Journal of Child Neurology

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>> Version of Record - May 15, 2013

OnlineFirst Version of Record - Jul 25, 2012

What is This?

The Effect of Diagnosis, Age, and Symptom Severity on Cortical Surface Area in the Cingulate Cortex and Insula in Autism Spectrum Disorders

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Abstract

Functional activity in the anterior cingulate cortex and insula has been reported to be abnormal during social tasks in autism spectrum disorders. However, few studies have examined surface morphometry in these regions and how this may be related to autism spectrum disorder symptomatology. In this study, 27 individuals with autism spectrum disorders and 25 controls between the ages of 7 to 39 years underwent structural magnetic resonance imaging. Our primary analysis examined differences in surface area in the cingulate and insula, between individuals with and without autism spectrum disorders, as well as age-related changes and associations with social impairments. Surface area in the right cingulate was significantly different between groups and decreased more rapidly with age in autism spectrum disorder participants. In addition, greater surface area in the insula and isthmus was associated with poorer social behaviors. Results suggest atypical surface morphometry in brain regions involved in social function, which appeared to be related to poorer social ability scores.

Autism spectrum disorders are associated with impaired social behaviors. These include, but are not limited to, difficulties with theory of mind, which is the ability to interpret the feelings and thoughts of another[1,2]; are intuition, meaning the formation of initial and quick impressions about others that are informed by reasoned judgments[3]; and also emotional insight, or the capacity to understand and be aware of one's own emotions and those of others.[4,5]

Many studies in individuals with autism spectrum disorders have reported structural and functional atypicalities in a well-established network of brain regions that mediate social functions.[6,7] These regions include the medial prefrontal cortex,[8] the orbitofrontal cortex,[9] the superior temporal sulcus,[5,10-12] the inferior occipital gyrus,[13] the fusiform gyrus,[5,13,14] and the amygdala.[15-20] The cingulate cortex and the insula may also contribute to social behaviors and may be functionally impaired in autism spectrum disorders.[4-6] However, research concerning potential structural atypicalities and their effect on symptomatology is lacking.

The anterior cingulate cortex is commonly implicated in mediating attention, response selection, and self-regulation in goal-directed behaviors, including self-control, -initiation, and -monitoring.[21-25] Functional brain imaging studies in individuals with and without psychiatric disorders have implicated the ventral part of the cingulate cortex in emotional self-control, in comparison to the dorsal cingulate that mediates cognitive processes.[21,24,26,27] In the typical population, increased activity in the anterior cingulate cortex occurs in individuals with greater social

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awareness and insight about their own and other people's perceptions of social situations.[21,26,27] The anterior cingulate cortex may act as part of the circuitry involved in theory-of-mind processes that integrates intuitive feelings into planned, deliberate behaviors.[3,28] The cellular basis of these processes is believed to be mediated by specialized cells in the anterior cingulate cortex known as von Economo neurons that mediate empathy, social interaction, and emotion.[3,28,29] In individuals with autism spectrum disorders, abnormal development of von Economo neurons in the anterior cingulate cortex may lead to impaired intuition.[3,28] In line with these findings is evidence suggesting that atypical activity in the medial prefrontal cortex–anterior cingulate cortex complex may lead to poor self-representation in autism.[30-33]

The insula projects to and receives afferent input from the anterior cingulate cortex.[34,35] The insula is also the primary receiver of viscerosensory input.[36] In turn, this region processes both appetitive and aversive physiological sensations that lead to emotional arousal and the conscious perception of one's own affective state.[37] The insula may also act as an interface between the orbitofrontal cortex and the amygdala to enable the translation of observed or imitated facial expression into felt emotion.[38] This interaction with the social brain network is thought to enable emotion understanding[38] and awareness.[4,26,39] Individuals with autism spectrum disorders show reduced activity in the insula relative to typically developing individuals during the imitation of emotional expressions.[40] Similarly, reduced activity in the insula and anterior cingulate cortex was shown to be associated with poorer self-reported awareness of an individual's own feelings and those of another.[4]

The above evidence suggests the functional involvement of the cingulate cortex and insula in social impairments in autism spectrum disorders. However, little is known about possible structural abnormalities in these areas, the developmental trajectories of these regions, and how they may contribute to social impairments. Thus, the primary objective of this study was to examine brain surface area of these areas, critical to social behaviors. Brain surface area is influenced both by the total neuronal number and the amount of cortical folding. Surface area is largely determined during the development of the cortical mantle. This process involves neuronal migration via radial glial cells to the cortical plate.[41,42] A greater number of radial glial cells would lead to a larger number of neurons in the cortex and increased surface area.[42] During the first weeks of gestation, neuronal progenitor cells divide symmetrically according to the process of mitosis.[41] Therefore, small epigenetic changes affecting the duration of symmetric growth can change the development of surface area.[42] Furthermore, these changes may be related to developing abilities and behaviors over childhood.[43,44]

The automated image analysis framework used to extract surface area values from the cingulate cortex and insula also provided surface area values for the parahippocampal gyrus, the isthmus of the cingulate, and each cortical lobe. As such, we explored surface area differences between groups in these regions as well.

Methods

Participants

Higher functioning autism spectrum disorder participants between the ages of 7 to 39 years were recruited from the Seaver Autism Center at Mount Sinai School of Medicine. Controls were recruited from local newspaper advertisements and through word of mouth and were group-matched on age, gender, and intelligence quotient (IQ). The autism spectrum disorder participants had a clinical diagnosis according to the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition,[45] and were psychotropic medication free. Diagnoses were confirmed at the time of testing using the Autism Diagnostic Observational Schedule–Generic[46] and the Autism Diagnostic Interview–Revised.[47] Any participants who had a primary psychiatric or medical condition (other than autism spectrum disorders in the autism spectrum disorder group) and a history of head injury, epilepsy, neuromotor impairment, or a genetic disorder associated with autism spectrum disorders were excluded. Additionally, controls were excluded if they had a first-degree relative with autism spectrum disorders. All participants were right handed and had an IQ over 70 as estimated by either the Wechsler Intelligence Scale for Children, fourth edition,[48] or the Wechsler Adult Intelligence Scale, fourth edition,[49] depending on their age.

Imaging

Participants were scanned on a Siemens Allegra 3-T magnetic resonance imaging (MRI) system (Munich, Germany), which has a maximum gradient strength of 40 mT/m and a slew rate of 400 mT/m/s. A low-resolution high-speed scout image was obtained, followed by a series of axial scans. For high-resolution structural images with excellent gray/white matter contrast, a T1-weighted magnetization-prepared rapid gradient echo sequence was used: isotropic resolution of 0.82 mm × 0.82 mm × 0.82 mm, matrix size of 256 × 256 × 208, field of view of 210 mm, 208 slices, repetition time of 2500 milliseconds, echo time of 4.38 milliseconds, inversion time (TI) of 1100 milliseconds, and an 8° flip angle fast low angle shot acquisition. Total scan time was approximately 10 minutes.

Surface Area Measurements

Figure 1 depicts a simplified version of how surface area measurements were obtained. Anatomic MRI scans were preprocessed using the CIVET processing pipeline[50,51] to classify tissue types (white matter, gray matter, and cerebrospinal fluid) in standard space. The constrained Laplacian anatomic segmentation using proximities was applied to extract hemispheric surfaces (gray and white matter).[52,53] Gray and white matter surfaces were extracted using an 80,000 polygon mesh, with 40,962 vertices. Each surface mesh started at the same point on the initial sphere before being deflated onto the participant volume, which was mapped onto standard space (defined by the Montreal Neurological Institute 305 symmetric template). This allowed for a similar spatial relation to exist between the vertices on each participant's deflated mesh.

The surface registration algorithm, SURFTRACC, used in this analysis is described in detail elsewhere[54-56]; it registers the surfaces from coarse to fine scale using an iterative local search for optimal vertex correspondence, based on feature field matching, and a regularization step to preserve the local surface topology. Surface area values for each cortical lobe (frontal, parietal, temporal, occipital), the isthmus of the cingulate gyrus, the parahippocampal gyrus, the cingulate, and the
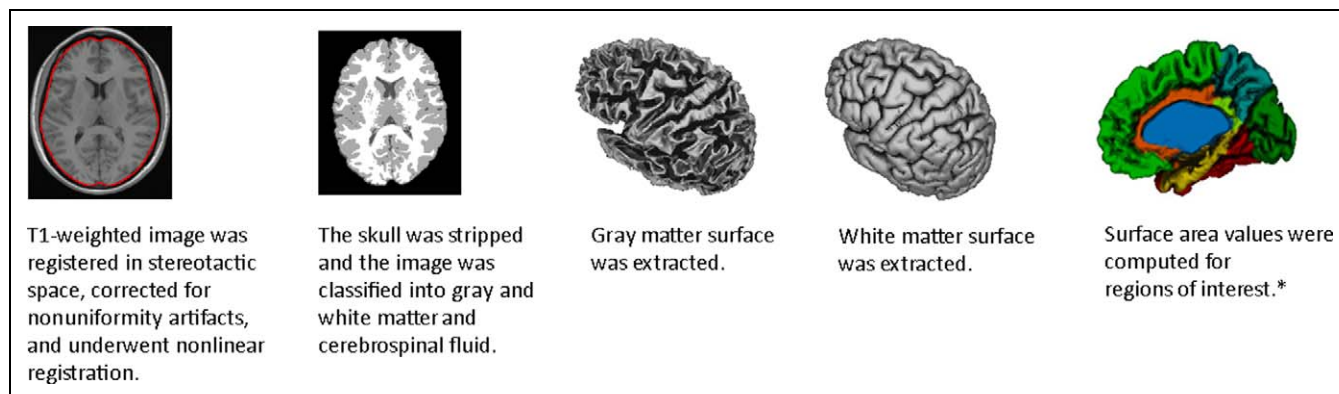
Figure 1. Surface area measurements. A simplified version of surface area measurements carried out on all T1-weighted images. The sequence of measurements is depicted from left to right. *On the midsurface map showing the regions of interest, the insula is not seen.

Table 1. Demographic Information.

	Autism Spectrum Disorders, Mean ± SD (95% CI)	Typically Developing Individuals, Mean ± SD (95% CI)	P Value
Age distribution			
7-20 y	n = 12, 14.9 ± 4.0 (12.4-17.5)	n = 10, 12.7 ± 4.6 (9.4-16.0)	t(20) = 2.22, P = .24
21-39 y	n = 15, 28.1 ± 5.0 (25.3-30.8)	n = 15, 28.5 ± 5.2 (25.6-31.4)	t(28) = −0.40, P = .83
Full group statistics			
Age, y	n = 27, 22.2 ± 8.0 (19.0-24.4)	n = 25, 22.2 ± 9.3 (18.33-26.0)	t(50) = −0.03, P = .98
FSIQ	105.1 ± 17.8 (98.03-112.1)	109.4 ± 17.0 (102.4-116.5)	t(50) = 0.90, P = .4
Gender (M:F)	21:6	17:8	χ^2 = .6, P = .4
ADI-R social	17.3 ± 7.3 (14.36-20.16)		

SD, standard deviation; CI, confidence interval; FSIQ, full-scale intelligence quotient; M, male; F, female; ADI-R, Autism Diagnostic Interview–Revised.

insula cortices, bilaterally, were determined for each participant using atlas-based regions of interest within the processing pipeline. Values were totaled to obtain an estimate of surface area of the whole brain.

MRI Assessment

Structural MRI scans were reviewed by a neuroradiologist for abnormalities of medical concern. Scans were also checked for image quality. Great care was taken to assess each anatomic scan both before and after processing to minimize the total number of excluded scans. First, scans were visually inspected by 2 authors (KARD-T and EGD) and searched for ghosting of images and blurriness. Scans were only considered for inclusion if they passed this initial screening. Next, cortical surfaces were viewed for any bridging, malformation of gyri, sulci, and any features that did not compare with anatomical scans. If any of these characteristics were present, those scans were excluded.

Statistical Analyses

Statistical analyses were performed using SAS (version 9.3, SAS Institute Inc, Cary, North Carolina). Multiple linear regression analyses were used to examine the effect of group, and age × group interaction effects on surface area for the regions measured. Gender was used as a covariate in the model. An additional multiple linear regression analysis was applied to the autism spectrum disorder data to examine the

relation between surface area and severity of social impairment, as measured by the Autism Diagnostic Interview–Revised and the Autism Diagnostic Observational Schedule–Generic, while controlling for age and gender.

Results

Participants

No obvious abnormalities were seen in white or gray matter in any of the scans nor any evidence of heterotopia. Surface area values from 52 individuals (27 from individuals with autism spectrum disorders and 25 from controls) were included in these analyses. A significant age difference was found between the excluded (mean age, 11.3 years) and included (mean age, 22.1 years) groups (unpaired *t* test, df = 73, t = 5.9, P < .05). However, the groups did not differ on IQ (included = 107.1 and excluded = 102.8) or symptom severity on the social domains of the Autism Diagnostic Interview–Revised (included = 17.3 and excluded = 16.0) and the Autism Diagnostic Observational Schedule–Generic (included = 7.7 and excluded = 6.3). Means and standard deviations for age IQ scores for autism spectrum disorder and control participants included in the analyses are shown in Table 1. Participant groups did not differ in age or in full-scale IQ.
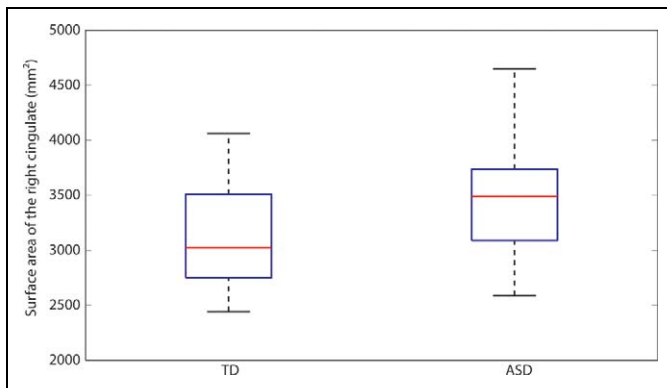
Figure 2. The effect of diagnosis on surface area in the right cingulate. Box plot demonstrating surface area differences in the right cingulate between typically developing individuals (TD) and those with autism spectrum disorders ($P = .03$, uncorrected). The red line indicates the group medians, the edges of the box plot identify the 25% and 75% percentiles, and the whiskers extend to the most extreme data points.

Effect of Group

The autism spectrum disorder group had a significantly greater surface area than the typically developing group in the right cingulate cortex ($P = .03$) (Figure 2). No other significant group differences were found when controlling for age and gender (Supplementary Table S1).

Age × Group Interaction

Results suggested a significant age × group interaction in the right cingulate ($P = .05$) (Figure 3A). Exploratory analyses in other regions revealed interaction effects that approached significance in the right isthmus ($P = .06$) (Figure 3B), right parietal lobe ($P = .07$), and left temporal lobe ($P = .08$) (Supplementary Table S2). In these 4 regions, surface area decreased more rapidly with age in individuals with autism spectrum disorders, while little age-related change was apparent in their typically developing peers.

Surface Area and Symptomatology

A significant relation was found between surface area in the right insula and left isthmus with social scores on the Autism Diagnostic Interview–Revised and Autism Diagnostic Observational Schedule–Generic, respectively. Greater surface area in the right insula was associated with more severe scores on the Autism Diagnostic Interview–Revised social domain ($P = .02$), and similarly, greater surface area in the left isthmus was associated with higher scores on the Autism Diagnostic Observational Schedule–Generic social domain ($P = .02$) (Table 2).

Discussion

The results of this pilot study show group differences in the surface area of the right cingulate cortex and in its developmental
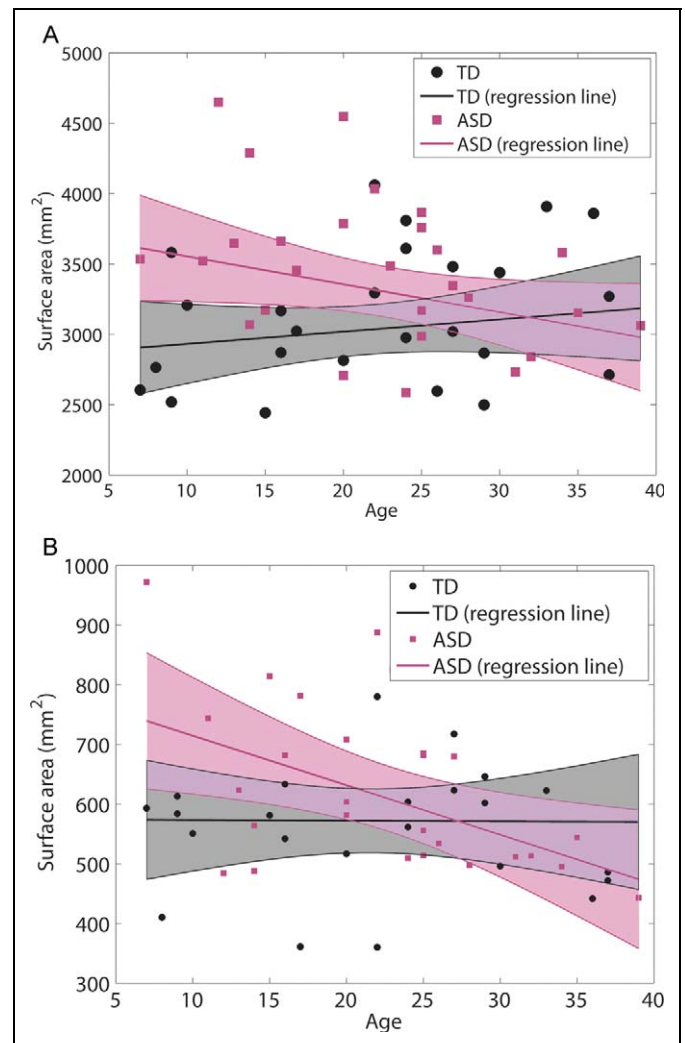
Figure 3. Age × diagnosis interaction in the right cingulate and isthmus. Scatter plots of the developmental trajectory of surface area in the right cingulate (A) and right isthmus (B) for typically developing individuals (TD) and individuals with autism spectrum disorders. The 95% confidence interval for each group is shown in the shaded regions.

trajectory. A trend toward significant differences in surface area development was also observed in the right isthmus, right parietal lobe, and left temporal lobe. Greater surface area in the right insula and left isthmus was also related to more severe social scores.

In the typical population, surface area across the brain has been found to decrease with age, although at different rates depending on the phylogenetic age of the cortical region.[57,58] Our results point to a significant increase in surface area in the right cingulate cortex in individuals with autism spectrum disorders compared to controls. Additionally, we found that surface area decreased more rapidly with age in individuals with autism spectrum disorders compared with controls in the right cingulate (the anterior cingulate and the isthmus). This is consistent with studies that have looked at age effects on surface area[59] and cortical folding[60] in the frontal lobe. Mak-Fan et

Table 2. Relation Between Surface Area in Regions of Interest and Scores on the Autism Diagnostic Interview–Revised (ADI-R) and Autism Diagnostic Observational Schedule–Generic (ADOS).

	ADI-R Social: *P* Value	ADOS Social: *P* Value
Whole brain	.33	.59
Hemisphere		
Right	.43	.70
Left	.25	.50
Frontal		
Right	.16	.36
Left	.16	.73
Temporal		
Right	.14	.09
Left	.45	.86
Parietal		
Right	.65	.16
Left	.51	.93
Occipital		
Right	.54	.90
Left	.22	.17
Cingulate		
Right	.17	.79
Left	.95	.19
Isthmus		
Right	.27	.75
Left	.09	.02*
Insula		
Right	.02*	.84
Left	.18	.82
Parahippocampus		
Right	.49	.25
Left	.46	.39

*Indicates a significant result.
All *p* values are uncorrected for multiple comparisons.

al[59] reported a trend of greater surface area in individuals with autism spectrum disorders that decreased more rapidly than controls. In addition, Hardan et al[60] reported greater cortical folding in the left frontal lobe for children and adolescents but not adults with autism spectrum disorders. Moreover, cortical folding decreased with age in individuals with autism spectrum disorders but not controls.[60] In contrast, Raznahan et al[61] reported minimal age-related changes across lobes including the frontal lobe in individuals with autism spectrum disorders. However, this apparent inconsistency may reflect differences in the age ranges represented or within the diagnostic criteria used among these studies.

In the present study, we also found that greater surface areas in the right insula and left isthmus were related to more impaired social behaviors on the Autism Diagnostic Interview–Revised and the Autism Diagnostic Observational Schedule–Generic, respectively. The insula has been observed to act in concert with the social brain network to enable emotional experience and awareness.[21,26] Atypical surface area in this region may be one of many mediating factors that could impair social function in autism spectrum disorders. The right anterior insula is also functionally connected to regions critical for executive functions and appears to play a role in the

monitoring of task performance and flexibility.[62,63] The function of the isthmus is poorly understood. Anatomically, the isthmus connects the cingulate with the parahippocampal gyrus located in the medial temporal lobe. By some definitions, the isthmus of the cingulate is part of the limbic structures,[64,65] which are suggested to play a role in mediating emotional responses and motivating behaviors.[66] Of note, although the correlations described above are of great interest, one should be cautious about conclusions relating anatomic data and behavioral deficits.

The findings of the current study also suggest potential maturation differences in the parietal and temporal lobes, which are involved in higher order processing such as spatial orientation,[67] multimodal integration,[68] semantics,[69,70] and emotion,[71] and which peak in maturity in adolescent years.[57,58] A difference in the developmental trajectory of these regions may underlie behavioral impairments observed in autism spectrum disorders on a number of the above-mentioned tasks. Previous morphometry studies have also found atypicalities in these lobes. For example, the location of the superior temporal sulci and the intraparietal sulci was found to be shifted in individuals with autism spectrum disorders.[60] In addition, the depth of the parietal operculum as it extends to the ventral postcentral gyrus and that of the intraparietal sulci were also found to be atypical in autism spectrum disorders relative to controls.[72]

No surface area differences were seen in the occipital or the frontal lobes. If morphological differences were present in the occipital lobes, they might not have been detected in our analyses due to the age range of our sample, as these areas have been shown to reach maturity within the first few years of life while our youngest participants were 7 years old.[58,73] Previous surface area studies also did not report a main effect of diagnosis in the frontal lobe.[59,61] However, studies that examined aspects of surface area such as cortical folding,[60] sulcal location,[74] and sulcal depth[72] have reported atypicalities in regions within the frontal lobe. Thus, future detailed studies are needed to provide further insight into the relation between regional surface areas and the location and depth of sulci.

While this study provides insight into the altered surface area in individuals with autism spectrum disorders, these findings should be replicated in a larger sample using a longitudinal study design to increase statistical power and decrease the heterogeneity within the groups. Our analyses were also limited to the lobular and anatomic regions automated in the pipeline used and may have missed diagnostic and developmental differences in other brain regions. Future larger studies that examine specific gyri or sulci within lobes, subcortical regions, and other components of brain structure such as cortical thickness and white matter integrity may be able to detect other structural changes in autism spectrum disorders.

The MRI resolution also limits our ability to examine potential abnormalities in the cytoarchitecture, organization, and synaptic distribution across the cortex, as surface area depends on properties of the cortical mantle, such as neuronal number, distribution, and arrangement.[41,42] Greater neuronal numbers particularly in the frontal lobes of children and adolescents

with autism spectrum disorders have been previously reported.[75] An excess number of neurons could affect surface area. However, combined surface area and neuropathology studies are required to fully understand the atypicalities seen in our sample.

Our main findings indicated that atypical surface area in the cingulate cortex and insula was associated with social impairments. However, these brain regions are also involved in other behaviors (such as attention and self-regulation), which have not been measured in this study. Changes in surface area could also relate to abnormalities in those behaviors. It would be beneficial for future studies to look into these relations.

Given the limited surface morphometry data currently available in the literature on persons with autism spectrum disorders, this study is informative, as it is consistent with previous reports of abnormalities in some specific brain regions across a wide age range. Thus, it provides a launching point for future investigations on surface morphometry in these regions and investigations into structural components that may contribute to atypical surface area.

In summary, the findings of this study suggest that atypical surface area in the right cingulate cortex is greater in individuals with autism spectrum disorders compared with controls and appears to be more pronounced in children and adolescents compared to adults. An association was also found with increased surface area in the right insula and left isthmus and more severe social scores as measured by diagnostic measures. These findings suggest atypical surface morphometry in regions of the brain involved in social function, which seem to be related to impaired social cognition.

Acknowledgments

The data for this study were collected at Mount Sinai School of Medicine in New York, New York. The analyses were carried out at Holland Bloorview Kids Rehabilitation Hospital and The Hospital for Sick Children. The findings of this study were presented at the International Meeting for Autism Research 2012 in Toronto, Ontario, Canada.

Author Contributions

KARD-T drafted the article. KARD-T and AK collaboratively performed the statistical analyses. EGD completed the surface area measurements. KARD-T and EGD performed quality assessment of MRI scans. MJT contributed resources toward completing the analyses. JPL is an expert on the image analysis pipeline used and provided resources and technical support. EA, LVS, and ATW collected the data. EA and JF supervised and conceived the study design. EA was the principal investigator on this study. All authors read, commented on, and approved the final article.

Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr Anagnostou has consulted without fees to Neuropharm, Proximagen, and Novartis and consulted with fees to Seaside Therapeutics. None of the other authors has any conflicts of interest to disclose.

Ethical Approval

This study was approved by the Mount Sinai School of Medicine Research Ethics Board and conducted in accordance with its guidelines. Written informed consent was obtained from all participants 18 years and older. All other participants provided written informed assent, and parents provided written informed consent in accordance with Research Ethics Board guidelines.

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