

# Corpus Callosum Morphometrics in Young Children with Autism Spectrum Disorder

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**Abstract** This study assessed midsagittal corpus callosum cross sectional areas in 3–4 year olds with autism spectrum disorder (ASD) compared to typically developing (TD) and developmentally delayed (DD) children. Though not different in absolute size compared to TD, ASD callosums were disproportionately small adjusted for increased ASD cerebral volume. ASD clinical subgroup analysis revealed greater proportional callosum reduction in the more severely affected autistic disorder (AD) than in pervasive developmental disorder-not otherwise specified (PDD-NOS) children. DD children had smaller absolute callosums than ASD and TD. Subregion analysis revealed widely distributed callosum differences between ASD and TD

children. Results could reflect decreased inter-hemispheric connectivity or cerebral enlargement due to increase in tissues less represented in the corpus callosum in ASD.

**Keywords** MRI · Autism · Brain structure · Corpus callosum

Autism is a disorder characterized by impairments in social interaction, communication and a markedly restricted repertoire of social activity and interests (DSM-IV, 1994). Although the brain structural abnormalities reported to be associated with this disorder have been variable, recent work suggests that at least younger children with autism exhibit increased brain weight and size, shown both in imaging and pathological studies (Bailey et al., 1993; Harden, Minschew, Mallikarjunn, & Keshavan, 2001; Piven et al., 1995; Piven, Arndt, Bailey, & Andreasen, 1996; Sparks et al., 2002). The distribution and substrate underlying this increased brain size remain less well characterized. Variability of findings reported in the literature may, at least in part, reflect the heterogeneous populations that have been studied, in particular varying symptom expression and broad age ranges.

In contrast to findings of an overall increase in brain size in younger children with autism, previous studies have generally reported a decrease in the size of the corpus callosum in patients with autism compared to controls (Egaas, Courchesne, & Saitoh, 1995; Harden, Minschew, & Keshavan, 2000; Manes et al., 1999), although not all have found differences (Elia et al., 2000; Gaffney & Tsai, 1987). Reports of a decrease in corpus callosum size, although reflecting heterogeneous autistic populations generally comprised of adolescents and adults, has been shown either for absolute measurements (Egaas et al., 1995; Harden et al., 2000; Manes et al., 1999) or after adjustment for

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brain volume. Alterations in corpus callosum size are of interest due to potential implications for abnormal inter-hemispheric connections in autism. In some reported studies, the corpus callosum has been subdivided to investigate whether focal colossal abnormalities might help identify specific projections to cerebral regions involved in the pathology. Although subdivision techniques have differed between studies, overall there has been little apparent consistency in findings with variable regional reduction in corpus callosum size reported (Egaas et al., 1995; Harden et al., 2000; Manes et al., 1999).

The intent of the current study was to characterize corpus callosum morphology in a group of 3–4 year-old children with ASD in comparison to chronologically age-matched typical developing (TD) children and mentally and chronologically age-matched developmentally delayed (DD) children, in relationship to increased cerebral volume findings previously demonstrated in this sample. Cerebral enlargement could be associated with proportional enlargement of the corpus callosum if the increase in cerebral volume was due to proportionate increases in all brain components, as observed for other regions including the cerebellum and hippocampus (although not the amygdalae which were disproportionately enlarged relative to overall cerebral volume among a subgroup of more severely affected children with autism) (Sparks et al., 2002). Conversely a smaller or disproportionate corpus callosum could reflect that the increase in brain volume was due to an increase in tissue components proportionately less represented in the corpus callosum than the remainder of the brain or, alternatively, that there were fewer inter-hemispheric neuronal connections in the brains of children with autism. Finally, we further evaluated the corpus callosum for any focal size differences that might implicate regional cerebral pathology in the autism group.

## Methods

### Subjects

The data set used in the current study consisted of three to four year old children with autism spectrum disorder (ASD) and comparison groups of chronological age-matched typical developing (TD) children and mental and chronological age-matched developmentally delayed (DD) children. This well characterized sample of young children with ASD has been demonstrated to have an increase in cerebral volume compared to age matched control groups of TD and idiopathic DD children (Sparks et al., 2002). The data set included 45 children with ASD (7 girls, 38 boys, mean age 47.4 months  $\pm$  4.2 SD; range 38–54 months); 26 children with TD (8 girls, 18 boys, mean age 47.5 months  $\pm$  6.2 SD;

range 36–56 months); and 14 children with DD (8 girls, 6 boys, mean age 47.5 months  $\pm$  5.6 SD; range 40–58 months).

Children with ASD or DD were evaluated at a multi-disciplinary center at the University of Washington (UW) Autism Center where they were diagnosed or had their original diagnosis confirmed. Both groups were evaluated using the Mullen Scales of Early Learning (Mullen, 1984) and the Vineland Adaptive Behavior Scales (Sparrow, Balla, & Cicchetti, 1984) to confirm current degree of developmental delay. The ASD and DD groups were group-matched based on the Mullen Composite Age Equivalent score (Mullen, 1984). Diagnosis for children in the ASD group was based on the Autism Diagnostic Interview-Revised (ADI-R) (Lord, Rutter, & Le Couteur, 1994), the Autism Diagnostic Observation Schedule-Generic (ADOS-G) (Lord et al., 1989, 2000) and a DMS-IV (DSM-IV, 1994) clinical assessment by a trained clinician. The ASD children were further divided into subgroups of autism disorder (AD) (3 girls, 26 boys, mean age 47 months  $\pm$  4.3 SD; range 38–54 months) and pervasive developmental disorder—not otherwise specified (PDD-NOS) (4 girls, 12 boys, mean age 48.6 months  $\pm$  3.8 SD; range 42–54 months); based on an integration of the findings from the clinical assessment and these two diagnostic tests. Specifically AD subjects met criteria for AD on the ADOS-G and by DSM-IV based clinical evaluation and meeting criteria for AD, or within two points of meeting criteria, on the ADI-R. The PDD-NOS diagnosis was made if the child met criteria for autism on the ADI-R but was classified as PDD-NOS on the ADOS-G and by the DSM-IV based clinical assessment (DSM-IV, 1994). The DD children were evaluated using the ADOS-G, developmental history, and a clinical assessment. These children did not meet the criteria for AD or PDD-NOS on both the ADOS-G and the clinical assessment which was based on the DSM-IV (DSM-IV, 1994), nor did they show elevated symptoms of autism on these measurements.

The TD group was recruited from the local community and evaluated either at the UW ( $n = 13$ ) or the NIH ( $n = 13$ ), as previously described, with direct evaluation as part of the workup (Giedd et al., 1996; Sparks et al., 2002). For TD children, there were no parental reports of language, social, motor or cognitive delay; speech therapy; emotional or psychiatric disturbances; or special services for learning problems, use of medication, major psychiatric disorder in first degree relative or special service requirements in school.

For all groups, children having significant motor or sensory impairment (e.g., blindness, deafness), major physical abnormalities, seizures, history of serious head injury, prenatal or perinatal difficulties, metal implants or children taking psychoactive medication on a regular basis

were excluded. Children with clinical phenotype or confirmed genetic syndrome (e.g., Fragile X syndrome, Down syndrome) were also excluded. Written parental/guardian informed consent, approved by the UW Internal Review Board or the NIH Internal Review Board, was obtained for each child participating in the study.

### MRI Scans

Children with ASD and DD underwent imaging during a continuous IV infusion of propofol at 180–220  $\mu\text{g}/\text{kg}$  per minute. TD children were scanned late at night while asleep. About 8 of the TD children received 25 mg oral diphenhydramine hydrochloride. All imaging studies were performed on a 1.5-T GE Signa Scanner. An MR 3-D SPGR volume sequence (repetition time (TR) = 33 ms, echo time (TE) = minimum, flip angle = 30, 22-cm or 24-cm field of view (FOV), and  $256 \times 256$  matrix) was acquired in the coronal plane with a slice thickness of 1.5 mm (3.0 mm reduced by ZIP (zero fill interpolation) to 1.5 mm) or 2 mm (NIH).

### Structural Measurements

Volumetric measurements were performed using MEASURE, a semi automated imaging analysis program developed at Johns Hopkins University (Barta, Dhingra, Royall, & Schwartz, 1997). Using MEASURE, the outline of the brain was traced in a semi-automated fashion, excluding extra-cerebral tissue, the cerebrospinal fluid, the

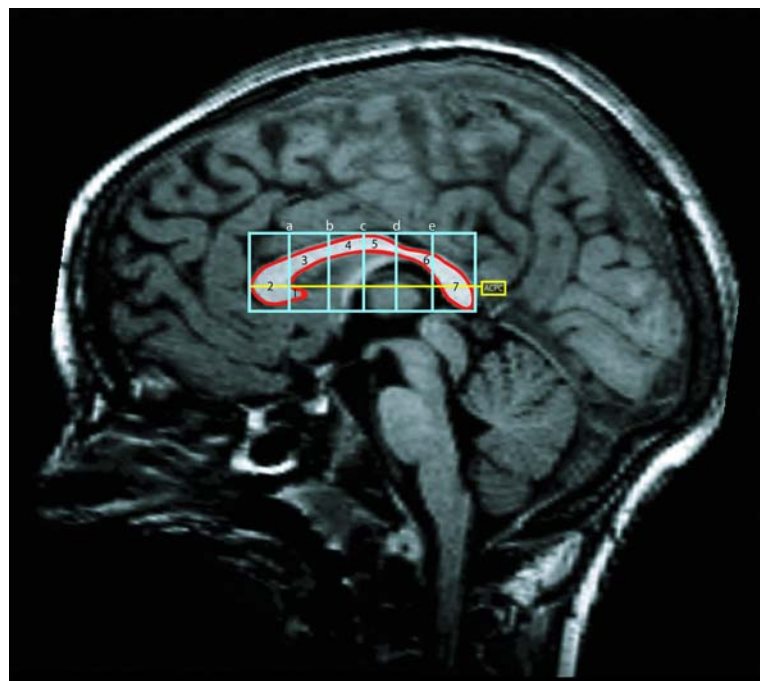
cerebellum and the brain stem (dividing from the brainstem at the midbrain pontine junction), resulting in a ‘stripped’ brain. Total cerebral volume was then calculated by summing up areas of successive coronal slices multiplied by slice thickness.

A midline sagittal reconstructed slice was created using MEASURE with the true mid-sagittal slice defined as a slice perpendicular to the corpus callosum in which the aqueduct of sylvius and the septum pellucidum were most clearly visualized. The outline of the corpus callosum was then manually traced in MEASURE from the mid-sagittal slice and this mid-sagittal slice area calculated. The corpus callosum was then sub-divided into 7 segments using a method described elsewhere (Witelson, 1989) (see Fig. 1).

All corpus callosum measurements were done by a single rater (I B-M) blinded to the subject identity and diagnosis. 6-month intra-rater reliability was assessed using randomly selected scans with a single measure interclass correlation coefficient of .96 ( $.49 \pm .08$  vs.  $.47 \pm .07$ ; 15 scans). Inter rater reliability (I B-M, DS) was similarly calculated at .90 ( $.50 \pm .08$  vs.  $.50 \pm .06$ ; 10 scans).

For 9 children, corpus callosum area could not be reliably measured due to inadequate image quality of the re-sliced sagittal image (1 ASD, 1 DD and 6 TD) or gross brain abnormalities (1DD). For children with useable data, there were no significant chronological age differences between groups (ANOVA  $F(3,75) = .45$ ,  $p_s = \text{ns}$ ). There were a greater percentage of girls in the DD group (58%) compared to the ASD (16%) and the TD groups (30%) ( $\chi^2 = 17.2$ ,  $df = 2$ ,  $P < .001$ ).

**Fig. 1** Corpus Callosum Morphometrics in Young Children with Autism Spectrum Disorder



## Statistical Analysis

Statistical analysis was done using SPSS statistical software version 11.0 (Chicago, IL). As gender potentially influences callosal and brain size independent of age, and the gender ratio between groups was different, analysis of variance (ANOVA) group comparisons were covaried for gender. Post hoc tests were performed with the TD group as the apriori comparison sample. This apriori approach was chosen for conceptual simplicity and to reduce the false positive error rate with multiple comparisons. Further analyses included the covariance of cerebral volume, and assessment of the corpus callosum/cerebral volume ratio, aimed to investigate whether the corpus callosum size scaled to cerebral volume.

## Results

### Total Midsagittal Corpus Callosum Area

Comparing absolute mid sagittal corpus callosal areas (Table 1) between diagnostic groups (ASD vs. DD vs. TD), covaried by gender, significant overall group differences were found ( $F(2,70) = 5.85, P = .004$ ). Post hoc analysis revealed significant TD > DD ( $P = .001$ ) but not TD vs. ASD differences ( $P = .28$ ). Co-varying both by gender and cerebral volume additionally revealed significant group differences ( $F(2,70) = 7.38, P = .001$ ). Post hoc tests revealed TD > DD ( $P = .001$ ) as well as TD > ASD differences ( $P = .038$ ). Additional evaluation of diagnostic group differences using the ratio of the corpus callosum to cerebral volume, covaried for gender, demonstrated

**Table 1** Corpus callosum cross-section areas and cerebral volumes for groups

	Mean $\pm$ SD	CC (cm <sup>2</sup> ) mean $\pm$ SD	CV (cc) mean $\pm$ SD
Clinical Groups			
ASD	.47 $\pm$ .07	1179.05 $\pm$ 85.54	
AD	.46 $\pm$ .07	1167.86 $\pm$ 85.14	
PDD	.51 $\pm$ .07	1200.67 $\pm$ 84.96	
DD	.41 $\pm$ .06	1071.15 $\pm$ 136.66	
TD	.50 $\pm$ .08	1091.46 $\pm$ 112.63	

SD = standard deviation

cov = covaried

PDD-NOS = pervasive developmental disorder not otherwise specified

AD = autistic disorder

DD = developmentally delayed

TD = typically developing

CV = cerebral volume (cc)

CC = corpus callosum cross-sectional area (cm<sup>2</sup>)

/CV = divided by cerebral volume

significant differences ( $F(2,70) = 7.38, P = .001$ ). Post hoc analysis demonstrated TD > DD ( $P = .001$ ) and TD > ASD ( $P = .003$ ) differences.

In keeping with our prior analytic approach (Sparks et al., 2002), we further subdivided the ASD group into AD and PDD-NOS subgroups. Group differences (AD vs. PDD-NOS vs. DD vs. TD) in corpus callosal areas, covaried by gender, were found ( $F(3,69) = 5.38, P = .002$ ). Post hoc tests revealed TD > DD ( $P = .001$ ) with trend TD > AD ( $P = .08$ ) but no TD vs. PDD-NOS ( $p = .78$ ) differences. When covaried both by gender and cerebral volume, group differences were again demonstrated ( $F(3,69) = 5.22, P = .003$ ), with post-hoc testing revealing TD > DD ( $P = .001$ ) and TD > AD ( $P = .014$ ) but not TD vs. PDD-NOS differences ( $P = .46$ ). Similarly, analysis of the ratio of corpus callosum to cerebral volume, covaried for gender, also demonstrated significant differences ( $F(3,69) = 5.37, P = .002$ ). Post hoc analysis demonstrated TD > DD ( $P = .001$ ) and TD > AD ( $P = .002$ ) and also trend TD > PDD differences ( $P = .082$ ).

### Mid Sagittal Corpus Callosum Subregion Areas

Results and statistical analysis of mid sagittal corpus callosum subregions are detailed in Table 2. Post hoc analysis, covaried for gender, revealed TD > AD in regions 1 and 3. When covaried for cerebral volume and gender, in addition to regions 1 and 3, significant TD > AD differences were also seen in regions 5 and 7. When a ratio of callosum subregion to cerebral volume (covaried for gender) was analyzed, significant TD > AD differences were seen in regions 1,3,4,5 and 7. Significant differences were only seen with TD > PDD-NOS when covaried for cerebral volume (and covaried for gender) in regions 3 and 7. Covaried for gender, significant TD > DD differences were seen in regions 3–7, and these differences remained when adjusted for cerebral volume either with covarying or ratios.

## Discussion

In this study, we were interested in evaluating for the size of the corpus callosum relative to our previous observations of increased cerebral volume in this sample of young children with autism. Our previous finding of an increase in cerebral volume might reflect either a proportional increase in all of its components (various cell types, intercellular space) or a disproportional increase in one or more constituent components. To examine this further, we measured the mid-sagittal slice area of the corpus callosum in this sample of children with ASD compared to both DD and TD control samples. Consistent with findings in normal adult subjects (Rauch & Jenkins, 1994), we reasoned that if all

**Table 2** Corpus callosum subregions and comparison amongst clinical groups

Corpus callosum subregions (mean ± SD) (cm <sup>2</sup> )							
	1	2	3	4	5	6	7
<b>Clinical groups</b>	Mean ± SD						
AD	.017 ± .007	.100 ± .020	.071 ± .013	.056 ± .008	.047 ± .007	.039 ± .011	.129 ± .020
PDD	.022 ± .010	.109 ± .022	.080 ± .012	.061 ± .008	.054 ± .009	.043 ± .013	.136 ± .022
DD	.018 ± .006	.090 ± .028	.062 ± .009	.052 ± .008	.044 ± .009	.033 ± .007	.112 ± .016
TD	.024 ± .008	.100 ± .022	.083 ± .015	.060 ± .010	.052 ± .011	.041 ± .008	.139 ± .020
<b>Statistics</b>	1	2	3	4	5	6	7
<i>F</i> , <i>P</i> -values	3.09, <i>P</i> = .03	1.55, <i>P</i> = ns	8.45, <i>P</i> < .001	3.47, <i>P</i> = .02	3.56, <i>P</i> = .02	2.15, <i>P</i> = .10	4.92, <i>P</i> = .004
AD-TD	<i>P</i> = .008	<i>P</i> = ns	<i>P</i> = .004	<i>P</i> = ns	<i>P</i> = ns	<i>P</i> = ns	<i>P</i> = ns
PDD-TD	ns	ns	ns	ns	ns	ns	ns
DD-TD	.08	ns	< .001	.008	.03	.04	< .001
<i>F</i> , <i>P</i> -values	3.57, <i>P</i> = .02	.80, <i>P</i> = ns	8.28, <i>P</i> < .001	3.08, <i>P</i> = .03	3.16, <i>P</i> = .03	1.64, <i>P</i> = ns	4.89, <i>P</i> = .004
AD-TD	.003	ns	.003	.08	.05	ns	.03
PDD-TD	ns	ns	ns	ns	ns	ns	ns
DD-TD	.08	ns	< .001	.008	.03	.04	< .001
<i>F</i> , <i>P</i> -values	4.09, <i>P</i> = .01	.83, <i>P</i> = ns	7.85, <i>P</i> < .001	3.27, <i>P</i> = .03	3.13, <i>P</i> = .03	1.93, <i>P</i> = ns	5.27, <i>P</i> = .002
AD-TD	.001	ns	< .001	.01	.009	ns	.005
PDD-TD	ns	ns	.02	ns	ns	ns	.03
DD-TD	.07	ns	< .001	.01	.03	.03	< .001
<b>/CV cov GENDER</b>							

components of the autistic brain were proportionally increased, the corpus callosum area should mirror the overall increase in cerebral volume. Our findings instead suggest that the corpus callosum, although not smaller in absolute measure in the ASD children compared to the TD controls, does not scale proportionately to their overall increase in cerebral volume. Thus, the ASD children exhibited smaller corpus callosums when adjusted (co-varied or ratio) for their larger cerebral volume.

We additionally co-varied for gender, which was significantly different among groups. There are data (Rauch & Jinkins, 1994; Sullivan, Rosenbloom, Desmond, & Pfefferbaum, 2001), although conflicting (Pozzilli et al., 1994), to suggest gender effects on corpus callosum size, independent of cerebral volume. Even after adjusting for gender, the difference in corpus callosum size relative to total cerebral volume remained for the ASD group.

Even at this early age we did not find evidence for enlargement of the corpus callosum, as would be expected if increases in cerebral volume were due to a proportional increase in all its components. One potential explanation for a finding of a disproportionately smaller corpus callosum is that the increase in autistic cerebral volume reflects tissue (neuronal or non neuronal) overgrowth that is less represented in the corpus callosum. The corpus callosum in such a case would be of similar size as the typically developing brain and any disproportionality between callosal size and cerebral volume would be solely due to an increase in hemispheric volume. If, for example, the increased cerebral volume was predominantly due to increased gray matter, there could be an increase in gray matter without a proportional increase in the corpus callosum. Alternatively, there could be a non-uniform increase in white matter in autistic children, as was reported by Herbert et al. who found increased outer zone cerebral white matter in an older group of autistic children without any significant difference in the corpus callosum cross-sectional area (Herbert et al., 2004). An isolated increase in white matter however has not been uniformly found in other studies, including Carper et al. who reported increase in gray and white matter in some but not all cerebral lobes (Carper, Moses, Tigue, & Courchesne, 2001). An increase in non-neuronal elements, less represented in the corpus callosum, would potentially be consistent with MR spectroscopy finding in this sample of ASD children of lower metabolite levels and transverse relaxation elongation in these patients (Friedman et al., 2003). These lower metabolite levels could reflect decreased cell density.

The disproportionately smaller size of the corpus callosum compared to an overall increase in cerebral volume among the ASD children alternatively could reflect disease-related differences in the inter-hemispheric connectivity within the brain. The ASD cerebral hemispheres

may contain increased numbers of neurons having fewer inter-hemispheric connections. Future studies utilizing diffusion tensor imaging or functional studies assessing functional connectivity might help elucidate this question and, in fact, preliminary diffusion tensor results have found differences in corpus callosum anisotropy (Barnea-Goraly et al., 2004).

Prior studies have generally found absolute measurements of the corpus callosum to be smaller in subjects with autism, or that the corpus callosum was smaller after adjusting for their larger total brain volume (Egaas et al., 1995; Harden et al., 2000; Manes et al., 1999). As these previous studies assessed populations generally older than the current sample of young children with autism, it is possible that age-related changes could result in a relative decrease during early childhood becoming an absolute decrease in corpus callosum size over time.

As other reports (Courchesne, Carper, & Akshoomoff, 2003) and previous analysis of this cohort (Sparks et al., 2002) have suggested volume differences of some brain substructures across clinical subgroups of autism, we differentiated the ASD cohort into those more severely affected (i.e., those with Autistic Disorder, AD) compared to a less severely affected group (PDD-NOS). Comparison of these ASD clinical subgroups (AD and PDD-NOS) revealed structural differences between these subgroups. When the corpus callosum to cerebral volume ratio was reanalyzed for these clinical subgroups, children with AD were found to have significantly smaller corpus callosum while a similar comparison for the group with PDD-NOS yielded only trend differences. Although this latter finding may reflect issues related to a smaller sample size, it is consistent with our prior work (Sparks et al., 2002) that similarly found that structural abnormalities tend to be more accentuated in the children with more classic autism illness expression (AD) as compared to those with fewer autism symptoms.

Some prior studies have incorporated evaluating subdivisions of the corpus callosum in attempt to elucidate possible regional differences in connectivity between cerebral hemispheres. Attempts at detecting regional differences by subdividing the corpus callosum have not yielded consistent results, with differences found in anterior (Harden et al., 2000), body (Manes et al., 1999; Piven, Bailey, Ranson, & Arndt, 1997) and posterior (Egaas, Courchesne, & Saitoh, 1995; Piven et al., 1997) areas of the corpus callosum. To this end we subdivided the corpus callosum to probe for any regional differences in size. When dividing the corpus callosum into subregions without adjustment for cerebral size, regions 1 and 3 were smaller in the AD group compared to TD controls. With covarying or ratio adjustment for cerebral volume, significant differences were seen in most subdivision, distributed through

the corpus callosum. We interpreted these findings to suggest a more diffuse process at work, rather than being driven by a single area of abnormality. The mid-sagittal area and shape does represent only a limited evaluation of the corpus callosum. Further development of more complex methodologies may reveal yet unappreciated structural differences in the corpus callosum between groups.

In studying this group of children, we did not test for handedness. Left handedness, or inconsistent right handedness, has been reported to be related to increased callosal size (Witelson, 1985) though not consistently shown (Kertesz, Polk, Howell, & Black, 1987). Proportionally the approximately 10% increased cerebral volume observed in current cohort of ASD children (Sparks et al., 2002) would render an approximately 6% increase in callosal area. Considering the 11% greater cross sectional callosal area found by Witelson in left-handed subjects, a gross over representation of left handed or inconsistent right handedness in the TD group would have been necessary to produce the smaller relative corpus callosum size in the ASD group on the basis of handedness alone. Similarly, assuming a normal distribution of handedness in the TD group, an entirely right handed ASD cohort would have been unlikely to produce the degree of difference in the corpus callosum observed between the ASD and TD groups.

In conclusion, our findings show that 3–4 year-old ASD children, previously demonstrated to have increased cerebral volume, also exhibit smaller than expected corpus callosums when adjusted for cerebral volume. This finding is accentuated in the subgroup of AD children with more “classic” autistic symptom expression. Further the size differences appear to be at least widely distributed through the corpus callosum with no single portion appearing to account for the relative smaller size of the corpus callosum in ASD. Considering the larger total cerebral volume of these children with autism, findings of a disproportionately smaller corpus callosum raise intriguing questions. Increases in autistic brain volume may be due to increase in non-neuronal elements such as astrocytes or intercellular tissue, which are less represented in the corpus callosum. Alternatively, these findings could suggest an alteration in inter-hemispheric connectivity in the autistic brain. Since autism seems to be a dynamic disease with age-related brain changes (Courchesne et al., 2001) between birth and adulthood, we are conducting ongoing longitudinal MRI studies of these children. Functional imaging studies may also help elucidate questions of differences in inter-hemispheric connectivity and further pathologic studies are warranted to determine the brain cellular composition in autism. Finally, our brain structural results further support the clinical distinction of AD and PDD-NOS subgroups of ASD.

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