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Increased gyrification, but comparable surface area in adolescents with autism spectrum disorders

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Autism spectrum disorders are associated with atypically excessive early brain growth. Recent studies suggest that later cortical development, specifically cortical thickness, during adolescence and young adulthood is also aberrant. Nevertheless, previous studies of other surface-based metrics (e.g. surface area and gyrification) at high-resolution in autism spectrum disorders are limited. Forty-one males with autism spectrum disorders and 39 typically developing males matched on age (mean ~17; range = 12–24 years) and IQ (mean ~113; range = 85–143) provided high-resolution 3 T anatomical magnetic resonance imaging scans. The FreeSurfer image analysis suite quantified vertex-level surface area and gyrification. There were gyrification increases in the autism spectrum disorders group (relative to typically developing subjects) localized to bilateral posterior cortices (cluster corrected $P < 0.01$). Furthermore, the association between vocabulary knowledge and gyrification in left inferior parietal cortex (typically developing group: positive correlation; autism spectrum disorders group: no association) differed between groups. Finally, there were no group differences in surface area, and there was no interaction between age and group for either surface area or gyrification (both groups showed decreasing gyrification with increasing age). The present study complements and extends previous work by providing the first evidence of increased gyrification (though no differences in surface area) at high resolution among adolescents and young adults with autism spectrum disorders and by showing a dissociation in the relationship between vocabulary and gyrification in autism spectrum disorders versus typically developing subjects. In contrast with previous findings of age-related cortical thinning in this same autism spectrum disorders sample, here we find that increases in gyrification are maintained across adolescence and young adulthood, implicating developmentally dissociable cortical atypicalities in autism spectrum disorders.

Keywords: autism; MRI; gyrification; cortical folding; surface area

Abbreviation: ASD = autism spectrum disorders

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Introduction

Autism spectrum disorders (ASD) are associated with atypical patterns of brain growth and development based on various metrics including head circumference, brain weight, and brain volume using MRI (for review, see Courchesne *et al.*, 2007). This atypical growth pattern may contribute to the increasingly recognized aberrant cortical connectivity in ASD (Booth *et al.*, 2011; Müller *et al.*, 2011; Vissers *et al.*, 2012). However, two aspects of brain structure that may be crucial to functional connectivity (White and Hilgetag, 2011) but have been relatively understudied in ASD are cortical gyrification (brain folding patterns) and surface area.

Cortical gyrification in autism spectrum disorders

Cortical gyrification is an early developing process (Clouchoux *et al.*, 2012) that may go awry in disorders such as ASD, with early developmental origin. Indeed, several post-mortem studies have indicated the presence of gyral abnormalities, such as polymicrogyria, in a significant minority of ASD cases examined (Ritvo *et al.*, 1986; Bailey *et al.*, 1998). The first study to assess gyrification in ASD using MRI identified the presence of polymicrogyria in 5 of 13 primarily adult subjects with high functioning ASD whereas two others had macrogyria (Piven *et al.*, 1990) based on expert ratings (i.e. qualitative examination) of scans. More recently, the primary metric used in various studies is the gyrification index, which is the ratio of the inner contour (including sulcal crevices) to the perimeter of the outer or superficially exposed surface, as first described and quantified by Zilles *et al.* (1988). At least two studies have used 2D methods to assess gyrification within limited cortical regions in ASD. Hardan *et al.* (2004) assessed the gyrification ratio in a single coronal slice of prefrontal cortex (the first slice anterior to the corpus callosum) among 30 males with ASD versus 32 matched typically developing male control subjects. No group differences emerged in the total sample, but when the sample was divided into those ≥ 18 years versus those < 18 years of age, diagnostic group differences emerged in the younger group. Children and adolescents with ASD had greater prefrontal gyrification than controls, whereas no differences were found among adults. Investigating a wide age range (8–38 years), Casanova *et al.* (2009) found no ASD-typically developing group differences in gyrification using 40 randomly selected coronal slices among 14 males with ASD compared with 28 typically developing males matched on age.

Although other studies have been completed on related metrics of sulcal morphometry (Levitt *et al.*, 2003), sulcal depth (Nordahl *et al.*, 2007), and gyral complexity (Williams *et al.*, 2012) in ASD, only two studies to date have assessed gyrification specifically across the entire cortex in ASD. Kates *et al.* (2009), using lateralized lobar-based averages, found greater gyrification in right parietal cortex among 14 lower functioning children with ASD compared with 14 typically developing control subjects. Meguid *et al.* (2010), comparing lower functioning children with ASD ($n = 10$) to those with fragile X syndrome ($n = 7$), found no

differences in a single 3D metric of gyrification across the entire cortex. This latter study did not include a typically developing control group, thus the atypicality of gyrification from normative expectations was not assessed.

Taken together, these studies generally implicate increased gyrification in ASD children and adolescents when diagnostic group differences are found; however, they have been limited in several important ways. Initial studies focused on gyrification using one (frontal cortex) coronal slice, rather than taking a whole brain approach. Studies examining gyrification across the entire cortex in ASD have included predominantly lower functioning individuals, complicating interpretations of the source of group differences (i.e. comorbid intellectual disability versus ASD alone). Sample sizes in the whole brain studies have been relatively small (< 15 per group), limiting power and the capability to detect group differences. The whole brain studies have focused on the developmental window of childhood, thus the periods of adolescence and young adulthood, when cortical atypicalities in ASD have been demonstrated (Wallace *et al.*, 2010) and when whole-brain gyrification continues to decrease during typical development (White *et al.*, 2010; Raznahan *et al.*, 2011), have been largely unexplored. Finally and perhaps most importantly, 3D methods that provide high-resolution metrics of local gyrification have not been used in a sample of individuals with ASD. Collapsing across the entire cortex or lobar regions may obscure more regionally specific gyrification differences in ASD that these more powerful techniques can detect.

To this point, recent advances in neuroimaging analysis methodologies have allowed the examination of local gyrification at ever increasing resolutions (e.g. the vertex level). Schaer *et al.* (2008) have developed a well validated and reliable methodology within the FreeSurfer software package that has been successfully applied to several neurodevelopmental disorders, including 22q deletion syndrome (Schaer *et al.*, 2009), intellectual disability (Zhang *et al.*, 2010), schizophrenia (Palaniyappan *et al.*, 2011) and conduct disorder (Hyatt *et al.*, 2012).

Gyrification and intelligence

Grey matter volume is the product of cortical thickness and cortical surface area. Interestingly, as compared to other mammals, humans have disproportionately large cortical surface area in relation to their associated grey matter volume. For example, although the human brain has a ~ 10 -fold increase in surface area compared with that of macaques, the cortex is only 2-fold thicker (Barondes *et al.*, 1997). This discrepancy becomes greater when descending the mammalian evolutionary chain. To accommodate this oversized cortical sheet [approximately three times the size of the inner surface of the skull in humans (Van Essen, 1997)], the brain folds in upon itself resulting in high levels of gyrification. This increased gyrification in humans versus other mammalian species may contribute to our considerable cognitive capacities (White *et al.*, 2010). Accordingly, individual differences in intelligence have been shown to positively correlate with global (Kates *et al.*, 2009) and local (Luders *et al.*, 2008) measures of gyrification in typically developing populations. Furthermore, individuals with intellectual impairments have reduced gyrification compared

to their typically developing peers (Bonnici *et al.*, 2007; Zhang *et al.*, 2010). In contrast, there is evidence to suggest that this relationship between gyrification and IQ does not hold in ASD. Kates *et al.* (2009) found that although there was a significant positive association between IQ and gyrification index (particularly in temporal and parietal lobes) in 14 typically developing children, no such correlation was found in a group of 14 children with ASD. However, it should be noted that in this study the IQ scores were considerably different between groups. The ASD group's average IQ fell in the range of intellectual impairment (mean = 66.6, SD = 18.27), whereas the control group's IQ (mean = 120.9, SD = 11.18) was well above the standardized average of 100. This discrepancy in IQ scores and ranges could have contributed to a positive association in one group and no association in the other. We therefore sought to examine the association between IQ (and component subtest performance) and gyrification in ASD and typically developing individuals matched on IQ, which also fell in the average or higher range of scores.

Surface area in autism spectrum disorders

Given that previous studies have demonstrated exaggerated brain growth in ASD during the preschool years (Courchesne *et al.*, 2007), it is somewhat surprising that only three studies to date have used surface-based MRI methods to directly quantify and compare surface area in samples of individuals with ASD versus typically developing control subjects. For 41 individuals (mean age = 34; range = 12–64 years) with ASD, Raznahan *et al.* (2009) found no difference in total surface area compared with 30 typically developing control subjects. In a subsequent study including additional subjects, Raznahan *et al.* (2010) found that there was neither a main effect of group nor a group \times age interaction in lobar-level surface area when comparing 76 individuals with ASD to 51 neurotypical control subjects ranging from 10–60 years of age. However, these studies were limited, such as failing to match groups on IQ and providing clinical characterization on a majority, but not all, of the ASD subjects. Among 25 children with ASD compared with 63 typically developing control subjects (ages 6–15 years), Mak-Fan *et al.* (2012) found no group differences in surface area, but there was a significant group \times age interaction in occipital lobe surface area; children with ASD exhibited greater occipital lobe surface area than typically developing controls, but only at the older end of their age range (centred at age 14.5 years). Taken together, the univariate studies (see Ecker *et al.*, 2010 for a multivariate approach that used high-resolution surface area, among other cortical metrics) suggest comparable surface area in ASD and typically developing groups of school-age children, adolescents and adults, though findings on group by age interactions for surface area are mixed. However, none of the aforementioned univariate studies assessed surface area at high-resolution (e.g. vertex-level), thus whether surface area group differences and interactions with age might be found from more fine grain assessment remains an open question.

Current study

The present study is the first to utilize 3D methods to examine both high-resolution local gyrification and surface area in age and IQ matched adolescent and young adult males with ASD versus typically developing males. We assess not only ASD-typically developing group differences for each of these metrics, but also the comparability of age-related changes in local gyrification and surface area during adolescence and young adulthood in each of these groups. Consistent with the extant literature, we expect to find greater gyrification in the ASD group than in the typically developing subjects, particularly in posterior cortical regions; however, we expect age-related changes in gyrification to be comparable between the two groups. We also explore other elements of cortical structure (i.e. pial surface area and sulcal depth/gyral height) that may contribute to any observed gyrification differences in ASD. Finally, we examine possible ASD-typically developing group discrepancies in the association between IQ (and component subtest performance) and local gyrification and any potential links between autistic traits and local gyrification in both groups. While IQ and its subcomponent processes are expected to be correlated with local gyrification in the typically developing group, this relationship will be diminished or absent in the ASD subjects. In the ASD group, we expect to find gyrification associated with autistic traits in regions where group differences are documented. For typically developing subjects, we expect that gyrification will be associated with autistic traits in regions where cortical structure has been previously linked with autistic traits in other typically developing samples (e.g. right superior temporal sulcus; Wallace *et al.*, 2012).

Materials and methods

Participants

Thirty-nine typically developing males between 12 and 23 years of age and 41 high-functioning males with an ASD between 12 and 24 years of age recruited from the Washington, DC metropolitan area participated in the study. All 41 participants with ASD met Diagnostic and Statistical Manual of Mental Disorders-IV diagnostic criteria as assessed by an experienced clinician (26 Asperger's syndrome, 11 high-functioning autism, three pervasive developmental disorder-not otherwise specified and one with either Asperger's syndrome or high-functioning autism, which could not be distinguished because of missing early language development data). Forty ASD participants received both the Autism Diagnostic Interview or Autism Diagnostic Interview-Revised (Le Couteur *et al.*, 1989; Lord *et al.*, 1994) and the Autism Diagnostic Observation Schedule (Lord *et al.*, 2000) administered by a trained, research-reliable clinician (one ASD participant received neither of these instruments). ASD participants received either Module 3 ($n = 13$) or 4 ($n = 27$) of the Autism Diagnostic Observation Schedule. All ASD participants' scores met cut-off for the category designated as 'Broad ASD' according to criteria established by the NICHD/NIDCD Collaborative Programs for Excellence in Autism (CPEA; see Lainhart *et al.*, 2006). Because the Autism Diagnostic Interview and Autism Diagnostic Observation Schedule do not provide an algorithm for Asperger's syndrome, Lainhart *et al.* (2006) developed criteria that include an individual on the broad autism spectrum if s/he meets

Table 1 Demographic characteristics

| | ASD (n = 41) | Typically developing (n = 39) |
|---|----------------|-------------------------------|
| Age | 16.75 (2.84) | 16.95 (2.71) |
| Full Scale IQ | 113.02 (14.88) | 114.23 (10.80) |
| Verbal IQ | 112.00 (16.78) | 112.79 (12.26) |
| Performance IQ | 110.95 (13.79) | 112.08 (10.78) |
| Handedness (R:L) | 37:4 | 35:4 |
| Social Responsive Scale total [‡] | 88.73 (27.28) | 19.88 (12.66) |
| Autism Diagnostic Interview, Social* | 18.95 (5.21) | — |
| Autism Diagnostic Interview, Verbal Communication* | 14.95 (4.61) | — |
| Autism Diagnostic Interview, Restricted and Repetitive Behaviour* | 5.65 (2.82) | — |
| Autism Diagnostic Observation Schedule, Social* | 8.18 (3.28) | — |
| Autism Diagnostic Observation Schedule, Communication* | 4.08 (1.72) | — |
| Autism Diagnostic Observation Schedule, Stereotyped behaviour* | 1.30 (1.59) | — |

Mean (SD).

[‡]ASD n = 37, typically developing n = 36.

*n = 40.

the Autism Diagnostic Interview cut-off for 'autism' in the social domain and at least one other domain or meets the Autism Diagnostic Observation Schedule cut-off for the combined social and communication score. Exclusion criteria for the ASD group included an IQ < 85 or any known comorbid medical conditions, such as fragile X syndrome or other genetic disorders, and brain trauma/injury. In the ASD group, 22 individuals were taking one or more psychotropic medications: 12 were taking stimulants, 14 were taking selective serotonin reuptake inhibitors, four were taking atypical antipsychotics, two were taking anxiolytics, one was taking a mood stabilizer and one was taking a norepinephrine agonist.

Parents of typically developing children and adults underwent telephone screenings. Typically developing individuals were excluded from participation if they had ever received mental health treatment for anxiety, depression, or any other psychiatric condition, taken psychiatric medications, required special services in school, been diagnosed with a genetic disorder or neurological disorder, or had brain trauma/injury that could potentially affect brain development and/or cognitive functioning. IQ scores were obtained from all participants. All Full Scale IQ scores were 85 or above, as measured by the Wechsler Abbreviated Scale of Intelligence (WASI; ASD: n = 34, typically developing: n = 39), Wechsler Adult Intelligence Scale-III (WAIS-III; ASD: n = 3), Wechsler Intelligence Scale for Children-III (WISC-III; ASD: n = 2), or Wechsler Intelligence Scale for Children-IV (WISC-IV; ASD: n = 2). Finally, parent ratings of autistic (primarily social-communication) traits, were obtained for both groups using the total score from the Social Responsiveness Scale (Constantino and Gruber, 2005), as it is the most psychometrically sound index based on factor analytical, reliability, and validity studies (Constantino *et al.*, 2004). Participant groups did not differ (all *P*-values > 0.05) in terms of Full Scale IQ, age, or handedness (Table 1). Informed assent and consent were obtained from all participants and/or their parent/guardian when appropriate in accordance with an NIH IRB approved protocol.

Imaging parameters

One high-resolution ($1.07 \times 1.07 \times 1.2$ mm) T₁-weighted structural image was obtained axially from each subject with a MPRAGE sequence (124 slices, 1.2 mm slice thickness, 224 × 224 acquisition

matrix, flip angle = 6°, field of view = 24 cm, inversion time = 725 ms) on a 3T General Electric Signa scanner using an 8-channel head coil.

Surface reconstruction and local gyrification index calculation

Version 5.1 of the FreeSurfer image analysis suite (<http://surfer.nmr.mgh.harvard.edu/>) was used to generate a cortical surface (composed of a mesh of triangles) allowing for the measurement of surface area and local gyrification index at each vertex. The technical details of the surface extraction procedures are described in previous publications (Dale *et al.*, 1999; Fischl *et al.*, 1999, 2004). Initial steps in this surface-based, multi-step, and semi-automated morphometric pipeline include visual inspection of data for motion artifacts, transformation to Talairach space, intensity normalization for correction of magnetic field inhomogeneities, and removal of non-brain tissues (e.g. skull stripping). The resulting surface models generated were reviewed for accuracy and manually edited in all cases due to over-inclusion of white matter around the optic nerve.

As previously mentioned, a measure of local gyrification index developed by Schaer *et al.* (2008) can be utilized in the context of the FreeSurfer analysis suite. This tool provides a 3D surface-based measure of gyrification, building upon the original 2D method applied to each coronal slice, as described by Zilles *et al.* (1988) and used by many others. The original gyrification index was defined as the ratio of the inner cortical contour to the perimeter of the outer surface (see Fig. 1 for a depiction in the coronal view). In FreeSurfer, tessellated outer (the hull surface) and inner (the pial surface) contours provide vertex-based surfaces for calculating 3D local gyrification index. Using each vertex as the centre point of a spherical 25 mm region of interest, the ratio of the convoluted inner pial surface to the closely fitting outer perimeter provides the local gyrification index metric at high resolution across the entire cortex. Detailed methodological information on surface area computation can be found in a recent study by Winkler *et al.* (2012). In short, surface area is quantified by assigning an area to each vertex equal to the average of its

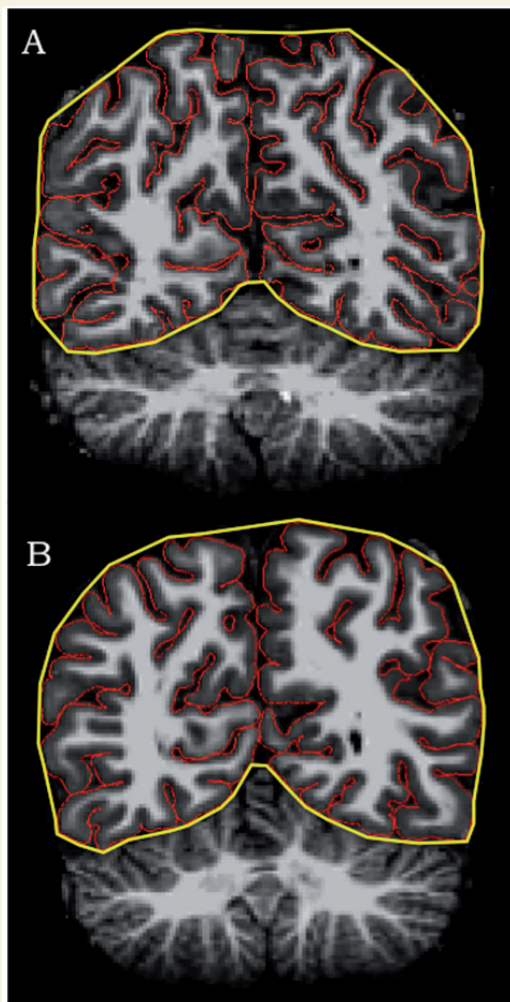


Figure 1 Coronal slice of MRI scans showing greater gyrification in left precuneus for (A) a male with an autism spectrum disorder versus (B) a typically developing male.

surrounding triangles. When the vertex areas are summed over all vertices, the total is equal to the sum of the areas of the triangles.

Vertex-level surface area and local gyrification index values were obtained and mapped onto a normalized cortical surface. Resulting surface area and local gyrification index maps were smoothed with a 5 mm full-width at half-maximum kernel.

Statistical analysis

Group differences in surface area and local gyrification index were examined on the surface maps vertex by vertex using a least squares general linear model. To control for multiple comparisons, cluster correction was completed using Monte Carlo simulation with 10 000

iterations (vertex-wise threshold of $P < 0.01$). Because previous work demonstrated interactions between age and other metrics of brain structure in adolescents and adults with ASD (Raznahan *et al.*, 2010; Wallace *et al.*, 2010), we examined age group (using a median split; ≤ 17 years versus > 17 years) by diagnosis (ASD versus typically developing) interactions on the vertex-level surface area and local gyrification index data. Younger and older participants did not differ (P -values > 0.05) in terms of IQ (for both ASD and typically developing groups) or symptomatology scores (for the ASD group only). We also explored the contribution of other elements of cortical structure to any observed group differences in gyrification by extracting values for each of these metrics (i.e. pial surface area and sulcal depth/gyral height) only within the clusters where the ASD group differed significantly from typically developing controls. Next, we evaluated ASD-typically developing group discrepancies in the association between local gyrification index (both vertex-level and in regions where group differences were found) and not only full-scale IQ (all subjects), but also performance on two subtests (ASD: $n = 38$, typically developing: $n = 39$ for both), Vocabulary (ASD: mean = 57.94, SD = 10.85; typically developing: mean = 58.21, SD = 7.67; $t = 0.12$, $P = 0.90$) and Matrix Reasoning (ASD: mean = 56.32, SD = 7.17; typically developing: mean = 56.08, SD = 7.40; $t = 0.14$, $P = 0.89$) using the different offset, different slope (DODS) design matrix provided by Qdec in FreeSurfer. Lastly, we investigated links between autistic traits (using the total score from the Social Responsiveness Scale) and gyrification in both groups. For the ASD group, Pearson correlations were used to evaluate this relationship only within regions of group difference surviving cluster correction, while for the typically developing group, this correlation was examined across the whole brain in FreeSurfer's Qdec application.

Results

Vertex \times vertex analyses conducted on the cortical surface revealed greater gyrification (cluster corrected $P < 0.01$) among ASD individuals as compared to typically developing individuals, but no differences in surface area. Greater gyrification was found in three clusters of posterior cortices, which were located bilaterally in lateral occipital regions and in left precuneus (Table 2 and Fig. 2). These regional gyrification increases were not due to differences in global brain size, as groups did not differ in intracranial volume. Interactions between age and diagnostic group were not significant for either surface area or local gyrification index (P -values > 0.05). However, there was a significant (cluster corrected $P < 0.01$) negative correlation between age and gyrification in large swaths of bilateral frontal, posterior temporal, and parietal cortices in the combined group of ASD and typically developing individuals (Table 3 and Fig. 3).

Follow-up analyses were completed in order to evaluate whether psychotropic medication usage may have had an effect on the local gyrification index group differences. The mean local gyrification index extracted from two of the three posterior cortical clusters did not differ between unmedicated ($n = 16$) and medicated ($n = 25$) subjects with ASD (P -values > 0.18), whereas local gyrification index in the left lateral occipital cluster was greater in the medicated group ($P = 0.04$). Furthermore, we found that unmedicated subjects with ASD demonstrated greater gyrification in these three posterior regions than did typically developing

Table 2 Cluster corrected ($P < 0.01$) regions differing in gyrification between the autism spectrum disorders group and the group of typically developing controls

| Region | Size (mm ²) | x | y | z | Clusterwise P-value | Number of vertices |
|--------------------------|-------------------------|-------|-------|------|---------------------|--------------------|
| Left lateral occipital | 1307 | -23.6 | -90.0 | 5.2 | 0.001 | 1910 |
| Left precuneus | 1160 | -9.2 | -58.6 | 52.8 | 0.003 | 2639 |
| Right temporal-occipital | 790 | 48.4 | -70.9 | 13.0 | 0.04 | 1347 |

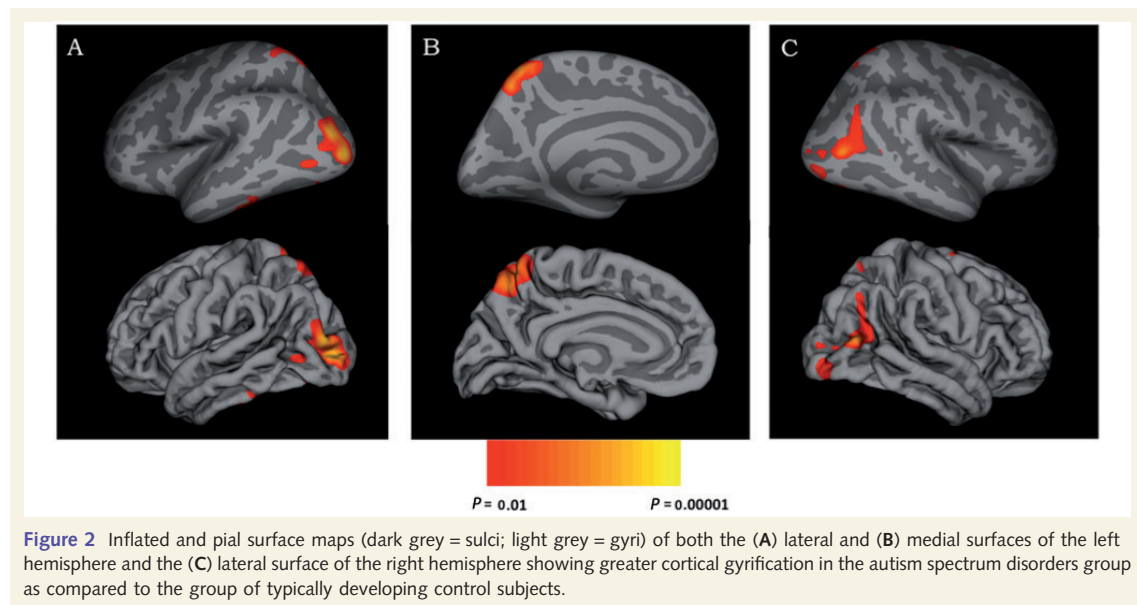


Figure 2 Inflated and pial surface maps (dark grey = sulci; light grey = gyri) of both the (A) lateral and (B) medial surfaces of the left hemisphere and the (C) lateral surface of the right hemisphere showing greater cortical gyrification in the autism spectrum disorders group as compared to the group of typically developing control subjects.

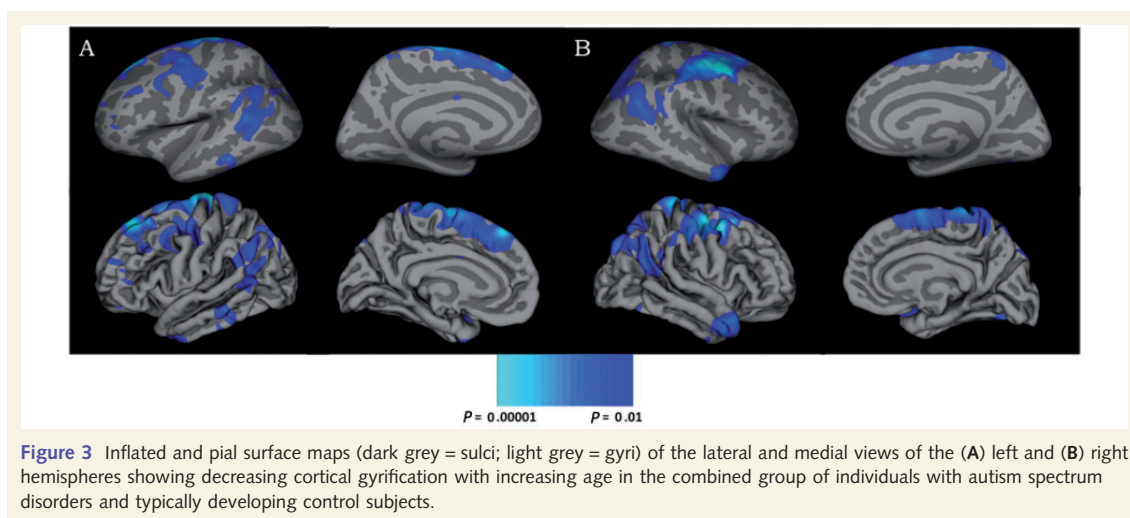
individuals, though the local gyrification index difference in only two of the three regions (the left precuneus and right posterior cortices) reached statistical significance ($P < 0.05$). Overall, these analyses (with diminished statistical power) corroborated the whole-brain analyses presented above, suggesting that increased gyrification in ASD is largely independent of psychotropic medication usage.

When exploring further within the three clusters where the ASD group had significantly increased local gyrification index compared with controls, we found that pial surface area was larger in the precuneus region of interest in the ASD group (ASD mean = 1924, SD = 271; typically developing mean = 1792, SD = 236), and sulcal depth/gyral height was greater in the ASD group in the left lateral occipital cortex (ASD mean = 0.07, SD = 0.09; typically developing mean = -0.002, SD = 0.08). Moreover, across the two groups, pial surface area was significantly correlated with local gyrification index in each of the three regions of interest (all $r > 0.22$, P -values < 0.05), while sulcal depth/gyral height was significantly associated with local gyrification index in the left lateral occipital cortex ($r = 0.43$, $P < 0.001$).

Finally, there were significant (cluster corrected $P < 0.01$) differences between ASD and typically developing individuals in the association between vocabulary performance and local gyrification index within left inferior parietal cortex in the vicinity of the supra-marginal/angular gyri [driven by a positive association between vocabulary scores and local gyrification index in the typically developing group ($r = 0.49$, $P = 0.001$), but no significant association in the ASD group ($r = -0.18$, $P = 0.29$)] (Fig. 4). In a separate whole brain analysis within the typically developing group alone, we found that significant associations between vocabulary performance and local gyrification index ($r = 0.51$, $P = 0.001$) were isolated to left inferior parietal cortex, overlapping extensively with the area showing significant ASD-typically developing group differences in its association with vocabulary scores (Fig. 5). Further corroborating these group-specific relationships, among the three clusters where ASD-typically developing group differences in local gyrification index were observed, local gyrification index was significantly correlated with vocabulary scores in two of them, the left and right lateral occipital cortices, but only in the typically developing group (left side, typically developing: $r = 0.45$,

Table 3 Cluster corrected ($P < 0.01$) regions demonstrating age-related decreases in gyrification in the combined sample of individuals with autism spectrum disorders and typically developing controls

| Region | Size (mm ²) | x | y | z | Clusterwise P-value | Number of vertices |
|-----------------------------|-------------------------|-------|-------|-------|---------------------|--------------------|
| Left superior frontal | 3918 | −16.0 | 38.2 | 41.6 | 0.0001 | 7947 |
| Left inferior parietal | 2237 | −49.6 | −47.9 | 17.8 | 0.0001 | 4713 |
| Left precentral | 2035 | −28.2 | −7.9 | 42.8 | 0.0001 | 4372 |
| Right caudal middle frontal | 6873 | 39.5 | 4.8 | 45.7 | 0.0001 | 15018 |
| Right inferior parietal | 3964 | 33.7 | −67.3 | 27.4 | 0.0001 | 7810 |
| Right middle temporal | 877 | 47.9 | 2.8 | −29.4 | 0.02 | 1403 |



$P = 0.004$; right side, typically developing: $r = 0.43$, $P = 0.006$). When comparing the magnitude of the correlations for the typically developing versus the ASD subjects through r to z transformations, both correlations in the typically developing group were significantly greater (left side, z difference = 2.13, $P = 0.03$; right side, z difference = 2.89, $P = 0.004$) than those found in the ASD group (left-side, ASD: $r = -0.01$, $P = 0.95$; right side, ASD: $r = -0.21$, $P = 0.20$). No group differences in the association between local gyrification index and either full-scale IQ or Matrix Reasoning performance were found. Also in contrast to vocabulary scores, we failed to find any significant (cluster corrected $P < 0.01$) relationship between parent ratings of primarily social-communication difficulties [assessed by the Social Responsiveness Scale total score (38)] and local gyrification index. However, after dropping the statistical threshold (to cluster-corrected $P < 0.05$), we did find a significant negative relationship between Social Responsiveness Scale ratings and local gyrification index ($r = 0.40$, $P = 0.02$) limited to the right superior temporal sulcus in ($n = 36$) typically developing subjects (Fig. 6).

Discussion

In the first study to assess surface area and gyrification at high-resolution in ASD, we found greater gyrification in left precuneus

and bilateral posterior temporal/lateral occipital regions of adolescent and young adult males with ASD as compared to age and IQ matched typically developing males, while surface area did not differ between groups. Moreover, whereas a robust positive correlation between vocabulary knowledge and gyrification was found in left inferior parietal cortex in the typically developing group, no such relationship was found in the ASD group. Finally, we found no group by age interactions for surface area and gyrification and noted gyrification decreases with age across large portions of bilateral frontal, posterior temporal and parietal cortices in the combined sample of ASD and typically developing individuals.

The current findings corroborate some earlier studies by showing increased gyrification in ASD (Hardan *et al.*, 2004), particularly in posterior parietal cortices (Kates *et al.*, 2009), and no differences in surface area (Raznahan *et al.*, 2009, 2010; Mak-Fan *et al.*, 2012). However, previous studies were limited in their resolution (e.g. lobar-based surface area and gyrification values), methods (e.g. for gyrification: not whole-brain; only selected coronal slices utilized), and/or sample size. Although not assessing gyrification, Nordahl *et al.* (2007) found deeper bilateral intraparietal sulci in a group of children and adolescents with Asperger's syndrome compared to typically developing controls, which is consistent with increased gyrification in ASD, as documented here.

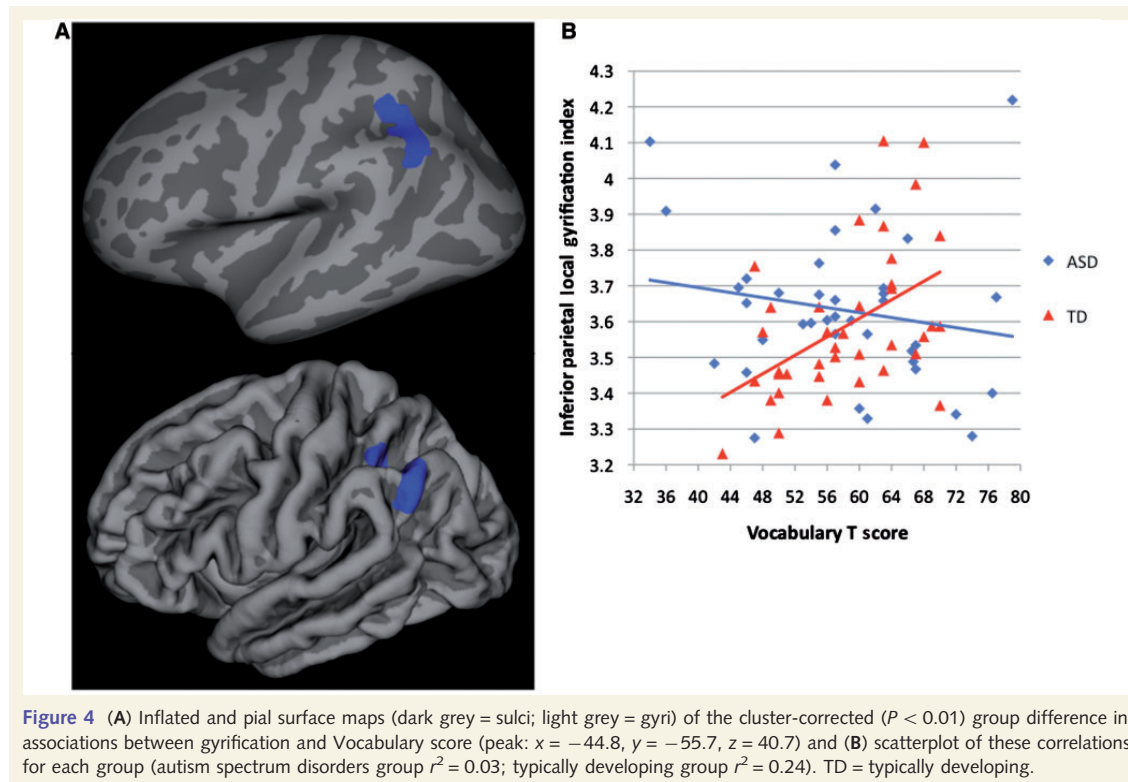


Figure 4 (A) Inflated and pial surface maps (dark grey = sulci; light grey = gyri) of the cluster-corrected ($P < 0.01$) group difference in associations between gyrification and Vocabulary score (peak: $x = -44.8$, $y = -55.7$, $z = 40.7$) and (B) scatterplot of these correlations for each group (autism spectrum disorders group $r^2 = 0.03$; typically developing group $r^2 = 0.24$). TD = typically developing.

Furthermore, unlike cortical thickness (Wallace *et al.*, 2010), there was no ASD-typically developing group difference in the relationship between age and both surface area and gyrification during adolescence and young adulthood. For surface area, this is similar to at least one previous study (Mak-Fan *et al.*, 2012). Both groups demonstrated decreasing gyrification with increasing age, consistent with prior studies demonstrating decreasing whole-brain (White *et al.*, 2010; Raznahan *et al.*, 2011) and lateralized lobar-level (Su *et al.*, 2013) gyrification during this age range in typically developing children and adolescents. This suggests that the greater gyrification among individuals with ASD is maintained during adolescence and young adulthood. Whether ASD and typically developing groups show comparable age-local gyrification index relationships at younger ages remains an open question for future research to explore.

The increased gyrification in ASD may represent one downstream consequence of an aberrant developmental trajectory of brain growth in these disorders. More specifically, recent work shows increased numbers of cortical neurons in ASD (Courchesne *et al.*, 2011), confirming some earlier post-mortem studies (for review, see Palmen *et al.*, 2004), though aberrant dendritic arborization and/or synaptic pruning may be the more likely cellular mechanisms driving atypical brain growth trajectories in ASD (Schumann *et al.*, 2011). There is also increasingly strong evidence of structural connectivity abnormalities in ASD at various

developmental windows based on diffusion imaging studies (Booth *et al.*, 2011; Vissers *et al.*, 2012). Given theories of gyrification resulting from cortical fibre tension (Van Essen, 1997), it may be that aberrant cortical folding is one result of these micro- and macro-level structural brain differences in ASD. These gyrification differences may, in turn, correlate with functional connectivity, which many studies indicate is aberrant in ASD (including many of the subjects included in this report) (Gotts *et al.*, 2012; for review, see Vissers *et al.*, 2012). Speculatively, it may be that the types of disruptions in regional cortical folding patterns found here result in less homogeneous endogenous fluctuations. In order to assess these possible associations, future studies could link the types of high-resolution gyrification metrics used here with both structural (e.g. using diffusion tensor imaging or diffusion spectrum imaging) and functional (e.g. using functional MRI or magnetoencephalography) connectivity.

Utilizing other structural metrics, we found that increased local gyrification index in ASD is directly associated with differences in both pial surface area and by sulcal/gyral morphometry. Within one of the three regions of interest (precuneus) where groups differed, the ASD group had increased pial surface area compared with typically developing control subjects. Furthermore, all three regions of interest demonstrated significant associations between local gyrification index and pial surface area across the groups. A different region of interest (left lateral occipital cortex)

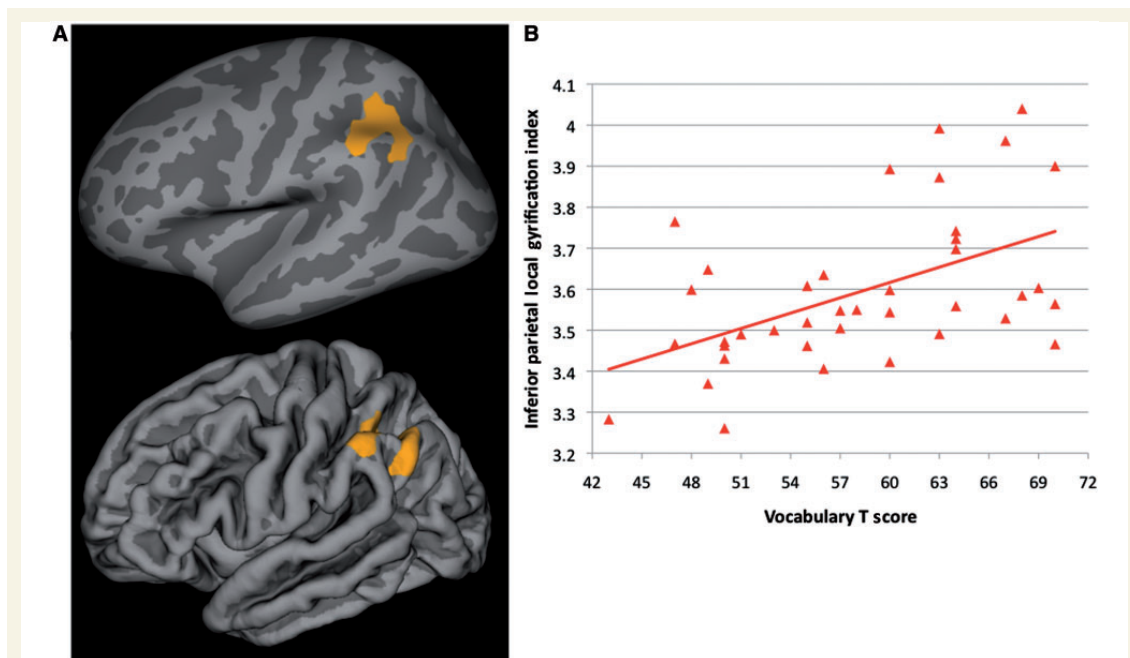


Figure 5 Within the typically developing males only, (A) inflated and pial surface maps (dark grey = sulci; light grey = gyri) of the cluster-corrected ($P < 0.01$) association between gyrification and Vocabulary score (peak: $x = -46.6$, $y = -40.1$, $z = 40.6$) and (B) scatterplot of this correlation ($R^2 = 0.26$).

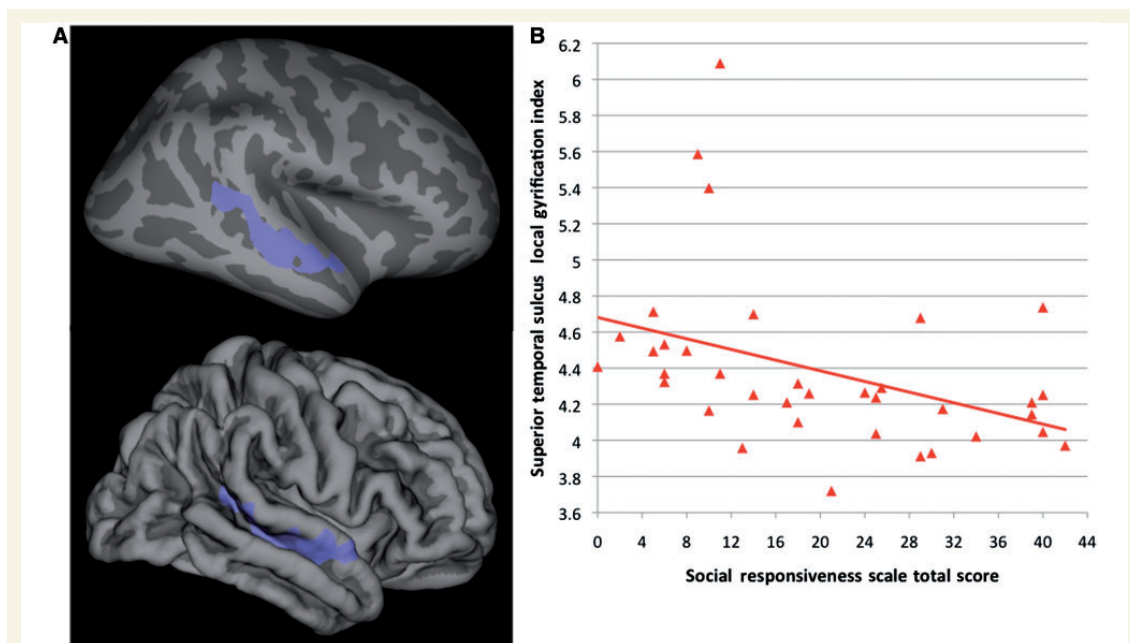


Figure 6 Within the typically developing males only, (A) inflated and pial surface maps (dark grey = sulci; light grey = gyri) of the cluster-corrected ($P < 0.05$) association between gyrification and total score from the Social Responsiveness Scale (peak: $x = 45.8$, $y = -39.0$, $z = 12.4$) and (B) scatterplot of this correlation ($R^2 = 0.16$), which does not change after removing the three highest gyrification values.

demonstrated not only increased sulcal depth/gyral height in the ASD group relative to controls, but also a significant association between local gyrification index and sulcal depth/gyral height across the groups. Taken together, these findings suggest that gyrification increases in ASD may be the result of the aetiological mechanisms, such as the number of radial units along the ventricular zone, that drive regionally specific surface areal expansion (Rakic, 1988).

Additionally, we found a discrepancy between groups in the vocabulary–local gyrification index correlation. Within left inferior parietal cortex, in the vicinity of the supramarginal/angular gyri we found that vocabulary knowledge was robustly correlated with local gyrification index in the typically developing group, though not in the ASD group. Similarly, within two of the three clusters (i.e. left and right lateral occipital cortices) where increased local gyrification index was found in the ASD group, there were also discrepant vocabulary–local gyrification index correlations (significant positive associations in the typically developing group, not in the ASD group). These significantly positive correlations in the typically developing group fit with previous postulations about the relationship between gyrification levels and cognitive abilities (White *et al.*, 2010). Moreover, the location (inferior parietal cortex) of the independent analyses revealing not only a group discrepancy in vocabulary–local gyrification index associations but also a strong correlation between vocabulary knowledge and gyrification in the typically developing group alone was highly concordant. Other measures of cortical structure (e.g. grey matter density) in this same region have been linked with individual differences in vocabulary knowledge (Mechelli *et al.*, 2004; Lee *et al.*, 2007). However, this is the first study, to our knowledge, to establish this relationship with gyrification and to show its dissociation in ASD. Placed in the context of the broader literature, our findings extend one prior study that found ASD–typically developing group discrepancies in IQ-lobar-level local gyrification index correlations in the temporal, parietal, and occipital lobes (Kates *et al.*, 2009). However, whereas their study included ASD and control participants with IQs that differed by >50 points, on average, the current study matched participants on IQ (with average range or higher scores). Taken together, these studies suggest that aberrant gyrification in ASD may disrupt the typically significant positive association between IQ-related measures (vocabulary knowledge in the current study) and cortical folding as observed in the typically developing controls here, in earlier studies of typically developing individuals (Luders *et al.*, 2008; Kates *et al.*, 2009), and in other clinical groups (e.g. bipolar disorder; McIntosh *et al.*, 2009).

Finally, we also found an indication that parent ratings of primarily social-communication difficulties were negatively correlated with local gyrification index in the right superior temporal sulcus of typically developing subjects. This preliminary finding was particularly noteworthy because it replicated—in a smaller group of subjects—our recent report of a strong relationship between Social Responsiveness Scale ratings and cortical structure (cortical thickness in that case) in right superior temporal sulcus in a much larger cohort of typically developing subjects (Wallace *et al.*, 2012).

There are several limitations to consider when evaluating this research. The ASD sample of this study was limited to males

who had average to above average IQ; therefore, these findings may not apply to lower functioning individuals and/or females on the autism spectrum. We chose to limit our sample to males because of earlier work demonstrating sex differences in surface area and gyrification (Raznahan *et al.*, 2011) during typical development. This study focused on ASD individuals with average range or higher IQ in order to isolate ASD-specific effects on surface area and local gyrification index and because of previous demonstrations of both surface area (Fahim *et al.*, 2012; Meda *et al.*, 2012) and gyrification (Bonnici *et al.*, 2007; Zhang *et al.*, 2010) reductions among individuals with syndromic and idiopathic intellectual impairments. Finally, the present cross-sectional study assessed age-related changes in surface area and gyrification among ASD and typically developing individuals, but the most stringent test of developmental effects requires longitudinal designs that could be utilized in future investigations.

Nevertheless, the present study makes a novel contribution to the existing literature by demonstrating increased gyrification but intact surface area at high-resolutions in adolescents and young adults with ASD and by showing a dissociation in the link between vocabulary knowledge and local gyrification index for those with ASD (no association) versus typically developing controls (a positive correlation). Furthermore, the negative correlation between age and gyrification is comparable for ASD and typically developing groups during adolescence/young adulthood, which stands in stark contrast to our previous findings of age-related cortical thinning in this same ASD sample (Wallace *et al.*, 2010) and suggests that there are developmentally dissociable cortical atypicalities in ASD. Future studies should link these types of gyrification measures with metrics of structural and functional connectivity and examine gyrification in younger ASD samples to further explore the age-dependence of this atypical increase in cortical folding. Finally, given the extensive smoothing field inherent to the local gyrification index quantification used here, future research could use complementary high-resolution metrics, such as intrinsic curvature (Ronan *et al.*, 2011), to further characterize ASD-specific atypicalities in cortical surface morphometry.

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