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Corpus Callosum Volume in Children with Autism

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Abstract

The corpus callosum (CC) is the main commissure connecting the cerebral hemispheres. Previous evidence suggests the involvement of CC in the pathophysiology of autism. However, most studies examined the mid-sagittal area and investigations applying more precise methods are warranted. The goal of this investigation is to apply a volumetric method to examine the size of the CC in autism and to identify any association with clinical features. An MRI-based morphometric study of the total CC volume and its 7 subdivisions was conducted and involved 22 children with autism (age range 8.1–12.7 years) and 23 healthy, age-matched controls. Reductions in the total volume of the CC and several of its subdivisions were found in the autism sample. Associations were observed between CC structures and clinical features including social deficits, repetitive behaviors, and sensory abnormalities. Volumetric alterations of the CC observed in this investigation are consistent with midsagittal area tracings of decreased CC size in autism. These findings support the aberrant connectivity hypothesis with possible decrease in interhemispheric communications.

Keywords

MRI; White Matter; Clinical Symptoms; Sensory Deficits

1. Introduction

Autism is a complex neurodevelopmental disorder characterized by severe deficits in social behavior, cognitive function, and language (Rapin & Katzman, 1998). It is part of a spectrum of pervasive developmental disorders often complicated by serious behavioral problems commonly including repetitive behaviors and restricted interests (American Psychological Association, 2000). While the exact etiology (ies) of autism remains elusive, numerous studies examining the brain and its functions have attempted to identify specific brain regions

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implicated in this disorder and their relationships to clinical features. Morphometric MRI is the most frequent neuroimaging methodology applied probably due to its safety, its utility in discriminating tissue characteristics and anatomy in vivo without ionizing radiation, noninvasiveness, and usefulness in individuals with autism and low levels of cognitive functioning. The most replicated structural findings are increased total brain volume involving grey and white matter structures contrasting with a decrease in the size of the corpus callosum (Brambilla et al., 2003). These findings have led to increased interest in white matter structures in autism. A recent morphometric study suggested a heterogeneous distribution of white matter volumetric abnormalities with enlargement seen almost exclusively in the radiate compartments and no significant differences seen in the deep/bridging compartments (Herbert et al., 2004). Diffusion tensor imaging study in individuals with autism reported reduced fractional anisotropy (FA) in several brain regions including corpus callosum (CC) regions (Barnea-Goraly et al., 2004; Alexander et al., 2007). These observations in combination with evidence of abnormal connectivity in autism (Just et al., 2004) have highlighted the contribution of white matter alterations to the pathophysiology of autism.

Several investigations have been conducted to examine CC in autism. The CC is the largest white matter structure consisting of axons projecting between the two cerebral hemispheres and therefore represents an index of interhemispheric connectivity (Piven et al., 1997). Abnormalities in CC size may demonstrate atypical neural development. Because it is topographically organized, regional abnormalities shed light on which parts of the brain are most affected. Previous MRI investigations measuring the mid-sagittal areas of the CC have demonstrated a reduction in CC size with discrepancies regarding which particular sub-regions are most affected. Additionally, most (Egaas et al., 1995; Piven et al., 1997; Manes et al., 1999; Hardan et al., 2000; Boger-Megiddo et al., 2006; Vidal et al., 2006) but not all studies (Gaffney et al., 1987; Elia et al., 2000) have reported regional alterations. While some research groups found reductions in anterior subregions (Manes et al., 1999; Hardan et al., 2000; Vidal et al., 2006), other investigators reported on decrease CC size in mid-body structures (Piven et al., 1997; Manes et al., 1999) or posterior sub-regions (Egaas et al., 1995; Piven et al., 1997; Manes et al., 1999). Differences between investigations have been related to study design and the failure to control for known confounding factors such as gender, handedness, and IQ. Additionally, disparities in results may be related to the tracings of only the mid-sagittal slice. In fact, reductions in the splenium and genu were observed in a recent investigation applying advanced morphometric methodology (statistical maps) but were not found while using the traditional method of midsagittal slice tracings (Vidal et al., 2006). Hence, the use of novel methodologies such as volumetric measurement may lead to more accurate and consistent results since it will provide more quantitative structural information about the region of interest.

In this study, we examined the volume of the CC in 22 children with autism and 23 age and gender-matched controls and we assessed the relationship between structural findings and clinical features. We also measured the volume of seven CC sub-regions based on the organization developed by Witelson and used in previous studies (Witelson, 1989; Hardan et al., 2000). As suggested by prior CC area investigations, we hypothesized that the total volume of the CC as well as several of its subdivisions will be reduced in the patient group when compared to controls. We also predicted the existence of correlations between CC size and several clinical features of autism as measured by the Autism Diagnostic Interview-Revised (ADI-R) (Lord et al., 1994) and the Sensory Profile Questionnaire (SPQ) (Dunn, 1994).

2. Methods

2.1. Subjects

Quantitative volumetric analysis was performed on brain MRIs of 45 boys: 22 children with PDD and 23 healthy controls (age range: 8–12 years). The study was confined to boys because

the sample size was too small to accommodate for the structural variability associated with gender. Subjects with pervasive developmental disorder (PDD) were referred to a research clinic from the community and met the following inclusion criteria: 1) diagnosis of PDD through expert clinical evaluation and two structured research diagnostic instruments including the ADI-R (Lord et al., 1994) and the Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 1989) and 2) absence of any neurological and genetic disorders. Those with autistic disorder met both ADI-R and ADOS criteria for autism. Subjects with PDD, Not Otherwise Specified (NOS) had ADOS scores ranging from seven to 10 while meeting ADI-R criteria for autism. Controls consisted of medically healthy individuals recruited from communities through advertisements in areas socially and economically comparable to the communities from which PDD subjects originated. In addition, controls were developmentally normal, free of neuropsychiatric disorders, had full-scale IQ (FSIQ) ≥ 70 , and negative family histories for neurological or psychiatric disorders. Additional exclusion criteria for both groups included hearing deficits, and ferromagnetic materials. After procedures were fully explained, parents of all participants or their legal guardians provided written informed consent. Verbal assent was obtained from all participants. The Institutional Review Board approved the methodology of the study, including MRI scanning of minors. The Hollingshead method (Hollingshead, 1975) was used to assess socioeconomic status (SES) of the family of origin of all participants. Handedness was determined by a parent questionnaire and observation during neuropsychological testing. The SPQ was obtained from participants' parents to assess sensory abnormalities (Dunn, 1994). The SPQ is a 125-item parent report questionnaire that evaluates sensory abnormalities and compared to available normative data. The items are written such that low scores reflect undesirable and abnormal behaviors. The SPQ includes section and factor clusters (Dunn, 1999). Section clusters include several domains such as sensory processing related to endurance/tone, modulation related to body position and movement and multisensory processing. Factor clusters include low endurance/tone, sensory seeking, and sensory sensitivity. Raw summary scores for section and factor clusters were used in this study as specified in the manual (Dunn, 1999).

2.2. Measurements

MRI scans were acquired using a 1.5-T GE Signa MR Scanner (General Electric Medical Systems, Milwaukee, WI, USA). For each subject, three different MR sequences were performed to generate a tissue classified image (segmented): longitudinal relaxation time (T1-weighted), proton density (PD-weighted), and transverse relaxation time (T2-weighted) all acquired in the coronal plane. The T1-weighted spoiled GRASS (SPGR) sequence was acquired using the following parameters: slice thickness = 1.5 mm, slice number = 124, echo time (TE) = 5 ms, repetition time (TR) = 24 ms, flip angle = 40°, number of excitations (NEX) = 2, field of view (FOV) = 26 cm, matrix = 256 $\times$ 192. Both PD-weighted and T2-weighted images were obtained with the following parameters: slice thickness = 3.0 or 4.0 mm, TE = 96 ms for T2 and 36 ms for PD, TR = 3000 ms, NEX = 1, FOV = 26 cm, matrix = 256 $\times$ 192 with an echo train length = 8. MRI data were identified by scan number alone to retain blindness of raters. Image processing was performed on a SGI workstation (Silicon Graphics Inc., Mountain View, CA) using the Brain Research: Analysis of Images, Networks, and Systems 2 (BRAINS2, University of Iowa, Iowa City, IA, USA) software package (Magnotta et al., 2002). Six brain-limiting points (anterior, posterior, superior, inferior, left, and right) were then identified to normalize the image data to the standard Talairach stereotactic three-dimensional space (Talairach & Tournoux, 1988) in which the anterior-posterior commissure line specifies the x-axis, a vertical line rising from the x-axis through the interhemispheric fissure specifies the y-axis, and a transverse orthogonal line with respect to x and y coordinates specifies the z-axis. After fitting the images sequences to a standard three-dimensional space, the pixels representing gray matter, white matter, and cerebrospinal fluid were identified using a segmentation algorithm applied to the T1-weighted, T2-weighted, and PD-weighted image

sequences as described elsewhere (White et al., 2003). Measurements were performed using the BRAINS2 masks as generated by a neural network and corrected by manual tracing (ICC >0.9). Total brain volume (TBV) was defined as the cerebrum, cerebellum, and brainstem while excluding cerebrospinal fluid.

2.3. Corpus Callosum Measurements

The volume of the CC was generated in all scans by tracing the CC on the mid-sagittal slice and the 6 adjacent para-sagittal slices on each side as obtained from the reformatted SPGR acquisition. The number of parasagittal slices was determined by the ability to reliably determine the CC contours on each slice. Tracings of CC on all 13 slices were conducted by raters who were blind to diagnosis and identification data. Subdivisions were measured based on the organization developed by Witelson and used in previous studies (Hardan et al., 2000). The boundaries of the different subdivisions were determined on each slice (total 13) based on the Witelson method allowing the establishment of vertical lines dividing each slice into 7 different regions (Figure 1). The AC-PC (anterior and posterior commissure) line was used to distinguish the rostrum from the rostral body. The regions below this line were included in the rostrum and the ones above it were considered as part of the rostral body. A computer script was developed to measure the volume of CC and the 7 subregions on all slices. Reliability measurements of the total CC volume and its subdivisions was assessed on 10 scans by 2 raters revealed a satisfactory intra-rater (ICC > 0.95) and inter-rater reliability (ICC>0.93).

2.4. Statistics

A Student's t-test was used to compare all the demographic data and CC measurements between autistic subjects and controls. A chi-square analysis was conducted to examine differences in handedness between the two groups. Analysis of covariance was applied to examine volumetric differences between the two groups while controlling for confounding factors such as total brain volume and total white matter. Pearson's correlations were used to examine the relationship between the CC volume and total brain volume, full-scale IQ, and age. Partial correlations were applied to examine relationships between CC volumes and scores from the three ADI-R clinical domains (qualitative impairments in reciprocal social interaction, communication, and repetitive behaviors and stereotyped patterns) while controlling for FSIQ. The relationships between CC structures, and sensory abnormalities as measured by the SPQ (Dunn, 1994) were also examined using regression analysis. A two-tailed statistical significant level was set at $P < 0.05$ for all analyses.

3. Results

There were no differences in any of the demographic characteristics between individuals with autism and controls except for FSIQ (Table 1). There was a greater proportion of left-handed participants in the autism group when compare to controls (Autism: 27% (6/22); controls: 4.3% (1/23); $\chi^2 = 4.5$; $df=1$; $P=0.034$). The volumes of the total CC as well as several of its subdivisions were significantly smaller in the PDD group as compared to controls, before and after controlling for total brain volume (Table 2). Similar results were obtained when controlling for total white matter volume (Table 2). No changes in the level of significance were observed when analyses were conducted while controlling for FSIQ, handedness, or age. No correlations were observed between CC volume and TBV as well as FSIQ in patients as well as in the control group. No associations were observed between CC volumes and age in the autism or the control groups. Analyzes were also conducted after excluding 4 individuals who were diagnosed with PDD, NOS. No changes in the level of significance were observed in the demographic data or in the CC volumes comparisons.

The association between CC volumes and clinical features as measured by the ADI-R and SPQ revealed several relationships. Correlations were observed between the isthmus volume and total ADI-R score ($r = -0.47$, $P = 0.031$) (Figure 2) and qualitative impairment in reciprocal social interaction ($r = -0.48$, $P = 0.03$) while controlling for FSIQ. Associations were also observed between stereotyped, repetitive, or idiosyncratic speech and the total volume of the CC ($r = -0.49$, $P = 0.025$) and several of its subdivisions including the anterior mid-body, ($r = -0.48$, $P = 0.028$) and the splenium ($r = -0.47$, $P = 0.03$). These relationships became more significant when analyses were conducted after excluding individuals with PDD, NOS. When controlling for FSIQ, participants group, and TBV, regression analyses revealed an association between the isthmus volume and the modulation related to body position and movement section as obtained from the SPQ ($B = -0.25$, $t = -2.2$, $P = 0.035$). Trends toward significance were also observed between the isthmus and the low endurance/tone factor ($B = -0.245$, $t = -1.993$, $P = 0.054$) and between anterior mid-body and the sensory seeking factor ($B = 0.22$, $t = 1.9$, $P = 0.064$).

4. Discussion

In this study, reduction in total CC volume and several of its subdivisions were observed supporting that autism is a disorder of connectivity involving inter- and intra-hemispheric communications with possible alterations of intracortical connections (Minschew and Williams, 2007). Our findings are consistent with previous investigations examining mid-sagittal surface area in children, adolescents, and adults with autism (Egaas et al., 1995; Filipek, 1996; Piven et al., 1997; Manes et al., 1999; Hardan et al., 2000; Chung et al., 2004; Vidal et al., 2006). These observations suggest that CC size reduction is more stable over time than increased brain volume and imply that different neurobiologic mechanisms underlie these two structural abnormalities with possibly more environmental factors affecting CC development (Sanchez et al., 1998). Our findings are also concordant with one previous volumetric study using voxels' number to determine CC size (Alexander et al., 2007). By including more quantitative structural information, volumetric strategies allow a more accurate estimation of the CC size and its subdivisions. This is particularly important in a disorder associated with macrocephaly, such as autism, since larger brains have relatively smaller CC than smaller brains (Jancke et al., 1997; Jancke et al., 1999).

The CC is the largest commissural white matter pathway connecting the left and right hemispheres with more than 300 million fibers (Hofer and Frahm, 2006). The CC plays a crucial role in communicating perceptual, cognitive, learned and volitional information and its alterations might affect the interhemispheric integration of these functions. Mounting evidence from structural studies has implicated the CC in the pathophysiology of autism. While morphometric MRI studies and recent DTI investigations have described abnormalities in CC, the cellular and developmental underpinnings have yet to be clarified. The formation of CC involves multiple steps including cellular proliferation and migration, axonal growth and glial patterning at the midline (Paul et al., 2007). Additionally, CC axon elimination appears to be related to increase synaptic density throughout the cerebral cortex (LaMantia and Rakic, 1990). A disruption in one or in several of these processes can explain the decrease in CC size. Therefore, the examination of these developmental activities might help in elucidating the neurobiology of CC abnormalities in PDD. Interestingly, the first axons to cross the midline arise from neurons in the cingulate cortex and anatomic as well as functional alterations have already been reported in this structure in autism (Haznedar et al., 1997; Hazlett et al., 2004; Korkmaz et al., 2006).

Structural MRI studies have consistently reported reductions in total CC size in autism but the exact subdivisions involved remain uncertain. The precise localization of these alterations is crucial to allow the identification of the specific brain regions involved. The CC is

topographically organized with anterior regions connecting the frontal lobes and posterior regions linking the occipital areas (Witelson, 1989). Additionally, most fibers serve homotopic interconnections between the hemispheres, and only a small number are heterotopic linking functionally different cortical areas (Clarke and Zaidel, 1994). Recent DTI-based tractography studies have mapped callosal radiations and found clear separation of callosal primary and sensory fiber bundles. More importantly, they observed that fibers originating in the motor cortex crossed through the posterior half of the CC. These observations have led to the reexamination of Witelson's classification and new segmentations have been suggested mainly at the anterior tip and the broad midbody area (Hofer et al., 2006; Huang et al., 2005). The implementation of these recommendations and the accounting for potentially confounding factors such as age, gender, cognitive functioning, and handedness, will help in elucidating the discrepancies observed in CC studies in autism.

The examination of the relationships between CC volumes and clinical features revealed the existence of several correlations warranting further investigation examining these associations while applying novel imaging techniques such as DTI and tractography. A correlation was observed between the total ADI-R score and the isthmus, a structure that connects association cortex involved in language and complex cognitive functions usually affected in autism (Narberhaus et al., 2008; Wood et al., 2008). This association should be examined in light of the rostro-caudal development of the CC with evidence indicating that the peak myelination of the isthmus occurs between 6 and 11 years of age (Thompson et al., 2000). These observations suggest that the development of the isthmus interacts with the experience of having autism since symptoms observed in this disorder appears very young in childhood.

While repetitive/stereotyped behaviors, social deficits, and sensory abnormalities were associated with smaller CC volumes, these relationships might not be specific to autism. Decrease CC size has been reported in children with OCD (Rosenberg et al., 1997; Farchione et al., 2002) which was also correlated with compulsive behaviors (Rosenberg et al., 1997). Smaller CC size has also been reported in individuals with Tourette's disorder and this reduction was correlated with tics severity (Plessen et al., 2004). Social deficits and sensory abnormalities have also been described in individuals with agenesis of CC (Paul et al., 2004; Doherty et al., 2006; Badaruddin et al., 2007). An investigation examining individuals with partial or complete absence of the CC revealed the existence of deficits in multiple domains including fluid and social intelligence (Paul et al., 2004). In a recent study of children with agenesis of CC, abnormal social development was observed with failure to develop peer relationships and impairment in the use of non-verbal behaviors (Badaruddin et al., 2007). Finally, decreased pain perception and sensitivity to touch have been found in a sample of children with agenesis of CC when compared to their siblings (Doherty et al., 2006).

This study suffers from several limitations including the age range, the gender of participants, and the exclusion of children with severe intellectual disability. The absence of correlations between CC volumes and age might be related to the limited age range of the sample and longitudinal studies are warranted to examine the age-related changes of the corpus callosum size over time. Adjustment of the p-value might be needed in light of the number of comparisons conducted. However, while p-value adjustments reduce the chance of making type I errors, they increase the chance of making type II errors, or require the increase of the sample size (Rothman, 1990; Feise, 2002). Therefore, replication studies with larger samples are warranted to confirm these findings. Furthermore, the use of informant-based instrument, such as the SPQ, to evaluate clinical features does not provide accurate assessment of these abnormalities and objective tools or laboratory tests would allow more specific and precise measurements of cognitive and sensory deficits. Methodological limitations include the arbitrary decision to measure only 13 sagittal slices, the inability to measure reliably more lateral slices, and the lack of validation of the volumetric method. Additionally, CC subdivisions were based on the

Witelson method and more recent strategies to parcelate the CC would have yielded more accurate information especially for the anterior regions.

5. Conclusion

In summary, this volumetric study provides additional evidence supporting the role of the CC in the pathophysiology of autism. However, these structural alterations should cautiously be examined in light of the evidence from animal studies suggesting that CC abnormalities could be related to environmental and social factors (Sanchez et al., 1998). An investigation of the effect of different rearing conditions on brain development in rhesus monkeys revealed a significant decrease in CC size involving mostly posterior regions in animals reared in isolation (Sanchez et al., 1998). These observations highlight the need to question whether neurobiologic abnormalities observed in autism are related to the etiology of the disorder or just a consequence of its clinical features. Therefore, future studies should examine longitudinal samples to examine the developmental trajectories of brain abnormalities and their relationships to clinical features.

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Figure 1.
Subdivisions of the CC in 7 regions: 1) Rostrum; 2) Genu; 3) Rostral body; 4) Anterior mid-body; 5) Posterior mid-body; 6) Isthmus; 7) Splenium

Figure 2.
Relationship of the isthmus volume (cc) in the autism group and total Autism Diagnostic Interview-Review (ADI-R) score.

Table 1

Sample Characteristics:

	PDD		Control		t-test	
	N = 22		N = 23		df = 43	
	Mean	SD	Mean	SD	T	P
Age	10.7	1.4	10.5	1.4	0.369	0.714
Full-scale IQ	95.09	20.4	116.2	13.2	-5.381	< 0.001
SES	4.5	0.59	4.41	0.59	0.522	0.604
ADI-R	51.2	7.6	--	--	--	--
ADOS	15.4	3	--	--	--	--

SES: Socio-Economic Status; ADI-R: Autism Diagnostic Interview-R; ADOS: Autism Diagnostic Observation Schedule.

Table 2
Volume of the corpus callosum and its 7 subdivisions in participants with autism and controls

Corpus callosum	PDD		Control		T Test		TBV as a covariate		TWM as a covariate	
	N=22		N=23		Df: 43		Df (2; 40)		Df (2; 40)	
	Mean	SD	Mean	SD	t	P	F	P	F	P
Total	5.83	1.04	6.63	0.87	-2.776	0.008	7.183	0.010	7.527	0.009
Rostrum (1)	0.06	0.05	0.08	0.05	-0.901	0.373	0.9709	0.330	0.785	0.381
Genu (2)	1.62	0.36	1.75	0.27	-1.316	0.195	1.517	0.225	1.702	0.199
Rostral body (3)	0.62	0.20	0.75	0.11	-2.046	0.049	3.932	0.054	4.235	0.046
Ant mid-body (4)	0.59	0.17	0.68	0.11	-1.998	0.052	3.594	0.065	3.911	0.055
Post mid-body (5)	0.53	0.14	0.61	0.11	-2.152	0.037	4.087	0.050	4.621	0.037
Isthmus (6)	0.55	0.16	0.64	0.19	-1.808	0.078	3.355	0.074	3.166	0.082
Splenium (7)	1.77	0.38	2.07	0.47	-2.346	0.024	5.213	0.028	5.377	0.025
TBV	1359.98	114.38	1339.00	101.10	0.653	0.517	--	--	--	--
TWM	480.2	44.66	487.1	48.8	-0.499	0.620	--	--	--	--

(Corresponding Witelson subdivision); Ant: Anterior; Post: Posterior; TBV: Total Brain Volume; TWM: Total White Matter