Reduced Gyrification Is Related to Reduced Interhemispheric Connectivity in Autism Spectrum Disorders

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Objective: Autism spectrum disorders (ASD) have been associated with atypical cortical gray and subcortical white matter development. Neurodevelopmental theories postulate that a relation between cortical maturation and structural brain connectivity may exist. We therefore investigated the development of gyrification and white matter connectivity and their relationship in individuals with ASD and their typically developing peers.

Method: T1- and diffusion-weighted images were acquired from a representative sample of 30 children and adolescents with ASD (aged 8–18 years), and 29 typically developing children matched for age, sex, hand preference, and socioeconomic status. The FreeSurfer suite was used to calculate cortical volume, surface area, and gyrification index. Measures of structural connectivity were estimated using probabilistic tractography and tract-based spatial statistics (TBSS).

Results: Left prefrontal and parietal cortex showed a relative, age-dependent decrease in gyrification index in children and adolescents with ASD compared to typically developing controls. This result was replicated in an age- and IQ-matched sample provided by the Autism Brain Imaging Data Exchange (ABIDE) initiative. Furthermore, tractography and TBSS showed a complementary pattern in which left prefrontal gyrification was negatively related to radial diffusivity in the forceps minor in participants with ASD.

Conclusion: The present study builds on earlier findings of abnormal gyrification and structural connectivity in the prefrontal cortex in ASD. It provides a more comprehensive neurodevelopmental characterization of ASD, involving interdependent changes in microstructural white and cortical gray matter. The findings of related abnormal patterns of gyrification and white matter connectivity support the notion of the intertwined development of 2 major morphometric domains in ASD.

Key Words: autism spectrum disorders, gyrification index, structural connectivity, development, forceps minor

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Autism spectrum disorders (ASD) are pervasive developmental disorders characterized by persistent deficits in social communication and social interaction and the presence of restricted, repetitive patterns of behavior, interests, or activities.[1] The early onset of symptoms, typically well before the age of 3 years, has been suggested to coincide with an overgrowth of cortical volume during the first years of life, followed by a gradual decrease.[2,3] This pattern appears not to be limited to specific brain areas, but to involve the entire cortex.[4,5] Post mortem research on childhood ASD has shown an excess of neurons and disorganization in all cortical laminae of the prefrontal cortex (PFC), suggesting that increases in brain size have an early onset, possibly during prenatal neurodevelopment.[6,7]

The brain's folding pattern is a strong marker of prenatal neurodevelopment.[8] Gyrification commences in gestational week 16 and greatly intensifies during the third trimester when the brain folds in on itself, as cortical volume—mostly white matter (WM)—and surface area (SA) rapidly increase.[9] To date, multiple theories have tried to explain the pattern of cortical folding. Tension-induced folding suggests that strongly interconnected regions pull toward each other and lead to the formation of gyri, whereas more sparsely connected fibers elongate to leave room for sulci.[10] The "gray matter hypothesis" suggests that gyrification may be the result of cell proliferation in the outer subventricular zone during early gestation.[11] This hypothesis is based on findings in transgenic mice, which showed increased cerebral cortical SA and human-like folds after controlling the cell cycle exit of neural precursors in the outer subventricular zone.[12]

Whole-brain studies have indeed shown a pattern of increased sulcal complexity[13] and differences in cortical shape[14] and sulcal pattern[15,16] in children and adolescents with ASD. However, 2 recent studies using 3-dimensional (3D) methodologies in ASD have reported conflicting results, with the first reporting increased gyrification in adolescents with ASD[17] and the second reporting decreased gyrification in a slightly younger sample.[18]

Supplemental material cited in this article is available online.

Gyrification and white matter development seem inextricably tied,[19] continuously remodeling the cortex throughout development.[20] Schaer *et al.*[18] interestingly showed a relationship between reduced gyrification index (GI) and reduced white matter connectivity in a small group of low-functioning children with ASD, in whom right prefrontal gyrification was positively correlated with the number of white matter fibers in ASD. This ties in with an ever-growing body of literature reporting development changes in (interhemispheric) connectivity in ASD, especially in prefrontal tracts such as the forceps minor (previously reviewed[21,22]).

However, considerable heterogeneity in symptom presentation and severity and the wide range of analysis methods used in these studies may have contributed to mixed reports on the relationship between gyrification and connectivity to date. In the current study, we set out to investigate the relationship between gyrification and white matter connectivity with a focus on age-related changes in a sample of children and adolescents with ASD. We specifically aimed at investigating the PFC given previous literature. We hypothesized that GI would be reduced in children and adolescents with ASD. Furthermore, we used an independent sample of high-functioning children and adolescents with ASD from the Autism Brain Imaging Data Exchange (ABIDE) initiative to replicate our findings.[23] We further hypothesized that this reduced cortical gyrification would be related to reduced connectivity, in line with earlier findings in a sample of lower-functioning children with ASD and current neurodevelopmental theories.

METHOD

Participants

A total of 30 children and adolescents aged 8 to 18 years with ASD, as well as 29 typically developing controls, were recruited and matched for age, sex, hand preference, and socioeconomic status (Table 1). Children and adolescents with ASD were recruited through family associations and the outpatient clinic of the Child and Adolescent Psychiatry Department at Hospital General Universitario Gregorio Marañon in Madrid, Spain (hereafter referred to as the Madrid sample).[24] Typically developing controls were recruited from the community at publicly funded schools with characteristics similar to those attended by participants with ASD and in the same geographic area.[25]

Children and adolescents with ASD were included if they fulfilled *DSM-IV-TR* criteria for pervasive developmental disorders at the time of assessment[26] and the Gillberg criteria[27] for Asperger syndrome. Board-certified child and adolescent psychiatrists with extensive experience in the field of ASD conducted all diagnostic assessments. Detailed information on the diagnostic assessments is given in Supplement 1 (available online).

Exclusion criteria for all participants included intellectual disabilities per *DSM-IV* criteria,[26] any neurological disorder, history of head trauma with loss of consciousness, and other contraindications to magnetic resonance imaging (MRI) scanning. The institutional review board of the Hospital General Universitario Gregorio Marañon in Madrid approved the protocol and informed consent form. All parents or legal guardians gave written informed consent after receiving complete information about the study, and all participants provided assent.

Demographic, Clinical, and Cognitive Assessment

For all participants, demographic data, including age, sex, ethnicity, parent and participant years of education, and socioeconomic

TABLE 1 Demographic and Clinical Characteristics of the Madrid Sample

	ASD (n = 30)	TDC (n = 29)	*P*
Age (y), mean (SD) [range]	12.7 (2.5) [8–18]	12.5 (2.8) [7–18]	.79
Sex (males/females)	29/1	28/1	.98
Hand preference (right/left/ambidextrous)[a]	26/1/2	23/1/3	.86
Total IQ,[b] mean (SD) [range]	91.8 (20.1) [53–134]	112.0 (13.4) [70–138]	<.001
Verbal IQ, mean (SD) [range]	93.7 (25.1) [51–139]	—	
Vocabulary	9.1 (4.3)	11.2 (2.9)	.02
Performance IQ,[b] mean (SD) [range]	87.1 (22.0) [44–132]	—	
Block design	8.2 (3.2)	11.5 (2.5)	<.001
Parental education (y)	14.2 (3.2)	14.0 (3.2)	.62
Participant education (y)	6.8 (2.8)	7.8 (2.5)	.19
Socioeconomic status	3.5 (1.3)	3.8 (1.2)	.46
Clinical characterization			
CGAS	49.2 (12.7)	94.2 (4.1)	<.001
Gillberg total score	12.6 (3.1)	—	
Medication, n (%)			
None	22 (73)		
APS	8 (27)		

Note: APS = Antipsychotic medication; ASD = autism spectrum disorders; CGAS = Children's Global Assessment Scale; SD = standard deviation; TDC = typically developing children.

[a] *Information on hand preference was missing for 3 participants.*

[b] *Total IQ was estimated for typically developing participants. Verbal and performance IQ were not available for typically developing children; vocabulary and block design subtest scores are reported for purposes of comparison.*