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Total Brain Volume and Corpus Callosum Size in Medication-Naïve Adolescents and Young Adults with Autism Spectrum Disorder

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Abstract

Background—Increased total brain volume (TBV) has been reported for children with autism spectrum disorder (ASD) but studies in older ASD subjects have been contradictory. Similarly, studies of corpus callosum (CC) area in ASD differ with regard to inclusion criteria, age, and IQ.

Methods—In the present study, TBV, gray matter (GM), and white matter (WM) volume as well as midsagittal CC area were compared between 15 medication-naïve, high-functioning adolescent and young adult ASD subjects and 15 healthy control individuals, and correlations with visuomotor coordination and imitation abilities were explored. In addition, computational surface-based methods were implemented to encode callosal thickness at high spatial resolution.

Results—Total brain volume, GM, and WM were increased and CC area was decreased in ASD subjects, a finding that was predominantly due to ASD subjects with lower IQ. Positive correlations of IQ with volume measures were observed only in control subjects. Autism spectrum disorder subjects showed reduced thickness in the posterior part of the CC. White matter volume showed a trend for negative correlation with dynamic balance and imitation abilities across groups.

Conclusions—This study replicates previous structural magnetic resonance imaging (MRI) findings in ASD, emphasizes the role of IQ differences, and adds some evidence for functional implications of structural findings.

Keywords

Autism; corpus callosum; motor abilities; voxel-based morphometry

Autism spectrum disorders (ASDs) are characterized by quantitative impairments in social interaction and communication, as well as restrictive, stereotyped, repetitive behaviors and interests. Autism spectrum disorders are predominantly genetically determined, and affected

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individuals show early abnormalities in brain development, resulting in specific anatomical findings as outlined below.

Total brain volume (TBV) has been observed to be increased in children with ASD in the majority of studies (1). This is in accordance with reports of accelerated head growth in the first 2 years of life, resulting in high rates of macrocephaly in ASD (2). Some studies also reported increased TBV in adolescents and adults with ASD (3) but others disputed this finding and reported a normalization of TBV (4). It is also unclear whether the reported increase in TBV might be due to an increase of cortical and subcortical gray matter (GM) volume (3), an increase in subcortical white matter (WM) volume (5), or an increase in both GM and WM volume.

The increase in TBV is in line with the hypothesis of reduced connectivity in ASD. More specifically, accelerated brain growth and increased brain size have been hypothesized to lead to reduced interhemispheric connectivity and higher local specialization to optimize neuronal computational speed (6). This reduced interhemispheric connectivity might result in reduced corpus callosum (CC) area, which was observed in ASD subjects (1). Again, studies of CC area and its subregions in ASD differ in terms of inclusion criteria, age, sex, and IQ. Studies that controlled for TBV and IQ differences between groups in ASD individuals observed decreased total CC size, as well as smaller posterior CC subregions (7), smaller CC body (8), and/or smaller anterior subregions of the CC (9). Another study, which did not control for TBV and IQ differences, did not observe differences in CC area between high-functioning autistic and control children (5). Results of a recent diffusion tensor imaging (DTI) study underscore the impact of IQ differences on CC morphology, as CC area was significantly smaller and radial diffusivity was strongly increased in ASD individuals with low performance IQ (10). Most studies of the size of the CC and its subregions in ASD samples implemented the Witelson parcellation scheme. As this parcellation approach arbitrarily subdivides the CC into seven regions according to its maximal length, it might not recognize subtle regional differences. Also, results might be affected by local variability in callosal shape.

In the present study, we compared TBV, GM, and WM, measured by voxel-based morphometry (VBM), as well as midsagittal CC area, studied by a region-of-interest based approach, between medication-naïve, high-functioning adolescent and young adult ASD subjects and healthy control individuals, group matched for age and sex. We expected an increase in TBV, GM, and WM and a decrease of CC size in ASD individuals. In addition, correlation patterns of visuomotor coordination and imitation abilities with TBV, GM, WM, and CC area were explored. Finally, we applied computational surface-based methods to encode callosal thickness at high spatial resolution without relying on callosal parcellation (11) to replicate findings of regional differences in CC morphology in ASD subjects.

Methods and Materials

Thirteen male and 2 female subjects with autism spectrum disorder (mean age 17.5 years, SD 3.5 years) and 13 male and 2 female age-matched control subjects (mean age 18.6 years, SD 1.1 years) with IQ > 70 were assessed. After complete description of the study, informed consent was obtained from all participants and/or their parents. The study design was approved by the local ethical committee (Ethikkommission der Ärztekammer des Saarlandes). Detailed inclusion and exclusion criteria, methods to assess visuomotor coordination and imitation abilities, magnetic resonance imaging (MRI) data acquisition, MRI image preprocessing, CC area and thickness measurements, and statistical analysis methods are reported in Supplement 1.

Results

Descriptive data of the sample are shown in Table 1. With adjustment for IQ and interaction of IQ*status, TBV, GM, and WM were larger in ASD than in control individuals (Table 2), predominantly due to individuals with low IQ (Table 1 in Supplement 2). The interaction effect of IQ*status on TBV, GM, and WM indicates contrasting correlations of IQ with TBV, GM, and WM in case and control individuals. While IQ was not associated with TBV, GM, or WM in ASD subjects, control individuals showed strong positive correlations (Table 2, Supplements 3–5). Midsagittal CC area was lower in ASD individuals when adjusted for WM, IQ, and for interaction terms WM*status and IQ*status. A positive correlation of WM with CC area was only observed in control but not in ASD individuals (Table 3; Table 2 in Supplement 2). Regional differences in CC morphology between ASD and control subjects were observed in the posterior part of the CC, with control individuals showing a significantly higher thickness than ASD individuals (Figure 1). White matter showed a trend for a negative association with dynamic balance and hand-finger imitation abilities across all groups (Table 3 in Supplement 2).

Discussion

In this study, TBV, GM, WM, and CC area were compared between 15 adolescents and young adults with ASD and 15 healthy control subjects, matched for gender and age. Our findings corroborate previous reports of an enlargement of TBV in adolescents and young adults with ASD (1), especially in individuals with average and below average IQ (70–110). The current analyses suggest that increases in TBV are due to increases in both GM and WM. Given that subjects in our study were medication-naïve, the observed volume increases cannot be attributed to treatment effects (12).

Our findings emphasize the strong impact of IQ differences on study outcomes. For example, positive correlations of IQ with TBV, GM, and WM were only observed in control but not in ASD individuals. Increased TBV, GM, and WM were predominantly observed in ASD individuals with IQ equal to or lower than the median IQ in our study. In a previous study on individuals with low-functioning autism (LFA), high-functioning autism (HFA), and Asperger syndrome (AS), only LFA and HFA subjects showed increased GM, whereas AS subjects did not show increased GM. Given that AS individuals showed significantly higher IQ scores than HFA in that study (13), findings might have been driven by IQ differences between groups. Gray matter and WM increase might be due to an overproduction of neurons, glia, or astrocytes; abnormal myelination; and/or decreased neuronal elimination (pruning). In one study, active neuroinflammatory processes have been shown to exist in the WM, cortex, and cerebellum of patients with autism (14). Neuropathological studies have reported abnormal neocortical minicolumns in 4- to 25-year-old individuals with ASD (15), possibly resulting in increased GM and WM. Increased WM in our study showed a trend for an association with reduced dynamic balance and hand-finger imitation abilities across groups. A recent study reported a positive correlation of neurological subtle signs as indicators of motor impairment with local WM in the primary motor and premotor cortices of 8- to 12-year-old children with ASD (16). Therefore, either local or global WM enlargement might contribute to motor and imitation impairment in ASD.

Corpus callosum area was smaller in ASD, likely due to individuals with high IQ and large WM. However, due to low sample size, the unadjusted post hoc comparison has to be viewed with caution. Reduced CC thickness was observed in the isthmus and anterior part of the splenium. Our findings are well in line with previous studies in age-, gender-, and IQ-matched samples (7–9). The CC isthmus and anterior part of the splenium connect primary

somatosensory, temporal, and posterior parietal fibers (17). Several functional and structural MRI studies have reported volumetric changes and altered function of right and left temporal and parietal regions in ASD (7,18). Reduction in CC thickness either might be the result of these structural and functional findings or might cause some of the functional differences between ASD and control individuals. Previous studies indicated CC hypoplasia, but not atrophy, and suggested a reduction in the number of axonal fibers traversing the CC (19,20). A recent DTI study reported reduced CC fractional anisotropy and increased mean diffusivity in ASD individuals, also indicative of CC microstructure changes (10).

Our study had several limitations. For example, the sample size was relatively small, so post hoc tests comparing ASD and control individuals with high/low IQ have to be viewed with caution and need to be replicated in a larger sample. Also, groups were not fully matched with regard to IQ measures. Similar to prior structural MRI studies, our study had a cross-sectional design, which does not allow conclusions about causality. Further structural MRI studies should implement a longitudinal approach to compare brain development in ASD and control children.

In conclusion, we replicated findings of increased TBV, GM, and WM in adolescent and adult ASD individuals and described the strong influence of IQ on these anatomical measures. Finally, CC area and posterior thickness were reduced, replicating previous studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Differences of callosal thickness between groups. Illustrated are regions of significantly increased callosal thickness in control subjects compared with ASD individuals (CTL > ASD). Analyses of covariance (ANCOVA) were performed with adjustment for IQ and WM. The color bar encodes the p values, with gray color indicating regions where no group differences were detected. The callosal anterior section is located on the left; the callosal posterior section points to the right. ANCOVA, analysis of covariance; ASD, autism spectrum disorder; CTL, control subjects; IQ, intelligence quotient; WM, white matter.

Table 1

Descriptive Data

	Autism Spectrum Disorder <i>n</i> = 15	Control Subjects <i>n</i> = 15	Statistic <i>t</i> Value/ χ^2 Value (<i>df</i>) <i>p</i> Value
Male/Female, <i>n/n</i>	13/2	13/2	
IQ, Mean (SD)	101.2 (21.2)	112.1 (18.0)	1.5 (28) .14
Age in Years, Mean (SD)	17.5 (3.5)	18.6 (1.1)	1.21 (17.1) .27
Right-Handed/Left-Handed, <i>n/n</i>	13/2	14/1	
Total Brain Volume in cm ³ , Mean (SD)	1253.5 (85.4)	1227.7 (150.6)	-.6 (22.2) .57
Gray Matter Volume in cm ³ , Mean (SD)	758.3 (70.2)	745.4 (90.6)	-.44 (28) .67
White Matter Volume in cm ³ , Mean (SD)	495.2 (47.5)	482.2 (71.1)	-.59 (28) .56
Brain Cerebrospinal Fluid in cm ³ , Mean (SD)	600.8 (112.4)	593.7 (101.5)	-.2 (28) .86
Corpus Callosum Area in mm ² , Mean (SD)	621.5 (44.6)	654.4 (124.0)	.97 (17.6) .35
Upper Face Apraxia Score, ^a Mean (SD)	26.0 (4.7)	32.0 (3.7)	3.5 (22) .002
Lower Face Apraxia Score, ^a Mean (SD)	93.8 (11.5)	111.8 (13.5)	3.5 (22) .002
Hand-Finger Imitation Score, ^a Mean (SD)	18.3 (4.2)	25.3 (2.5)	4.9 (17.7) .0001
ZN Grooved Peg Board, ^a Mean Z-Score (SD)	-1.7 (1.6)	-.2 (.9)	9.0 (1) .003
ZN Dynamic Balance, ^a Mean Z-Score (SD)	-5.6 (4.5)	.2 (1.0)	15.9 (1) <.0001

df, degrees of freedom; IQ, intelligence quotient; SD, standard deviation; ZN, Zurich Neuromotor Assessment; Z-Score, standardized score with mean = 0 and SD = 1.

^aHigher values: better performance.

Table 2

Total Brain, Gray, and White Matter Volumes in Autism Spectrum Disorder and Control Subjects Adjusted for IQ

Dependent Variables	Total Brain Volume in cm ³	Gray Matter Volume in cm ³	White Matter Volume in cm ³	Multivariate Main Effect Wilks' Lambda, <i>F</i> (Num <i>df</i> , Den <i>df</i>) <i>p</i> Value
Associated Factors				
ASD, Adjusted Mean (SE)	1246.1 (29.2)	752.5 (20.0)	493.6 (15.2)	Status
Control Subjects, Adjusted Mean (SE)	1202.7 (29.6)	731.3 (20.3)	471.3 (15.3)	.75, 4.1 (2,25) <i>p</i> = .029 ^a
Statistic Case-Control Status; <i>F</i> Value (<i>df</i>) <i>p</i> Value	8.5 (1) .007 ^a	6.7 (1) .016 ^a	4.9 (1) .035 ^a	
IQ				
IQ, β -Estimate (SE)	1.6 (1.1)	.8 (.7)	.9 (.6)	
Statistic IQ; <i>t</i> Value (<i>df</i>) <i>p</i> Value	1.5 (1) .141	1.1 (1) .304	1.6 (1) .134	.91, 1.3 (2,25) <i>p</i> = .297
IQ*status				
IQ in ASD, β -Estimate (SE)	-1.4 (1.1)	-1.1 (.9)	-.3 (.6)	
IQ in Control Subjects, β -Estimate (SE)	4.6 (1.9) ^a	2.6 (1.2) ^a	2.0 (.9) ^a	.77, 3.8 (225) <i>p</i> = .037 ^a
Statistics IQ*Case-Control Status; <i>F</i> Value (<i>df</i>) <i>p</i> Value	7.8 (1) .010 ^a	6.3 (1) .019 ^a	4.4 (1) .047 ^a	

ASD, autism spectrum disorder; den, denominator; *df*, degrees of freedom; IQ, intelligence quotient; num, numerator; SE, standard error of the mean.

^a *p* < .05.

Table 3

Corpus Callosum Area in Autism Spectrum Disorder and Control Subjects Adjusted for WM and IQ

Associated Factors	Corpus Callosum Area in mm ²	Statistics <i>F</i> Value (<i>df</i>) <i>p</i> Value
ASD, Adjusted Mean (SE)	618.4 (17.9)	8.1 (1) .010 ^a
Control Subjects, Adjusted Mean (SE)	650.2 (18.7)	
WM, β -Estimate (SE)	.5 (.2)	5.3 (1) .031 ^a
WM in ASD, β -estimate (SE)	.0 (.3)	
WM in control subjects, β -estimate (SE)	1.0 (.4) ^a	WM*status 4.4 (1) .046 ^a
IQ, β -Estimate (SE)	.7 (.7)	1.1 (1) .310
IQ in ASD, β -estimate (SE)	-.5 (.6)	
IQ in control subjects, β -estimate (SE)	2.0 (1.4)	IQ*status 3.1 (1) .088

$R^2 = .58$. Model statistics: $F = 6.5$, model df 5, error df 24, $p = .006$.

ASD, autism spectrum disorder; df , degrees of freedom; IQ, intelligence quotient; SE, standard error of the mean; WM, white matter volume.

^a $p < .05$.