reviewed by a pediatric neuroradiologist and screened for significant clinical findings. A calibration phantom (Magpham Alzheimer's Disease Neuroimaging Initiative; Phantom Laboratory) was scanned at the end of each MRI session using an MPRAGE pulse sequence matched to the study sequence. The phantom was used to derive a 3D image distortion map for each child's MRI scan. Distortion correction was carried out on all T1-weighted images to adjust for hardware-induced variation, which has been recognized as an important source of error [Fox & Freeborough, 1997]. These procedures have been described in detail previously [Nordahl et al., 2011, 2012].

MR Image Processing

The FreeSurfer Software Suite (version 5.1.0, http://surfer.nmr.mgh.harvard.edu) was used to create a three-dimensional model of the cortical surface for CT and SA measurements [Dale et al., 1999, Fischl et al., 1999]. The automated processing stream included motion correction, transformation to Talairach space, intensity normalization and removal of non-brain tissue. Spatial intensity gradients across tissue classes were used to create surface maps that are capable of detecting submillimeter differences between areas. Each pial and white matter surface was composed of approximately 160,000 vertices arranged in a

triangular mesh. The CT value was calculated as the shortest distance between the pial and white matter surfaces at each vertex. The SA measurement was obtained by computing the sum of areas of each triangle. After automated surface reconstruction, surfaces of each subject were visually inspected and manually edited by two neuroanatomically trained researchers (HO and AL) who were unaware of subject diagnosis.

The final cortical segmentations were generated based on a subject-independent probabilistic atlas included in the FreeSurfer suite which yields 34 cortical subregions per hemisphere [Desikan et al., 2006]. The labeled atlas and cortical surface of each subject were co-registered in spherical space to minimize geometric distortion [Fischl et al., 1999]. The probabilities of label-location concordance, spatial neighborhood relationships and local curvature information were computed to achieve vertex-to-vertex correspondence of cortical subregions. Within each cortical subdivision, volume, thickness, and surface area measurements were then calculated.

TCV was measured using a template-based automated method as in Nordahl et al. [2011]. In short, each participant image was brought into study specific-template space. A mask with the brainstem and cerebellum removed was applied to all participant images which were then transformed back to native space for TCV calculation.

Statistical Analysis

Group differences in continuous demographic and clinical characteristics were assessed using one-way analyses of variance (ANOVA) with diagnostic group as a three-level (ASD-DM, ASD-N, and TD) factor. If the main effect of group was significant, post-hoc pairwise comparisons were conducted using the Tukey–Kramer method to adjust for multiple comparisons. Mixed-effects linear models were used to estimate group differences in the main outcomes (GV, CT, and SA) across different regions [Laird & Ware, 1982]. These models allowed us to treat region as a repeated measure factor and to adjust for the effects of important variables such as age; they also can accommodate missing measurements on some of the participants. Since a fundamental aim of the current study was to determine whether the increased brain size in the ASD-DM group was due to increased cortical thickness, increased cortical surface area or both, we did not control for total cerebral volume. All outcomes were fourth root transformed prior to the analysis to stabilize the variances and better approximate normal distributions. In order to investigate laterality differences for each dependent variable (CT, SA, and GV), separate models were fit for right and left hemisphere. In all core models, the independent variables were group (ASD-DM, ASD-N, and TD), region of the brain (as a 34 level categorical variable), age, and the interaction between group and region. This allowed us to assess if there were global group and regional differences, and to evaluate if the pattern of between-group differences varied across regions. To account for the repeated nature of the data, the core models also included two random effects: one for child and another one for lobe. This approach allowed the measurements from the same child to be correlated, and the correlation to be stronger for regions of the brain from the same lobe. Following a significant group by region interaction, the model-estimated coefficients were used to construct two sets of linear contrasts to evaluate separately (a) all 34 regional differences between the two ASD groups (weighted average of

ASD-DM and ASD-N) relative to TD, and (b) all 102 pairwise differences among the three groups (ASD-DM, ASD-N, TD) at each region. For each of these families of linear contrasts, the *P*-values were adjusted for multiple comparisons using a step-down resampling-based technique [Westfall & Young, 1993]. This is a nonparametric method to control the family-wise error rate in which the data are resampled with replacement a large number of times, a *P*-value is computed for each sample, and the adjusted *P*-value is calculated as the proportion of samples with *P*-values that were smaller than the raw *P*-value based on the original data. These adjusted *P*-values incorporate all correlations and distributional characteristics. All tests were two-tailed, with $\alpha = 0.05$. Residual analyses and graphical diagnostics determined that the model assumptions were adequately met. Analyses were implemented using PROC GLIMMIX in SAS Version 9.4 [SAS Institute, 2002–2010].

Results

Subject Characteristics

Demographic and clinical characteristics of the participants in this study are shown in Table 1. One-way ANOVA showed that the ASD-DM, ASD-N, and TD groups were matched on age ($F = 0.31$, $P = 0.74$). Pairwise comparisons indicated that, as expected, the ASD-N and ASD-DM groups had significantly lower DQ, VDQ, and NVDQ scores compared to the TD group (all $P < 0.001$, after adjusting for multiple comparisons). The two ASD groups did not differ from each other on DQ, VDQ and NVDQ scores (all $P > 0.35$). Furthermore, the ADOS severity scores were similar for the ASD-DM group and ASD-N group ($P = 0.55$).

Total Cerebral Volume

One-way ANOVA indicated significant group differences in TCV ($F = 27.7$, $P \leq 0.001$) (Table 1). This difference was driven primarily by the ASD-DM group since pair-wise comparisons revealed larger TCV in the ASD-DM group compared to both the ASD-N and TD groups (both adjusted $P < 0.001$) and no significant group difference in TCV between the ASD-N and the TD groups ($P = 0.07$). The mean height for participants was similar across all groups ($F = 0.69$, $P = 0.50$).

Gray Matter Volume

The FreeSurfer pipeline provides estimates of gray matter volume in 34 cortical regions in both the left and right hemispheres (Table 2, Fig. 1) The results of the mixed effect analyses (Table 3) revealed significant main effects of group in both left ($F = 26.4$, $P < 0.001$) and right ($F = 28.0$, $P < 0.001$) hemispheres, as well as significant two-way interactions between group and region in the left ($F = 1.90$, $P < 0.001$) and right ($F = 1.57$, $P < 0.001$) hemispheres. The major findings can be summarized as follows: (a) All ASD vs. TD: After controlling for multiple comparisons, increased GV was observed in 16/34 regions in the left hemisphere and 20/34 regions in the right hemisphere in the ASD group compared to the TD group. (b) ASD-DM vs. TD: The ASD-DM group had more cortical volume than the TD group in 22/34 regions in the left hemisphere and 24/34 regions in the right hemisphere. (c) ASD-N vs. TD: When the ASD-DM group was removed from the total ASD group (leaving the ASD-N group), increased GV was observed only in the left fusiform gyrus. (d) ASD-DM

vs. ASD-N: Increased GV was observed in 19/34 regions in the left hemisphere and 18/34 regions in the right hemisphere in the ASD-DM group compared to the ASD-N group.

To summarize, significant GV differences between boys with ASD compared to TD boys were observed in many cortical regions. However, most of the GV differences were driven by the boys with the disproportionately enlarged brains.

Cortical Thickness

There was no significant main effect of group in either the left ($F = 0.65$, $P = 0.52$) or the right ($F = 0.58$, $P = 0.56$) hemisphere (Table 4). Nor was there a significant two-way interaction between group and region in either the left ($F = 1.16$, $P = 0.18$) or right ($F = 0.83$, $P = 0.83$) hemisphere. Thus, the increased grey matter volume in the ASD group was not related to increased cortical thickness even in the ASD-DM group. The lack of cortical thickness findings does not appear to be due to the integration of data across the surfaces of 34 regions. Freesurfer allows vertex-based analysis of cortical thickness using the QDEC application although QDEC only allows comparisons between two groups of samples. However, in preliminary analyses, we compared cortical thickness between all of the pairs of the three groups of subjects in the study (TD vs. ASD-N, TD vs. ASD-DM, ASD-N vs. ASD-DM). We found that cortical thickness was comparable between groups regardless of the pairs that were analyzed. Since we opted to use statistical models that encompassed all three subject groups, we have not presented the vertex-based QDEC data.

Surface Area

In the mixed effect model, a main effect of group was found for the left ($F = 24.9$, $P < 0.001$) and the right ($F = 28.0$, $P < 0.001$) hemisphere (Table 5). There was also a two-way interaction between group and region in the left ($F = 1.96$, $P < 0.001$) and right ($F = 1.64$, $P < 0.001$) hemisphere. The results for SA (Table 6) can be summarized as follows (Fig. 1): (a) All ASD vs. TD: There was increased SA (ASD greater than TD) in 14/34 regions in the left hemisphere and 12/34 regions in the right hemisphere (Fig. 1B); (b) ASD-DM vs. TD: There was significantly greater SA in the ASD-DM group compared to the TD group in 16/34 regions in the left hemisphere and 17/34 regions in the right hemisphere (Fig. 1C); (c) ASD-N vs. TD: There were no regions that demonstrated increased SA in the ASD-N group compared to the TD group; decreased SA was observed in the left caudal middle frontal gyrus (Fig. 1D). There was a trend level increase in SA ($P = 0.08$) in the left fusiform gyrus of the ASD-N group; (d) ASD-DM vs. ASD-N: The ASD-DM group had increased SA in 14/34 regions in the left hemisphere and 15/34 regions in the right hemisphere compared to the ASD-N group (Fig. 1E). All of the regions with increased SA were regions with increased GV in the ASD-DM group compared to the other two groups.

To summarize, in contrast to the lack of significant differences in cortical thickness between the ASD and TD groups, there were substantial and widespread differences in cortical surface area. It is the group of boys with ASD and disproportionate megalencephaly that are driving both the grey matter volume and surface area findings.

Discussion

We have investigated cortical gray matter volume, cortical thickness and cortical surface area in a large and well-characterized, sample of 112, 3-year-old boys with ASD and 50 age-matched TD boys. An overarching goal of this study was to determine what accounted for the increased cortical size in the subset of boys that we had previously identified who have brain size disproportionate to body size [Nordahl et al., 2011].

When all boys with ASD were compared to the TD controls, cortical gray matter volume and surface area were increased whereas cortical thickness was not different. When the group of boys with ASD were subdivided into those with megalencephaly (ASD-DM) vs. those with brains of normal size (ASD-N), the increased surface area was observed in the boys with enlarged brains but not in the group of boys with normal-sized brains. While the increase in surface area extended across many cortical regions, not all cortical areas demonstrated increases. The major finding in this study is that the observed increase in cortical gray matter volume in boys with ASD is due almost entirely to an increase of surface area.

Only two previous publications have reported data on cortical thickness and surface area in young children with ASD comparable to the subjects in the current study [Hazlett et al., 2011; Raznahan et al., 2013]. Hazlett et al. [2011] found no significant differences in CT but observed increased SA in 2-year-old (range of ages = 18–35 months) children with ASD. While their results are consistent with those presented here, there were significant differences in study design. The Hazlett et al. study included both males and females (ASD; $n = 59$ including 51 males and 8 females, Control; $n = 38$ including 28 males and 10 females), and the control group was composed of both typically developing children ($n = 26$) as well as children with developmental delay ($n = 12$). They did not divide their population of subjects into those with megalencephaly vs. normal-sized brains. In addition, SA was not measured directly, but was estimated by dividing regional cortical volume by regional CT.

More recently, Raznahan et al. [2013] reported no differences in SA but increased cortical thickness of some regions of the cerebral cortex in boys with ASD who were 2 to 5-years-old [Raznahan et al., 2013]. Their findings, therefore, are in stark contrast to the findings in the current study. There were substantial differences in the composition of the two cohorts and also substantial technical and analytic differences that may contribute to the different findings. First, the number of boys in the Raznahan et al. [2013] cohort was much smaller than in the current study. Theirs included 66 boys with ASD and 29 typically developing controls whereas our study had a cohort that was nearly twice as large (112 boys with ASD and 50 typically developing boys). Beyond the relatively small number of subjects with ASD, it is striking that they did not detect an increase in total brain volume in their ASD cohort although many laboratories have repeatedly replicated this finding [Amaral et al., 2008; Courchesne et al., 2001; Hazlett et al., 2005, 2011; Nordahl et al., 2011; Schumann et al., 2010]. This raises the possibility that, for whatever reason, their cohort had few, if any, boys with disproportionate megalencephaly. Since differences in grey matter volume and surface area in the current study were driven primarily by the group of boys with the disproportionately enlarged brains, this may be the reason why Raznahan et al. did not

observe either total brain volume or surface area differences in their ASD group. This does not explain why the Raznahan et al. study observed differences in cortical thickness and the current study did not. Neither the boys with ASD and megalencephaly nor the boys with ASD and normal brain volume demonstrated differences in cortical thickness. A second difference between the current study and Raznahan et al. is the average age of the participants; they were older in the Raznahan et al. study. The average age in their study was around 46 months (range 24–71 months), while our subjects were younger (mean 36 months) and more homogeneous (range 26–44 months). It is not clear how these age differences might contribute to the different findings. Third, there were substantial differences in the analytic approaches taken in each study. The Raznahan et al. study used CIVET [Zijdenbos, Forghani, & Evans, 2002], whereas the current study used FreeSurfer, to measure CT and SA. Both CIVET and FreeSurfer employ surface based methods. As far as we know, there is no published study that has directly compared the difference between the outputs of the two software packages. Free-Surfer is, however, the most commonly used pipeline to investigate cortical surface anatomy. Raznahan et al. also used a region and vertex approach whereas we used a region approach. They failed to show statistically significant group differences of CT in global and lobar level i.e., regional analyses. Their vertex-level analysis suggested increased CT in the ASD group in certain cortical regions including the superior frontal gyrus, middle frontal gyrus, superior temporal sulcus and rostral intraparietal sulcus. While it is unfortunate that these two studies have come to opposite conclusions regarding surface area and cortical thickness in boys with ASD, this outcome speaks to the need of having adequate sample sizes for MRI studies of ASD and of the advantage of utilizing a common set of analytic procedures.

These differences also speak to the issue of how imaging and other neuropatholgoical studies deal with the heterogeneity of ASD. While it is widely acknowledged that ASD has an incredibly complex genetic architecture [Abrahams & Geschwind, 2008; Jeste & Geschwind, 2014] and enormous variation in the severity of core and co-morbid symptoms [Lord, Cook, Leventhal, & Amaral, 2000], neuroanatomical and neuropathological studies tend to treat ASD as a homogeneous disorder. This potentially adds a large measure of arbitrariness to findings that are dependent on the composition of the cohort under study. While we observed increased SA in the ASD group, this result was largely driven by the ASD-DM subgroup. Megalencephaly is a well-established phenotype of ASD [Chawarska et al., 2011; Courchesne et al., 2001, 2003; Davidovitch et al., 1996; Fombonne et al., 1999; Kanner, 1968; Klein et al., 2013; Lainhart et al., 2006; Miles et al., 2000; Sacco et al., 2007; Woodhouse et al., 1996]. No previous MRI study, however, has investigated cortical surface anatomy in ASD with megalencephaly. Despite the substantial cortical overgrowth in the ASD-DM group, cortical thickness was comparable to the TD group. These results support the conclusion that the early cortical overgrowth that is observed in a subset of children with ASD [Nordahl et al., 2011] is due to increased surface area rather than increased cortical thickness.

While surface area was increased in the ASD-DM group relative to the TD controls, this was not uniform across all cortical regions. Surface area was increased in 16/34 regions in the left hemisphere and 17/34 regions in the right hemisphere. The greatest increases in SA were observed in the left fusiform gyrus and left rostral anterior cingulate. The fusiform gyrus is

considered to play an important role in normal face processing and alterations in its function have been related to social disability in ASD [Dziobek, Bahnemann, Convit, & Heekeren, 2010]. Interestingly, the one region that demonstrated increased grey matter volume (and a trend towards increased surface area) in the group of boys with ASD and a normal sized brain was the left fusiform gyrus. The anterior cingulate cortex has been implicated in various social, emotional and cognitive functions, such as response monitoring and affective regulation [Allman, Hakeem, Erwin, Nimchinsky, & Hof, 2001]. The fusiform gyrus and the anterior cingulate cortex are important components of the "social brain network" which is thought to be impaired in ASD [Kennedy & Adolphs, 2012]. Some of the other brain regions that demonstrated greater surface area tended to be those that are associated with the social and cognitive functions that are altered in ASD. Although surface area differences in regions such as primary motor, somatosensory and visual cortices can not be specifically related to ASD deficits.

The cellular, neurobiological substrate of the increased SA in ASD remains unclear. The number of neural stem cells that divide symmetrically in the ventricular zone before the onset of neurogenesis determines the number of radial cortical columns. The proliferation of progenitor cells, which divide asymmetrically, determines the number of neurons within the radial columns [Rakic, 1988, 1995, 2007, 2009]. According to this model, CT is determined by the number of cells within a column whereas SA is determined by the number of cortical columns. Casanova, Buxhoeveden, and Gomez [2003] and Casanova, Buxhoeveden, Switala, and Roy [2002] reported that reductions in minicolumnar width and peripheral neuropil spacing were observed in layer III of the neocortex of individuals with ASD, indicating a disturbance in minicolumnar organization. However, it is not clear whether a particular cortical area has an excess of cortical columns compared to TD controls or whether this is more characteristic of large brains from individuals with ASD than normally sized brains. There is a glaring lack of understanding of what is the cellular basis of the enlarged brain size in ASD which speaks to the urgent need for increased studies of larger numbers of postmortem brains from well characterized individuals with ASD.

Several candidate genes that affect brain size have been reported. PTEN (phosphatase and tensin homolog deleted on chromosome 10), for example, has been implicated in the cortical overgrowth associated with ASD. PTEN is a negative regulator of the PI3K/AKT pathway, which controls cell growth and proliferation [Sansal & Sellers, 2004]. Previous studies have demonstrated that PTEN mutation mouse develops megalencephaly and displays behavioral abnormalities consistent with ASD [Kwon et al., 2006; Zhou & Parada, 2012]. PTEN germline mutations are present in 1–5% of individuals with ASD [Zhou & Parada, 2012] and most of them have megalencephaly [Buxbaum et al., 2007; Herman et al., 2007; McBride et al., 2010; Orrico et al., 2009; Varga, Pastore, Prior, Herman, & McBride, 2009]. We have carried out preliminary analyses of the genetic composition of the ASD-DM group (unpublished observations). What is clear is that no single mutation characterizes the individuals in this group. One of these children, for example, demonstrated a loss of function mutation of CHD8 [Bernier et al., 2014] which is commonly associated with the megalencephalic form of ASD. But, only one of the ASD-DM boys had this mutation. It is likely, therefore, that there are several genetic architectures that could lead to the large brain form of ASD.

Surface area and cortical thickness are thought to be genetically independent [Panizzon et al., 2009; Winkler et al., 2010] and modulated by different neurobiological mechanisms. For SA, β-catenin and caspase 3/9 have been reported to be influential proteins. Mice expressing a stabilized β-catenin transgene in neural precursors develop an increased number of progenitor cells in the ventricular zone, which lead to a larger number of radial columns and increased SA [Chenn & Walsh, 2003]. Caspase 3/9 mutations cause decreased apoptosis of progenitor cells and radial glial cells, which subsequently increases SA [Haydar, Kuan, Flavell, & Rakic, 1999]. The extent to which these proteins are contributory to the megalencephalic form of ASD remains to be seen.

Conclusions

To explore what features of cortical organization contribute to brain enlargement in young children with ASD, we investigated cortical grey matter volume, thickness and surface area in 3-year-old boys with ASD compared to age-matched typically developing controls. We found an increased grey matter volume in children with ASD that is due primarily to an increase of surface area and not to increased cortical thickness. These findings of increased grey matter volume and surface area in ASD were driven largely by the group of children with disproportionate megalencephaly. These results emphasize the need for stratifying subjects with ASD in meaningful ways in order to understand the variations in underlying neuroanatomy and neuropathology. They also emphasize the need for expanded postmortem brain analyses of the genetics and underlying cellular changes that might contribute to the megalencephalic form of ASD.

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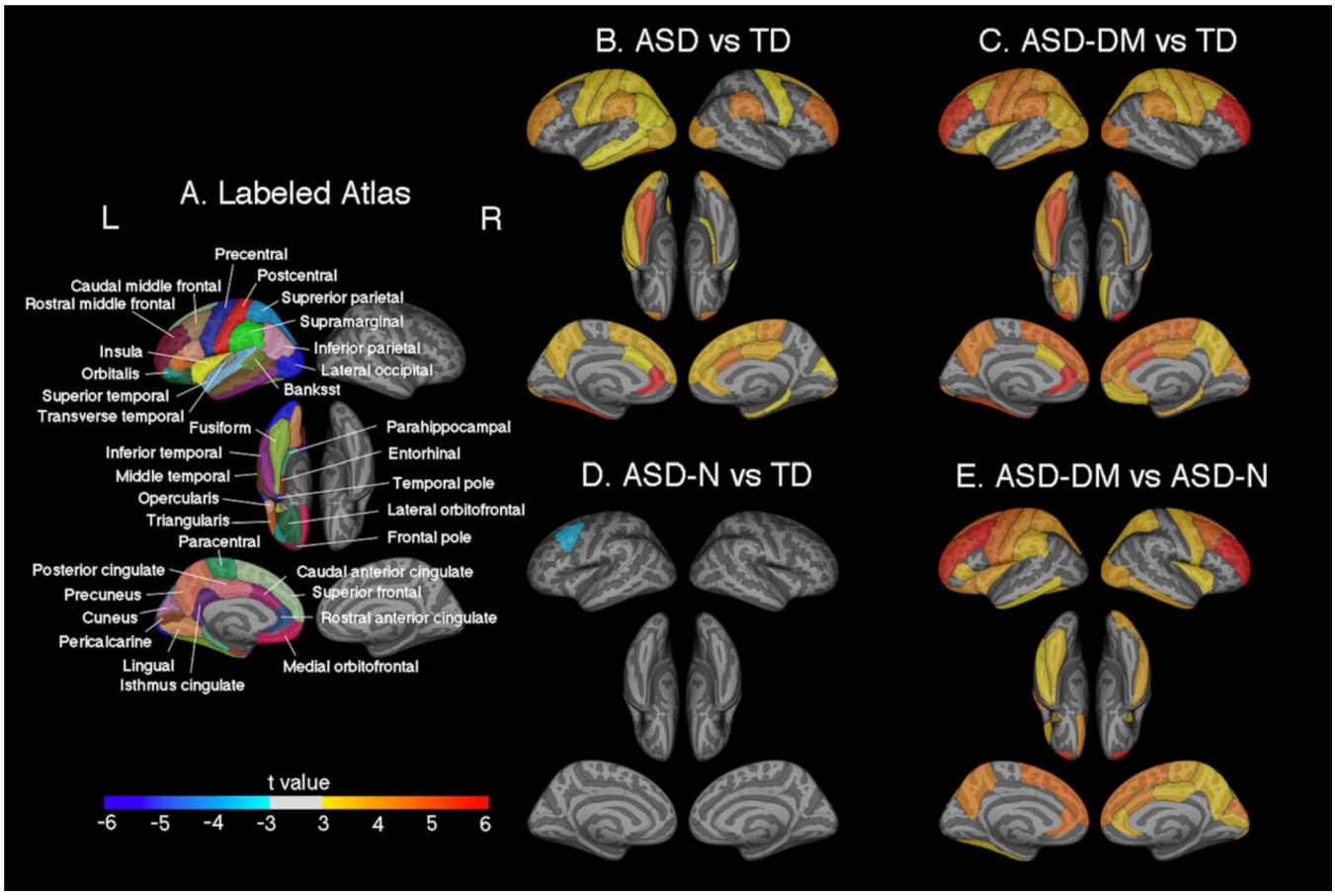

Figure 1. Illustration of the results of the FreeSurfer analysis of cortical surface area

(A) Labeled atlas showing the 34, color-coded regions that are identified by FreeSurfer. The right hemispere presents inflated surface maps where dark grey represents sulci and light grey represent gyri of the cortical surface; lateral, ventral and medial views are illustrated. (B) Regions of increased SA in the ASD group compared to the TD group. (C) Regions of increased SA in the ASD-DM group compared to the TD group. (D) Region of decreased SA in the ASD-N group compared to the TD group. (E) Regions of increased SA in the ASD-DM group compared to the ASD-N group. For A–D, the colored legend at left represents the *t* values indicating magnitude of difference. Regions in red/yellow and dark blue/light blue survived multiple comparison adjustment (adjusted $P < 0.05$). Warm colors indicate greater surface area in the direction of the stated comparison (e.g., ASD vs. TD) and cold colors indicate less surface area in the direction of the stated comparison (see text for detailed description).

Table 1

Demographic and Clinical Characteristics With Mean TCV and Height

	ASD-DM (*n* = 17)	ASD-N (*n* = 95)	TD (*n* = 50)
Age (months)	36.0 ± 5.1	36.3 ± 5.3	35.6 ± 4.9
DQ	58.6 ± 22.7[a]	64.6 ± 21.1[a]	105.4 ± 12.1[b]
VDQ	51.0 ± 27.0[a]	56.4 ± 26.5[a]	107.0 ± 13.0[b]
NVDQ	66.3 ± 20.8[a]	72.8 ± 18.5[a]	103.8 ± 14.7[b]
ADOS severity	7.6 ± 2.1	7.9 ± 1.7	—
TCV (cm^3)	1140.1 ± 60.5[a]	1013.1 ± 76.5[b]	983.7 ± 77.4[b]
Height (cm)	36.8 ± 2.1	37.2 ± 2.5	36.7 ± 2.5

Data are presented as mean ± SD.

ASD, autism spectrum disorder; TD, typical development; ASD-DM, ASD with disproportionate megalencephaly; ASD-N, ASD without megalencephaly; DQ, developmental quotient; VDQ, verbal DQ; NVDQ, non verbal DQ; ADOS, autism diagnostic observation schedule; TCV, total cerebral volume.

[a,b]Different letters denote groups that are significantly different after adjusting for multiple comparisons using Tukey–Kramer method ($P < 0.05$).

Table 2

Summary of Gray Matter Volume (mm^3) for Left (L) and Right (R) Hemispheres

		ASD		ASD-DM		ASD-N		TD	
		mean	**(SD)**	**mean**	**(SD)**	**mean**	**(SD)**	**mean**	**(SD)**
Frontal lobe									
Caudal middle frontal	L	8029	(1516)	9546	(1779)	7757	(1298)	8324	(1467)
	R	7358	(1536)	8549	(1685)	7145	(1415)	7377	(1349)
Frontal pole	L	1044	(192)	1087	(216)	1037	(187)	1035	(171)
	R	1403	(256)	1421	(271)	1400	(254)	1346	(207)
Lateral orbitofrontal	L	9738	(996)	10803	(939)	9548	(883)	9441	(857)
	R	9431	(989)	10245	(856)	9285	(943)	9152	(809)
Medial orbitofrontal	L	6735	(765)	7196	(917)	6653	(708)	6486	(830)
	R	6964	(789)	7531	(697)	6863	(764)	6515	(580)
Paracentral	L	4199	(784)	4711	(672)	4107	(770)	4171	(575)
	R	4827	(883)	5518	(761)	4703	(849)	4466	(698)
Pars opercularis	L	6282	(1165)	6753	(1295)	6198	(1126)	6029	(844)
	R	5158	(938)	5383	(880)	5118	(947)	4866	(813)
Pars orbitalis	L	2853	(409)	3111	(375)	2807	(399)	2760	(408)
	R	3591	(432)	3926	(373)	3531	(416)	3516	(459)
Pars triangularis	L	4904	(749)	5578	(716)	4784	(692)	4849	(706)
	R	5784	(947)	6406	(1084)	5672	(881)	5521	(801)
Precentral	L	15528	(1876)	17615	(1704)	15155	(1653)	15139	(1600)
	R	15533	(1809)	17207	(1336)	15233	(1721)	15088	(1639)
Rostral middle frontal	L	22052	(2381)	24590	(1774)	21598	(2187)	21149	(2224)
	R	22725	(2775)	25718	(2590)	22189	(2458)	21795	(2248)
Superior frontal	L	28689	(3034)	31440	(2760)	28197	(2821)	27888	(2513)
	R	27733	(2774)	30635	(2154)	27214	(2550)	26834	(2862)
Temporal lobe									
Banks superior temporal sulcus	L	3384	(613)	3549	(605)	3355	(613)	3212	(610)
	R	3191	(589)	3249	(493)	3181	(606)	2920	(364)
Entorhinal	L	2036	(362)	2214	(352)	2004	(356)	1924	(342)

		ASD		ASD-DM		ASD-N		TD	
		mean	(SD)	mean	(SD)	mean	(SD)	mean	(SD)
	R	1891	(437)	2221	(518)	1832	(396)	1689	(304)
Fusiform	L	12755	(1512)	14027	(1284)	12528	(1440)	11576	(1174)
	R	12434	(1645)	13359	(2070)	12269	(1511)	11852	(1548)
Inferior temporal	L	13208	(1996)	14514	(1735)	12975	(1957)	12594	(1838)
	R	12742	(2007)	14259	(1750)	12470	(1934)	12564	(1763)
Middle temporal	L	13798	(1849)	14909	(1949)	13599	(1768)	12970	(1569)
	R	15385	(1913)	16517	(2049)	15183	(1825)	14574	(1471)
Parahippocampal	L	2407	(323)	2609	(397)	2371	2296	2403	(667)
	R	2347	(441)	2714	(570)	2282	(381)	2187	(413)
Superior temporal	L	15085	(1716)	16156	(1780)	14893	(1642)	14164	(1221)
	R	14517	(1538)	15167	(1132)	14400	(1577)	13719	(1296)
Temporal pole	L	2572	(329)	2645	(287)	2559	(336)	2541	(310)
	R	2288	(377)	2364	(434)	2274	(367)	2188	(319)
Transverse temporal	L	1584	(287)	1791	(355)	1547	(258)	1548	(226)
	R	1230	(219)	1385	(271)	1202	(198)	1204	(212)
Parietal lobe									
Inferior parietal	L	18200	(2557)	19720	(2752)	17928	(2437)	17366	(2211)
	R	21750	(2664)	23071	(2661)	21514	(2608)	20960	(2314)
Postcentral	L	13061	(1754)	14488	(1954)	12806	(1596)	12566	(1564)
	R	12400	(1655)	13504	(1703)	12203	(1575)	11861	(1477)
Precuneus	L	13663	(1533)	15344	(1531)	13362	(1332)	13071	(1579)
	R	13976	(1598)	15287	(1835)	13742	(1441)	13601	(1372)
Superior parietal	L	18622	(2408)	20427	(1955)	18299	(2346)	17930	(2055)
	R	18721	(2281)	20300	(2260)	18439	(2178)	18157	(1755)
Supramarginal	L	15344	(2080)	16755	(1759)	15091	(2040)	14504	(1773)
	R	14428	(2071)	15615	(2118)	14215	(2000)	13253	(1752)
Occipital lobe									
Cuneus	L	4069	(660)	4587	(409)	3976	(655)	3921	(575)
	R	4071	(883)	4811	(415)	3939	(880)	3910	(828)
Lateral occipital	L	14782	(1907)	16157	(2026)	14536	(1787)	13878	(1747)

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		ASD		ASD-DM		ASD-N		TD	
		mean	(SD)	mean	(SD)	mean	(SD)	mean	(SD)
Lingual	R	14412	(2119)	16203	(2070)	14092	(1972)	13547	(1766)
	L	8667	(1299)	9415	(994)	8533	(1306)	8212	(1316)
	R	8883	(1251)	9787	(1032)	8721	(1222)	8465	(1288)
Pericalcarine	L	2682	(479)	2950	(408)	2634	(477)	2528	(422)
	R	2790	(499)	3189	(341)	2719	(490)	2664	(483)
Cingulate									
Caudal anterior cingulate	L	2407	(553)	2694	(536)	2355	(542)	2241	(438)
	R	2648	(684)	3126	(799)	2562	(628)	2381	(473)
Isthmus cingulate	L	3655	(583)	4104	(631)	3575	(539)	3488	(420)
	R	3301	(542)	3473	(482)	3270	(549)	3246	(477)
Posterior cingulate	L	4459	(734)	4670	(614)	4421	(750)	4279	(576)
	R	4492	(805)	5068	(922)	4389	(742)	4143	(721)
Rostral anterior	L	3618	(666)	4230	(590)	3509	(621)	3192	(506)
Cingulate	R	2686	(533)	3063	(527)	2618	(508)	2503	(488)
Insula									
Insula	L	7953	(895)	8882	(1009)	7787	(767)	7757	(834)
	R	8002	(878)	8887	(963)	7844	(765)	7710	(928)

Data are presented as mean (SD).

Table 3

Results of the Mixed-Effect Models for Gray Matter Volume in Left (L) and Right (R) Hemispheres

		ASD vs TD		ASD-DM vs TD		ASD-N vs TD		ASD-DM vs ASD-N	
		Estimate (SE)	***P***	**Estimate (SE)**	***P***	**Estimate (SE)**	***P***	**Estimate (SE)**	***P***
Frontal lobe									
Caudal middle Frontal	L	0.08 (0.06)	0.555	0.33 (0.09)	**0.014**	−0.17 (0.05)	0.094	0.50 (0.08)	**<0.001**
	R	0.13 (0.06)	0.238	0.34 (0.09)	**0.016**	−0.09 (0.06)	0.971	0.42 (0.09)	**<0.001**
Frontal pole	L	0.03 (0.06)	0.785	0.06 (0.09)	1.000	−0.01 (0.05)	1.000	0.07 (0.08)	1.000
	R	0.06 (0.06)	0.523	0.07 (0.09)	1.000	0.05 (0.06)	1.000	0.03 (0.09)	1.000
Lateral orbitofrontal	L	0.18 (0.06)	0.055	0.33 (0.09)	**0.009**	0.02 (0.05)	1.000	0.31 (0.08)	**0.009**
	R	0.15 (0.06)	0.118	0.28 (0.09)	0.119	0.03 (0.06)	1.000	0.25 (0.09)	0.157
Medial orbitofrontal	L	0.14 (0.06)	0.173	0.23 (0.09)	0.277	0.05 (0.05)	0.999	0.18 (0.08)	0.613
	R	0.22 (0.06)	**0.013**	0.33 (0.09)	**0.025**	0.11 (0.06)	0.847	0.22 (0.09)	0.355
Paracentral	L	0.10 (0.06)	0.416	0.24 (0.09)	0.218	−0.05 (0.05)	1.000	0.29 (0.08)	**0.025**
	R	0.27 (0.06)	**0.001**	0.44 (0.09)	**<0.001**	0.09 (0.06)	0.936	0.35 (0.09)	**0.004**
Pars opercularis	L	0.14 (0.06)	0.181	0.24 (0.09)	0.250	0.04 (0.05)	1.000	0.19 (0.08)	0.480
	R	0.15 (0.06)	0.118	0.21 (0.09)	0.561	0.09 (0.06)	0.936	0.11 (0.09)	0.989
Pars orbitalis	L	0.12 (0.06)	0.265	0.22 (0.09)	0.349	0.02 (0.05)	1.000	0.20 (0.08)	0.447
	R	0.11 (0.06)	0.334	0.22 (0.09)	0.493	0.00 (0.06)	1.000	0.21 (0.09)	0.409
Pars triangularis	L	0.13 (0.06)	0.213	0.30 (0.09)	**0.038**	−0.03 (0.05)	1.000	0.33 (0.08)	**0.004**
	R	0.18 (0.06)	0.051	0.32 (0.09)	**0.036**	0.05 (0.06)	1.000	0.27 (0.09)	0.099
Precentral	L	0.21 (0.06)	**0.010**	0.43 (0.09)	**<0.001**	0.00 (0.05)	1.000	0.43 (0.08)	**<0.001**
	R	0.20 (0.06)	**0.033**	0.37 (0.09)	**0.004**	0.02 (0.06)	1.000	0.35 (0.09)	**0.003**
Rostral middle frontal	L	0.26 (0.06)	**0.001**	0.47 (0.09)	**<0.001**	0.06 (0.05)	0.999	0.41 (0.08)	**<0.001**
	R	0.28 (0.06)	**<0.001**	0.51 (0.09)	**<0.001**	0.05 (0.06)	1.000	0.46 (0.09)	**<0.001**
Superior frontal	L	0.21 (0.06)	**0.011**	0.39 (0.09)	**0.001**	0.03 (0.05)	1.000	0.36 (0.08)	**0.001**
	R	0.24 (0.06)	**0.005**	0.43 (0.09)	**<0.001**	0.04 (0.06)	1.000	0.39 (0.09)	**<0.001**
Temporal lobe									
Banks superior temporal sulcus	L	0.14 (0.06)	0.200	0.19 (0.09)	0.585	0.08 (0.05)	0.980	0.12 (0.08)	0.982
	R	0.16 (0.06)	0.090	0.19 (0.09)	0.724	0.14 (0.06)	0.466	0.05 (0.09)	1.000
Entorhinal	L	0.15 (0.06)	0.146	0.24 (0.09)	0.250	0.06 (0.05)	0.998	0.18 (0.08)	0.619

		ASD vs TD		ASD-DM vs TD		ASD-N vs TD		ASD-DM vs ASD-N	
		Estimate (SE)	***P***	**Estimate (SE)**	***P***	**Estimate (SE)**	***P***	**Estimate (SE)**	***P***
	R	0.28 (0.06)	**<0.001**	0.44 (0.09)	**<0.001**	0.12 (0.06)	0.724	0.32 (0.09)	**0.014**
Fusiform	L	0.35 (0.06)	**<0.001**	0.51 (0.09)	**<0.001**	0.20 (0.05)	**0.019**	0.31 (0.08)	**0.011**
	R	0.20 (0.06)	**0.033**	0.31 (0.09)	**0.047**	0.09 (0.06)	0.971	0.22 (0.09)	0.355
Inferior temporal	L	0.23 (0.06)	**0.004**	0.39 (0.09)	**0.001**	0.07 (0.05)	0.990	0.31 (0.08)	**0.009**
	R	0.16 (0.06)	0.114	0.34 (0.09)	**0.014**	−0.03 (0.06)	1.000	0.37 (0.09)	**0.001**
Middle temporal	L	0.24 (0.06)	**0.001**	0.37 (0.09)	**0.002**	0.12 (0.05)	0.613	0.25 (0.08)	0.098
	R	0.22 (0.06)	**0.011**	0.34 (0.09)	**0.015**	0.10 (0.06)	0.897	0.24 (0.09)	0.217
Parahippocampal	L	0.08 (0.06)	0.555	0.16 (0.09)	0.832	−0.01 (0.05)	1.000	0.17 (0.08)	0.696
	R	0.22 (0.06)	**0.011**	0.37 (0.09)	**0.004**	0.07 (0.06)	0.995	0.30 (0.09)	**0.032**
Superior temporal	L	0.24 (0.06)	**0.002**	0.36 (0.09)	**0.003**	0.13 (0.05)	0.501	0.23 (0.08)	0.200
	R	0.20 (0.06)	**0.031**	0.27 (0.09)	0.126	0.12 (0.06)	0.671	0.15 (0.09)	0.897
Temporal pole	L	0.04 (0.06)	0.785	0.07 (0.09)	1.000	0.00 (0.05)	1.000	0.07 (0.08)	1.000
	R	0.09 (0.06)	0.396	0.12 (0.09)	0.989	0.06 (0.06)	0.999	0.07 (0.09)	1.000
Transverse temporal	L	0.10 (0.06)	0.395	0.22 (0.09)	0.373	−0.01 (0.05)	1.000	0.23 (0.08)	0.200
	R	0.10 (0.06)	0.396	0.20 (0.09)	0.625	−0.01 (0.06)	1.000	0.21 (0.09)	0.442
Parietal lobe									
Inferior parietal	L	0.22 (0.06)	**0.006**	0.36 (0.09)	**0.003**	0.08 (0.05)	0.968	0.28 (0.08)	**0.038**
	R	0.18 (0.06)	0.059	0.29 (0.09)	0.090	0.07 (0.06)	0.995	0.22 (0.09)	0.370
Postcentral	L	0.21 (0.06)	**0.011**	0.38 (0.09)	**0.001**	0.04 (0.05)	1.000	0.33 (0.08)	**0.004**
	R	0.20 (0.06)	**0.025**	0.34 (0.09)	**0.015**	0.07 (0.06)	0.995	0.27 (0.09)	0.078
Precuneus	L	0.25 (0.06)	**0.001**	0.44 (0.09)	**<0.001**	0.06 (0.05)	0.999	0.38 (0.08)	**<0.001**
	R	0.17 (0.06)	0.084	0.31 (0.09)	**0.039**	0.02 (0.06)	1.000	0.29 (0.09)	**0.040**
Superior parietal	L	0.22 (0.06)	**0.008**	0.38 (0.09)	**0.001**	0.05 (0.05)	1.000	0.34 (0.08)	**0.003**
	R	0.18 (0.06)	0.059	0.32 (0.09)	**0.032**	0.03 (0.06)	1.000	0.29 (0.09)	**0.045**
Supramarginal	L	0.25 (0.06)	**0.001**	0.40 (0.09)	**<0.001**	0.05 (0.03)	0.934	0.30 (0.08)	**0.015**
	R	0.31 (0.06)	**<0.001**	0.44 (0.09)	**<0.001**	0.06 (0.03)	0.683	0.26 (0.09)	0.105
Occipital lobe									
Cuneus	L	0.17 (0.06)	0.069	0.32 (0.09)	**0.015**	0.02 (0.05)	1.000	0.31 (0.08)	**0.013**
	R	0.22 (0.06)	**0.010**	0.45 (0.09)	**<0.001**	0.00 (0.06)	1.000	0.45 (0.09)	**<0.001**
Lateral occipital	L	0.27 (0.06)	**<0.001**	0.42 (0.09)	**<0.001**	0.12 (0.05)	0.593	0.30 (0.08)	**0.019**

		ASD vs TD		ASD-DM vs TD		ASD-N vs TD		ASD-DM vs ASD-N	
		Estimate (SE)	***P***	**Estimate (SE)**	***P***	**Estimate (SE)**	***P***	**Estimate (SE)**	***P***
	R	0.29 (0.06)	**<0.001**	0.49 (0.09)	**<0.001**	0.10 (0.06)	0.922	0.39 (0.09)	**<0.001**
Lingual	L	0.21 (0.06)	**0.009**	0.34 (0.09)	**0.007**	0.09 (0.05)	0.944	0.25 (0.08)	0.099
	R	0.22 (0.06)	**0.013**	0.36 (0.09)	**0.006**	0.07 (0.06)	0.995	0.29 (0.09)	**0.040**
Pericalcarine	L	0.17 (0.06)	0.069	0.28 (0.09)	0.071	0.06 (0.05)	0.997	0.22 (0.08)	0.277
	R	0.19 (0.06)	**0.046**	0.34 (0.09)	**0.014**	0.03 (0.06)	1.000	0.31 (0.09)	**0.020**
Cingulate									
Caudal anterior cingulate	L	0.19 (0.06)	**0.023**	0.32 (0.09)	**0.017**	0.07 (0.05)	0.993	0.25 (0.08)	0.107
	R	0.29 (0.06)	**<0.001**	0.47 (0.09)	**<0.001**	0.11 (0.06)	0.815	0.36 (0.09)	**0.002**
Isthmus cingulate	L	0.17 (0.06)	0.069	0.31 (0.09)	**0.027**	0.03 (0.05)	1.000	0.27 (0.08)	**0.048**
	R	0.06 (0.06)	0.523	0.13 (0.09)	0.986	0.00 (0.06)	1.000	0.12 (0.09)	0.977
Posterior cingulate	L	0.11 (0.06)	0.323	0.18 (0.09)	0.710	0.05 (0.05)	1.000	0.12 (0.08)	0.968
	R	0.26 (0.06)	**0.001**	0.41 (0.09)	**0.001**	0.11 (0.06)	0.812	0.30 (0.09)	**0.036**
Rostral anterior cingulate	L	0.36 (0.06)	**<0.001**	0.55 (0.09)	**<0.001**	0.17 (0.05)	0.101	0.38 (0.08)	**<0.001**
	R	0.22 (0.06)	**0.011**	0.37 (0.09)	**0.005**	0.07 (0.06)	0.990	0.29 (0.09)	**0.039**
Insula									
Insula	L	0.16 (0.06)	0.098	0.32 (0.09)	**0.018**	0.00 (0.05)	1.000	0.32 (0.08)	**0.009**
	R	0.19 (0.06)	**0.045**	0.34 (0.09)	**0.016**	0.04 (0.06)	1.000	0.30 (0.09)	**0.033**

Mixed-effects linear models were used to estimate group differences in **gray matter volume** across different regions. Data were fourth root transformed prior to analysis.

P-values were adjusted for multiple comparisons. Those *P*-values that survived correction for multiple comparisons (adjusted $P < 0.05$) are indicated by bold values.

Table 4

Summary of Cortical Thickness (mm) for Left (L) and Right (R) Hemispheres

		ASD		ASD-DM		ASD-N		TD	
		mean	**(SD)**	**mean**	**(SD)**	**mean**	**(SD)**	**mean**	**(SD)**
Frontal lobe									
Caudal middle frontal	L	2.99	(0.13)	3.01	(0.10)	2.98	(0.14)	2.98	(0.11)
	R	2.96	(0.13)	2.98	(0.10)	2.96	(0.14)	2.96	(0.13)
Frontal pole	L	3.52	(0.32)	3.49	(0.29)	3.53	(0.33)	3.53	(0.30)
	R	3.37	(0.30)	3.34	(0.31)	3.37	(0.30)	3.36	(0.34)
Lateral orbitofrontal	L	3.27	(0.14)	3.22	(0.17)	3.27	(0.14)	3.26	(0.14)
	R	3.17	(0.16)	3.16	(0.15)	3.17	(0.17)	3.19	(0.13)
Medial orbitofrontal	L	3.14	(0.19)	3.07	(0.20)	3.15	(0.19)	3.14	(0.15)
	R	3.14	(0.18)	3.09	(0.18)	3.14	(0.19)	3.09	(0.14)
Paracentral	L	2.81	(0.15)	2.86	(0.15)	2.80	(0.15)	2.82	(0.13)
	R	2.75	(0.15)	2.78	(0.13)	2.75	(0.16)	2.75	(0.14)
Pars opercularis	L	3.10	(0.14)	3.12	(0.15)	3.10	(0.14)	3.10	(0.14)
	R	3.09	(0.13)	3.12	(0.11)	3.09	(0.14)	3.09	(0.14)
Pars orbitalis	L	3.39	(0.20)	3.28	(0.17)	3.41	(0.20)	3.41	(0.21)
	R	3.41	(0.21)	3.35	(0.20)	3.42	(0.21)	3.40	(0.26)
Pars triangularis	L	3.06	(0.15)	3.10	(0.13)	3.06	(0.15)	3.07	(0.15)
	R	3.05	(0.14)	3.10	(0.15)	3.04	(0.14)	3.03	(0.17)
Precentral	L	2.82	(0.13)	2.86	(0.10)	2.81	(0.13)	2.82	(0.12)
	R	2.74	(0.13)	2.78	(0.11)	2.74	(0.14)	2.76	(0.12)
Rostral middle frontal	L	3.01	(0.12)	2.97	(0.08)	3.01	(0.13)	3.00	(0.13)
	R	2.96	(0.13)	2.93	(0.10)	2.97	(0.13)	2.97	(0.13)
Superior frontal	L	3.33	(0.14)	3.30	(0.12)	3.34	(0.14)	3.35	(0.12)
	R	3.26	(0.14)	3.24	(0.09)	3.26	(0.14)	3.26	(0.13)
Temporal lobe									
Banks superior temporal sulcus	L	3.00	(0.18)	3.01	(0.16)	3.00	(0.18)	2.94	(0.19)
	R	3.08	(0.20)	3.05	(0.23)	3.09	(0.20)	3.08	(0.18)
Entorhinal	L	3.59	(0.30)	3.61	(0.27)	3.58	(0.31)	3.59	(0.27)

		ASD		ASD-DM		ASD-N		TD	
		mean	(SD)	mean	(SD)	mean	(SD)	mean	(SD)
	R	3.64	(0.36)	3.74	(0.32)	3.62	(0.37)	3.64	(0.29)
Fusiform	L	3.08	(0.12)	3.10	(0.10)	3.08	(0.13)	3.03	(0.12)
	R	3.13	(0.13)	3.14	(0.08)	3.13	(0.14)	3.13	(0.13)
Inferior temporal	L	3.23	(0.15)	3.26	(0.12)	3.22	(0.15)	3.21	(0.14)
	R	3.25	(0.15)	3.28	(0.13)	3.25	(0.15)	3.25	(0.13)
Middle temporal	L	3.39	(0.15)	3.43	(0.16)	3.39	(0.15)	3.36	(0.14)
	R	3.47	(0.13)	3.48	(0.13)	3.47	(0.14)	3.45	(0.13)
Parahippocampal	L	3.05	(0.28)	3.02	(0.28)	3.06	(0.29)	3.07	(0.30)
	R	2.97	(0.24)	3.00	(0.21)	2.96	(0.25)	2.94	(0.26)
Superior temporal	L	3.22	(0.16)	3.25	(0.14)	3.21	(0.17)	3.16	(0.14)
	R	3.25	(0.15)	3.23	(0.11)	3.25	(0.15)	3.22	(0.14)
Temporal pole	L	3.86	(0.27)	3.89	(0.27)	3.85	(0.27)	3.81	(0.24)
	R	3.93	(0.23)	3.97	(0.21)	3.93	(0.23)	3.91	(0.25)
Transverse temporal	L	2.91	(0.25)	2.92	(0.19)	2.90	(0.26)	2.92	(0.22)
	R	2.96	(0.25)	2.98	(0.22)	2.96	(0.25)	2.94	(0.29)
Parietal lobe									
Inferior parietal	L	3.12	(0.13)	3.13	(0.09)	3.12	(0.14)	3.10	(0.10)
	R	3.12	(0.13)	3.14	(0.10)	3.11	(0.14)	3.14	(0.09)
Postcentral	L	2.48	(0.17)	2.47	(0.11)	2.48	(0.18)	2.48	(0.16)
	R	2.47	(0.16)	2.48	(0.11)	2.47	(0.17)	2.46	(0.17)
Precuneus	L	2.98	(0.14)	3.00	(0.11)	2.97	(0.15)	2.96	(0.11)
	R	2.89	(0.15)	2.88	(0.12)	2.89	(0.16)	2.89	(0.14)
Superior parietal	L	2.74	(0.13)	2.76	(0.10)	2.74	(0.13)	2.74	(0.13)
	R	2.73	(0.13)	2.72	(0.11)	2.73	(0.13)	2.74	(0.13)
Supramarginal	L	3.11	(0.15)	3.11	(0.14)	3.11	(0.15)	3.12	(0.11)
	R	3.14	(0.14)	3.16	(0.13)	3.13	(0.15)	3.13	(0.14)
Occipital lobe									
Cuneus	L	2.31	(0.19)	2.39	(0.18)	2.30	(0.19)	2.27	(0.15)
	R	2.25	(0.19)	2.32	(0.14)	2.24	(0.20)	2.24	(0.17)
Lateral occipital	L	2.50	(0.14)	2.54	(0.13)	2.49	(0.15)	2.47	(0.15)

		ASD		ASD-DM		ASD-N		TD	
		mean	(SD)	mean	(SD)	mean	(SD)	mean	(SD)
Lingual	R	2.58	(0.15)	2.66	(0.12)	2.57	(0.15)	2.56	(0.14)
	L	2.36	(0.15)	2.45	(0.11)	2.35	(0.15)	2.33	(0.14)
Pericalcarine	R	2.42	(0.14)	2.47	(0.11)	2.41	(0.14)	2.39	(0.14)
	L	1.94	(0.16)	2.01	(0.16)	1.93	(0.16)	1.90	(0.14)
	R	1.87	(0.14)	1.92	(0.17)	1.86	(0.13)	1.83	(0.14)
Cingulate									
Caudal anterior cingulate	L	3.24	(0.29)	3.23	(0.22)	3.24	(0.30)	3.26	(0.30)
	R	3.01	(0.26)	2.99	(0.22)	3.01	(0.27)	2.98	(0.25)
Isthmus cingulate	L	2.97	(0.23)	3.07	(0.15)	2.95	(0.24)	2.99	(0.18)
	R	2.89	(0.22)	2.93	(0.16)	2.88	(0.23)	2.93	(0.20)
Posterior cingulate	L	3.06	(0.17)	3.08	(0.19)	3.06	(0.17)	3.04	(0.16)
	R	2.94	(0.16)	2.94	(0.13)	2.93	(0.16)	2.90	(0.15)
Rostral anterior cingulate	L	3.64	(0.23)	3.62	(0.22)	3.65	(0.24)	3.65	(0.19)
	R	3.48	(0.23)	3.45	(0.19)	3.48	(0.23)	3.50	(0.21)
Insula									
Insula	L	3.58	(0.15)	3.54	(0.12)	3.59	(0.15)	3.55	(0.14)
	R	3.55	(0.15)	3.53	(0.12)	3.55	(0.15)	3.52	(0.16)

Data are presented as mean (SD).

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Table 5

Summary of Cortical Surface Area (mm^2) for Left (L) and Right (R) Hemispheres

		ASD		ASD-DM		ASD-N		TD	
		mean	**(SD)**	**mean**	**(SD)**	**mean**	**(SD)**	**mean**	**(SD)**
Frontal lobe									
Caudal middle frontal	L	2893	(542)	3430	(633)	2797	(466)	3034	(567)
	R	2692	(564)	3129	(627)	2613	(517)	2720	(506)
Frontal pole	L	390	(71)	410	(83)	387	(68)	393	(62)
	R	540	(89)	537	(87)	540	(90)	526	(76)
Lateral orbitofrontal	L	3293	(367)	3706	(389)	3219	(312)	3215	(354)
	R	3242	(379)	3533	(364)	3190	(359)	3128	(276)
Medial orbitofrontal	L	2451	(276)	2652	(304)	2415	(256)	2366	(279)
	R	2575	(278)	2815	(200)	2532	(269)	2460	(250)
Paracentral	L	1625	(300)	1802	(261)	1593	(297)	1612	(226)
	R	1893	(345)	2150	(293)	1847	(335)	1745	(264)
Pars opercularis	L	2309	(437)	2445	(450)	2285	(433)	2229	(304)
	R	1857	(343)	1903	(339)	1848	(345)	1760	(301)
Pars orbitalis	L	1039	(152)	1160	(147)	1017	(143)	999	(148)
	R	1283	(164)	1421	(135)	1259	(157)	1266	(159)
Pars triangularis	L	1791	(270)	2013	(271)	1752	(251)	1777	(254)
	R	2135	(355)	2330	(413)	2099	(334)	2054	(301)
Precentral	L	5925	(746)	6641	(570)	5797	(701)	5765	(591)
	R	6046	(763)	6606	(565)	5946	(752)	5835	(651)
Rostral middle frontal	L	8291	(928)	9352	(702)	8102	(832)	8007	(873)
	R	8685	(1085)	9952	(1141)	8458	(909)	8336	(911)
Superior frontal	L	9615	(1045)	10623	(956)	9435	(958)	9310	(771)
	R	9517	(1056)	10533	(808)	9335	(992)	9230	(917)
Temporal lobe									
Banks superior temporal sulcus	L	1108	(204)	1149	(197)	1101	(205)	1079	(208)
	R	1008	(188)	1030	(163)	1005	(193)	922	(124)
Entorhinal	L	701	(120)	757	(120)	691	(118)	665	(125)

		ASD		ASD-DM		ASD-N		TD	
		mean	(SD)	mean	(SD)	mean	(SD)	mean	(SD)
	R	651	(145)	743	(167)	635	(135)	587	(124)
Fusiform	L	4616	(557)	5036	(459)	4541	(541)	4233	(444)
	R	4396	(611)	4677	(734)	4345	(576)	4184	(540)
Inferior temporal	L	4568	(656)	4965	(541)	4497	(652)	4384	(653)
	R	4401	(678)	4882	(581)	4315	(660)	4372	(641)
Middle temporal	L	4765	(629)	5079	(670)	4709	(608)	4548	(531)
	R	5162	(670)	5476	(721)	5106	(649)	4948	(529)
Parahippocampal	L	893	(113)	965	(110)	880	(109)	891	(263)
	R	861	(156)	986	(203)	839	(136)	808	(146)
Superior temporal	L	5188	(532)	5467	(537)	5138	(518)	4959	(410)
	R	4934	(468)	5166	(383)	4893	(472)	4702	(389)
Temporal pole	L	859	(94)	869	(77)	858	(97)	864	(92)
	R	756	(117)	771	(140)	753	(113)	731	(96)
Transverse temporal	L	618	(118)	691	(137)	604	(110)	608	(107)
	R	477	(98)	539	(126)	466	(89)	474	(103)
Parietal lobe									
Inferior parietal	L	6466	(908)	6950	(993)	6380	(869)	6223	(800)
	R	7734	(961)	8118	(969)	7665	(949)	7446	(848)
Postcentral	L	5877	(653)	6520	(728)	5762	(570)	5677	(584)
	R	5594	(666)	6061	(688)	5510	(629)	5383	(501)
Precuneus	L	4968	(527)	5544	(526)	4865	(459)	4795	(556)
	R	5212	(626)	5701	(609)	5124	(590)	5071	(455)
Superior parietal	L	7397	(897)	8075	(640)	7276	(884)	7160	(721)
	R	7522	(870)	8183	(893)	7403	(815)	7294	(625)
Supramarginal	L	5464	(756)	5956	(622)	5376	(747)	5162	(620)
	R	5032	(719)	5388	(723)	4968	(704)	4639	(608)
Occipital lobe									
Cuneus	L	1958	(282)	2136	(173)	1927	(286)	1912	(246)
	R	2012	(369)	2317	(208)	1958	(365)	1942	(351)
Lateral occipital	L	6408	(780)	6894	(816)	6321	(744)	6110	(641)

		ASD		ASD-DM		ASD-N		TD	
		mean	(SD)	mean	(SD)	mean	(SD)	mean	(SD)
Lingual	R	6046	(800)	6663	(701)	5935	(768)	5740	(613)
	L	4030	(564)	4229	(406)	3995	(583)	3896	(576)
	R	4035	(513)	4363	(449)	3977	(503)	3896	(533)
Pericalcarine	L	1321	(220)	1396	(190)	1308	(224)	1277	(194)
	R	1455	(242)	1630	(153)	1424	(242)	1419	(231)
Cingulate									
Caudal anterior cingulate	L	815	(181)	906	(165)	799	(179)	758	(130)
	R	963	(237)	1141	(262)	931	(219)	869	(169)
Isthmus cingulate	L	1346	(222)	1459	(226)	1325	(217)	1279	(154)
	R	1251	(210)	1297	(161)	1243	(217)	1219	(193)
Posterior cingulate	L	1562	(274)	1626	(226)	1551	(281)	1509	(213)
	R	1651	(295)	1861	(310)	1614	(278)	1543	(280)
Rostral anterior cingulate	L	1182	(241)	1389	(224)	1144	(225)	1038	(178)
	R	898	(190)	1038	(199)	872	(179)	835	(180)
Insula									
Insula	L	2186	(285)	2468	(342)	2135	(243)	2153	(250)
	R	2238	(286)	2494	(323)	2192	(254)	2188	(280)

Data are presented as mean (SD).

Table 6

Results of the Mixed-Effect Model for Cortical Surface Area in Left (L) and Right (R) Hemispheres

		ASD vs. TD		ASD-DM vs. TD		ASD-N vs. TD		ASD-DM vs. ASD-N	
		Estimate (SE)	***P***	**Estimate (SE)**	***P***	**Estimate (SE)**	***P***	**Estimate (SE)**	***P***
Frontal lobe									
Caudal middle frontal	L	0.04 (0.05)	0.765	0.23 (0.07)	**0.045**	−0.15 (0.04)	**0.026**	0.38 (0.06)	**<0.001**
	R	0.08 (0.05)	0.404	0.25 (0.07)	**0.031**	−0.08 (0.04)	0.886	0.33 (0.07)	**<0.001**
Frontal pole	L	0.01 (0.05)	0.993	0.04 (0.07)	1.000	−0.03 (0.04)	1.000	0.06 (0.06)	1.000
	R	0.02 (0.05)	0.659	0.02 (0.07)	1.000	0.02 (0.04)	1.000	0.00 (0.07)	1.000
Lateral orbitofrontal	L	0.13 (0.05)	0.067	0.27 (0.07)	**0.005**	0.00 (0.04)	1.000	0.27 (0.06)	**0.001**
	R	0.13 (0.05)	0.113	0.23 (0.07)	0.084	0.03 (0.04)	1.000	0.20 (0.07)	0.136
Medial orbitofrontal	L	0.12 (0.05)	0.179	0.20 (0.07)	0.148	0.03 (0.04)	1.000	0.17 (0.06)	0.304
	R	0.14 (0.05)	0.064	0.24 (0.07)	**0.042**	0.04 (0.04)	1.000	0.20 (0.07)	0.146
Paracentral	L	0.07 (0.05)	0.605	0.17 (0.07)	0.350	−0.03 (0.04)	1.000	0.21 (0.06)	0.068
	R	0.21 (0.05)	**<0.001**	0.34 (0.07)	**<0.001**	0.08 (0.04)	0.897	0.26 (0.07)	**0.006**
Pars opercularis	L	0.09 (0.05)	0.441	0.15 (0.07)	0.643	0.03 (0.04)	1.000	0.12 (0.06)	0.833
	R	0.09 (0.05)	0.298	0.12 (0.07)	0.940	0.07 (0.04)	0.972	0.05 (0.07)	1.000
Pars orbitalis	L	0.12 (0.05)	0.167	0.21 (0.07)	0.084	0.02 (0.04)	1.000	0.19 (0.06)	0.116
	R	0.08 (0.05)	0.405	0.17 (0.07)	0.435	−0.02 (0.04)	1.000	0.19 (0.07)	0.188
Pars triangularis	L	0.09 (0.05)	0.441	0.21 (0.07)	0.117	−0.03 (0.04)	1.000	0.23 (0.06)	**0.015**
	R	0.12 (0.05)	0.158	0.21 (0.07)	0.167	0.03 (0.04)	1.000	0.18 (0.07)	0.292
Precentral	L	0.16 (0.05)	**0.017**	0.31 (0.07)	**<0.001**	0.00 (0.04)	1.000	0.31 (0.06)	**<0.001**
	R	0.15 (0.05)	**0.036**	0.28 (0.07)	**0.008**	0.03 (0.04)	1.000	0.24 (0.07)	**0.018**
Rostral middle frontal	L	0.20 (0.05)	**0.001**	0.38 (0.07)	**<0.001**	0.02 (0.04)	1.000	0.35 (0.06)	**<0.001**
	R	0.23 (0.05)	**<0.001**	0.43 (0.07)	**<0.001**	0.03 (0.04)	1.000	0.40 (0.07)	**<0.001**
Superior frontal	L	0.17 (0.05)	**0.005**	0.32 (0.07)	**<0.001**	0.02 (0.04)	1.000	0.30 (0.06)	**<0.001**
	R	0.17 (0.05)	**0.009**	0.33 (0.07)	**<0.001**	0.02 (0.04)	1.000	0.31 (0.07)	**<0.001**
Temporal lobe									
Banks superior temporal sulcus	L	0.06 (0.05)	0.605	0.09 (0.07)	0.992	0.02 (0.04)	1.000	0.07 (0.06)	1.000
	R	0.12 (0.05)	0.115	0.15 (0.07)	0.746	0.10 (0.04)	0.548	0.04 (0.07)	1.000
Entorhinal	L	0.11 (0.05)	0.252	0.17 (0.07)	0.416	0.04 (0.04)	1.000	0.12 (0.06)	0.833

		ASD vs. TD		ASD-DM vs. TD		ASD-N vs. TD		ASD-DM vs. ASD-N	
		Estimate (SE)	***P***	**Estimate (SE)**	***P***	**Estimate (SE)**	***P***	**Estimate (SE)**	***P***
	R	0.19 (0.05)	**0.002**	0.29 (0.07)	**0.003**	0.09 (0.04)	0.736	0.20 (0.07)	0.132
Fusiform	L	0.25 (0.05)	**<0.001**	0.36 (0.07)	**<0.001**	0.13 (0.04)	0.081	0.22 (0.06)	**0.030**
	R	0.14 (0.05)	0.064	0.22 (0.07)	0.114	0.07 (0.04)	0.972	0.15 (0.07)	0.633
Inferior temporal	L	0.16 (0.05)	**0.020**	0.26 (0.07)	**0.007**	0.05 (0.04)	1.000	0.21 (0.06)	**0.045**
	R	0.10 (0.05)	0.289	0.23 (0.07)	0.069	−0.03 (0.04)	1.000	0.26 (0.07)	**0.005**
Middle temporal	L	0.14 (0.05)	**0.039**	0.22 (0.07)	0.055	0.06 (0.04)	0.978	0.16 (0.06)	0.377
	R	0.13 (0.05)	0.098	0.21 (0.07)	0.154	0.06 (0.04)	0.996	0.15 (0.07)	0.584
Parahippocampal	L	0.06 (0.05)	0.605	0.13 (0.07)	0.839	0.00 (0.04)	1.000	0.13 (0.06)	0.733
	R	0.15 (0.05)	**0.036**	0.26 (0.07)	**0.015**	0.04 (0.04)	1.000	0.22 (0.07)	0.060
Superior temporal	L	0.13 (0.05)	0.067	0.20(0.07)	0.129	0.07 (0.04)	0.966	0.14 (0.06)	0.682
	R	0.13 (0.05)	0.094	0.19 (0.07)	0.243	0.07 (0.04)	0.940	0.12 (0.07)	0.898
Temporal pole	L	0.00 (0.05)	0.993	0.01 (0.07)	1.000	−0.02 (0.04)	1.000	0.02 (0.06)	1.000
	R	0.04 (0.05)	0.600	0.06 (0.07)	1.000	0.03 (0.04)	1.000	0.03 (0.07)	1.000
Transverse temporal	L	0.07 (0.05)	0.605	0.15 (0.07)	0.587	−0.02 (0.04)	1.000	0.17 (0.06)	0.292
	R	0.06 (0.05)	0.582	0.15 (0.07)	0.750	−0.02 (0.04)	1.000	0.17 (0.07)	0.389
Parietal lobe									
Inferior parietal	L	0.14 (0.05)	**0.039**	0.24 (0.07)	**0.024**	0.05 (0.04)	1.000	0.19 (0.06)	0.116
	R	0.13 (0.05)	0.111	0.20 (0.07)	0.214	0.06 (0.04)	0.994	0.14 (0.07)	0.736
Postcentral	L	0.16 (0.05)	**0.011**	0.30 (0.07)	**0.001**	0.03 (0.04)	1.000	0.27 (0.06)	**0.001**
	R	0.15 (0.05)	0.059	0.25 (0.07)	**0.028**	0.04 (0.04)	1.000	0.21 (0.07)	0.084
Precuneus	L	0.17 (0.05)	**0.008**	0.31 (0.07)	**<0.001**	0.03 (0.04)	1.000	0.28 (0.06)	**0.001**
	R	0.13 (0.05)	0.111	0.25 (0.07)	**0.036**	0.01 (0.04)	1.000	0.23 (0.07)	**0.031**
Superior parietal	L	0.15 (0.05)	**0.022**	0.28 (0.07)	**0.002**	0.03 (0.04)	1.000	0.25 (0.06)	**0.004**
	R	0.14 (0.05)	0.064	0.26 (0.07)	**0.016**	0.02 (0.04)	1.000	0.24 (0.07)	**0.024**
Supramarginal	L	0.19 (0.05)	**0.001**	0.31 (0.07)	**<0.001**	0.02 (0.02)	0.999	0.23 (0.06)	**0.018**
	R	0.22 (0.05)	**<0.001**	0.31 (0.07)	**0.001**	0.04 (0.02)	0.894	0.18 (0.07)	0.293
Occipital lobe									
Cuneus	L	0.10 (0.05)	0.355	0.19 (0.07)	0.216	0.00 (0.04)	1.000	0.19 (0.06)	0.148
	R	0.16 (0.05)	**0.026**	0.31 (0.07)	**0.001**	0.00 (0.04)	1.000	0.31 (0.07)	**<0.001**
Lateral occipital	L	0.17 (0.05)	**0.009**	0.27 (0.07)	**0.006**	0.07 (0.04)	0.966	0.20 (0.06)	0.094

		ASD vs. TD		ASD-DM vs. TD		ASD-N vs. TD		ASD-DM vs. ASD-N	
		Estimate (SE)	***P***	**Estimate (SE)**	***P***	**Estimate (SE)**	***P***	**Estimate (SE)**	***P***
	R	0.19 (0.05)	**0.002**	0.33 (0.07)	**<0.001**	0.06 (0.04)	0.990	0.27 (0.07)	**0.005**
Lingual	L	0.11 (0.05)	0.242	0.17 (0.07)	0.378	0.04 (0.04)	1.000	0.13 (0.06)	0.798
	R	0.13 (0.05)	0.098	0.23 (0.07)	0.071	0.04 (0.04)	1.000	0.19 (0.07)	0.167
Pericalcarine	L	0.08 (0.05)	0.503	0.14 (0.07)	0.789	0.03 (0.04)	1.000	0.11 (0.06)	0.931
	R	0.11 (0.05)	0.183	0.22 (0.07)	0.085	0.00 (0.04)	1.000	0.23 (0.07)	**0.040**
Cingulate									
Caudal anterior cingulate	L	0.14 (0.05)	**0.043**	0.23 (0.07)	**0.038**	0.05 (0.04)	0.998	0.18 (0.06)	0.193
	R	0.23 (0.05)	**<0.001**	0.37 (0.07)	**<0.001**	0.08 (0.04)	0.897	0.29 (0.07)	**0.001**
Isthmus cingulate	L	0.12 (0.05)	0.179	0.19 (0.07)	0.199	0.04 (0.04)	1.000	0.15 (0.06)	0.489
	R	0.06 (0.05)	0.582	0.09 (0.07)	0.994	0.02 (0.04)	1.000	0.07 (0.07)	0.999
Posterior cingulate	L	0.07 (0.05)	0.605	0.11 (0.07)	0.935	0.03 (0.04)	1.000	0.08 (0.06)	0.995
	R	0.18 (0.05)	**0.005**	0.30 (0.07)	**0.002**	0.07 (0.04)	0.980	0.23 (0.07)	**0.031**
Rostral anterior cingulate	L	0.28 (0.05)	**<0.001**	0.43 (0.07)	**<0.001**	0.13 (0.04)	0.115	0.30 (0.06)	**<0.001**
	R	0.18 (0.05)	**0.006**	0.30 (0.07)	**0.002**	0.06 (0.04)	0.996	0.25 (0.07)	**0.016**
Insula									
Insula	L	0.10 (0.05)	0.252	0.23 (0.07)	**0.043**	−0.02 (0.04)	1.000	0.25 (0.06)	**0.005**
	R	0.11 (0.05)	0.183	0.22 (0.07)	0.084	0.00 (0.04)	1.000	0.23 (0.07)	**0.044**

Mixed-effects linear models were used to estimate group differences in cortical surface area across different regions. Data was fourth root transformed prior to analysis.

P-values were adjusted for multiple comparisons. Those *P*-values that survived correction for multiple comparisons (adjusted $P < 0.05$) are indicated by bold values.