Published in final edited form as:

Autism. 2011 March ; 15(2): 223–238. doi:10.1177/1362361310386506.

Quantitative Analysis of the Shape of the Corpus Callosum in Autistic Individuals

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Abstract

Multiple studies suggest that the corpus callosum in patients with autism is reduced in size. This study attempts to elucidate the nature of this morphometric abnormality by analyzing the shape of this structure in 17 high-functioning patients with autism and an equal number of comparison participants matched for age, sex, IQ, and handedness. The corpus callosum was segmented from T1 weighted images acquired with a Siemens 1.5 T scanner. Transformed coordinates of the curvilinear axis were aggregated into a parametric map and compared across series to derive regions of statistical significance. Our results indicate that in subjects with autism reduction in size of the corpus callosum occurs over all of its subdivisions (genu, body, splenium) with a small area of overgrowth at its caudal pole. Since the commissural fibers that traverse the different anatomical compartments of the corpus callosum originate in disparate brain regions our results suggest the presence of widely distributed cortical abnormalities in people with autism.

Keywords

Autistic Disorder; Cerebral Cortex/growth & development; Corpus Callosum; Magnetic Resonance Imaging

Introduction

There is at present a convergence of findings stemming from structural neuroimaging studies indicating a reduction in size of the corpus callosum in subjects with autism (Frazier & Hardan, 2009; Lainhart et al., 2005). This applies both to areal measurements (e.g., using one medial sagittal slice) and to volumetric assessments (Freitag et al., 2009; Hardan et al., 2009; Keary et al., 2009). Modeling of the corpus callosum using meta-regression analyses has shown medium effect size with area magnitude reductions decreasing along its caudal extent (i.e., genu→splenium) (Frazier & Hardan, 2009). The fact that the corpus callosum is smaller in autistic individuals is all the more striking when considering that total brain size apparently exhibits an age-dependent volumetric increase (Hrdlicka, 2008).

The present study aims at elucidating the nature of the corpus callosum abnormality in autistic individuals. It complements previous morphometric studies by quantifying the shape of the corpus callosum outline and performing comparisons across series of autistic and normative subjects. Since commissural fibers bear a strict topographic relationship to originating/projecting cortical areas, focal shape abnormalities of the corpus callosum could help pinpoint which cortical region, or regions, are involved in the pathophysiology of autism. In addition, focal abnormalities of the corpus callosum could provide clues as to the timing and nature of a particular pathological change. Relevant to these statements is the putative scenario suggested by those studies in autism reporting morphometric abnormalities of the caudal portion of the corpus callosum (i.e., splenium) (see below).

At birth, there is an exuberance of callosal axons which is subsequently normalized during the first four months of life (LaMantia & Rakic, 1990). The overall growth pattern of the corpus callosum is therefore the result of myelination which according to T1 MRI studies happens during the first year after birth (Paus et al., 2001). Concurrent to the postnatal pruning/myelination processes the splenium grows faster than other regions of the corpus callosum (Giedd et al., 1999). Local abnormalities of the splenium, as reported for some series of autistic patients, would therefore be suggestive of a process acting during the postnatal period (Egaas et al., 1995).

In this study we examine the outline of the corpus callosum in a series of patients with autism and age- matched comparison subjects. The morphometric method employed in our study provides a point by point descriptor of corpora callosa contours while being invariant to translation, rotation, and scaling. Inverse construction allowed for multidimensional representations of the contours and anatomical depiction of the changes. The basic hypothesis of the study was that individuals with autism would exhibit a generalized reduction in size of the corpus callosum.

Methods

The two groups of participants consisted of 17 high-functioning autistic adolescents and adults (14 males, 3 females) and 17 matched controls (Table 1). Comparison subjects were paired with individuals with autism on the basis of sex, age, ethnicity, handedness, and full scale IQ (Wechsler, 1999). All participants diagnosed with autism and most of the comparison group were recruited from the University of Pittsburgh's Collaborative Program of Excellence in Autism (CPEA). Written informed consent was obtained from all subjects following explanation of the procedures.

Participants diagnosed with autism were given the ADOS (Lord et al., 1989) and a parent/guardian or family member answered the ADI-R (Lord et al., 1994). Cutoff scores for ADOS were Communication: 3, Social: 6, and Social/Communication Total: 10. Standard diagnostic cutoffs were utilized with the ADI-R. Participants diagnosed with autism did not

have comorbid or causative conditions (chromosomal, neurologic, infectious), had no history of seizures, perinatal brain injury, or head trauma, and were in good general medical health. The group of individuals with autism had both verbal and full-scale IQ ≥ 80 to ensure adequate cooperation during procedures and testing, as well as to ensure good match to controls.

Candidates within the comparison group were screened for neurologic, psychiatric, and medical disorders, and their family history was screened for the same. Inclusion criteria for comparison individuals included: good general physical health, no regular use of psychotropic medications, good performance at school or on the job, and good peer relationships based on self-report or staff observations during testing. Exclusion criteria for comparison subjects included: first-, second-, or third-degree relative diagnosed with ASD, personal and/or family history of psychiatric disorders, learning disability, perinatal brain injury, and head trauma. Both groups were screened for metal, claustrophobia, and body mass ≤ 114 kg, any of which would interfere with MRI scanning.

T1-weighted images were acquired with Siemens MAGNETOM Vision 1.5 T scanners using an MPRAGE acquisition sequence. The two devices were located at University of Pittsburgh Medical Center (Shadyside) and Washington University School of Medicine. A single scanner operator employed identical scanning protocols at both locations. Previously reported DTT data from this equipment (Conturo et al., 2008) found that the two scanners produce equivalent results. Each volume included 128 sagittal slices, comprising the entire head with a pixel size 1 mm^2 and slice spacing 1.25 mm.

Corpus callosum segmentation and mapping

Probabilistic model of the corpus callosum's shape—Most of the recent literature on image segmentation employ level set-based representations of shape, in which a region's boundary is the locus of points where some function F takes a constant value $F(x, y, z) = F_0$. The constant can always be taken as zero by using $F' = F - F_0$ in lieu of F , so we can interpret the value of $F(x, y, z)$ as a measure of (signed) distance from the surface to the point (x, y, z) . Then the region's shape is approximated by the closest linear combination of training shapes. The main drawback of this representation is that the space of signed distance functions is not closed with respect to linear operations. Linear combinations of the distance functions may result in level sets with invalid or even physically impossible topology, e.g. the approximation may be self-intersecting.

To circumvent this limitation, we represent the shape of the corpus callosum having been learned from a training set of co-registered MRI with a “soft” template, or probabilistic 3D model, $s: R \rightarrow [0,1]$, where $s(x, y, z)$ is the empirical probability that the voxel (x, y, z) in anatomical space R belongs to the corpus callosum. The soft template is constructed as follows:

1. Co-align the training set of MRI using a rigid 3D registration with mutual information as a similarity measure (Viola & Wells, 1995).
2. Manually segment the corpus callosum from each MRI in the aligned set.
3. Estimate the voxel-wise probabilities $s(x, y, z)$ as the fraction of aligned images where voxel (x, y, z) was labeled as belonging to the corpus callosum.

Once constructed, s is used to facilitate segmentation of the corpus callosum from an MRI. Let $\mathbf{g}$ denote a given grayscale MRI, and let $\mathbf{m}$ denote the desired binary region map (i.e. $\mathbf{m}(x, y, z) = 1$ for (x, y, z) inside the corpus callosum, and $\mathbf{m}(x, y, z) = 0$ otherwise). Proceed as follows:

1. Align $\mathbf{g}$ to a prototype selected from the training set for s , again using mutual information as a similarity measure.
2. Estimate the probability distribution of voxel values within the corpus callosum, $P(\mathbf{g}|\mathbf{m})$, by fitting a bimodal linear combination of discrete Gaussians.
3. From $P(\mathbf{g}|\mathbf{m})$ and the learned probabilistic shape model s , construct an initial region map $\mathbf{m}$.
4. Use the initial region map to update the conditional intensity $P(\mathbf{g}|\mathbf{m})$, and iterate. For details see (El-Baz & Gimel'farb, 2009).

Mapping—Comparison of the corpus callosum between different subjects and groups is facilitated by mapping their respective boundaries into a standardized coordinate system. We employed a pseudocylindrical system (ρ, ϕ, z) based upon the medial axis of the corpus callosum extending from splenium to genu (Figure 1), i.e. the centerline. The mapping is defined as follows (Casanova et al., 2010): A given point on the boundary of the corpus callosum lies in some plane intersecting the centerline at a right angle. The arc length along the centerline from the splenium to the point of intersection becomes the z coordinate. Then ϕ is the polar angle in the orthogonal plane measured clockwise from anatomical right, and ρ is the straight-line (Euclidean) distance from the boundary point to the point of intersection.

The construction is analogous to the cylindrical equal-area projection sometimes used for maps of the Earth or other bodies. Of course the mapping is not equal-area in the case of the corpus callosum, which is far from spherical in shape. It must not be presumed that each pixel in Figure 2 represents a similarly sized patch of the CC boundary.

Statistics

The boundary of each corpus callosum was treated as a two dimensional map $\rho(\phi, z)$ providing the effective radius of the corpus callosum in a given direction from a given point along the centerline. Each matched pair of transformed surfaces was differenced pointwise, $\Delta\rho(\phi, z) = \rho_{\text{autism}}(\phi, z) - \rho_{\text{control}}(\phi, z)$. The pairwise differences were aggregated pointwise to yield a statistical parametric map of t statistics with 16 degrees of freedom. Regions where $\Delta\rho$ was statistically significant—i.e. where we reject the null hypothesis $\Delta\rho(\phi, z) = 0$ —were identified by thresholding the raw two-sided P -values using the method of Benjamini and Hochberg (1995) with a false discovery rate $q^* = 0.05$.

Results

Mean age of the participants with autism was 26.1 years (s.d. 10.8 years) at the time of MRI acquisition, while mean age of the comparison clients was 26.5 years (s.d. 10.9 years). There was no significant difference between groups in age (paired $t = 0.78$; 16 d.f.; $P = 0.45$), and no paired subjects differed in age by more than three years. Mean IQ scores of those with autism were full-scale 105 (s.d. 9.4), verbal 103 (s.d. 10.3), and performance 108 (s.d. 9.2). Among the comparison clients mean IQ scores were full-scale 104 (s.d. 8.3), verbal 101 (s.d. 10.3), and performance 107 (s.d. 12.6). Again there was no significant difference between groups (paired $t = -0.48, -0.97, -0.26$, respectively; 16 d.f.; $P = 0.64, 0.35, 0.80$, respectively). Paired subjects did not differ by more than 14 IQ points (full-scale), or by 15 and 16 points on the verbal and performance scales, respectively.

White matter in autism was reduced bilaterally along the body of the corpus callosum, where $\Delta\rho$ took values as low as -4.3 mm (s.d. 2.3 mm) on the left side and -2.8 mm (s.d. 1.6 mm) on the right. There was apart from this an increase of up to $\Delta\rho = 2.3$ mm (s.d. 2.4 mm) in the region proximate to the right cingulate gyrus. There was also a reduction in the splenium

in autism, of up to $\Delta\rho = -5.1$ mm, although it was not statistically significant. There was otherwise no significant difference around the medial sagittal plane (Figure 2, Figure 3).

Where $\Delta\rho$ was significantly negative along the left side, there was a slight positive trend with increasing z . That is, $\Delta\rho$ was more negative on the left posterior body of the CC than on the left anterior body (Figure 4). There was no significant evidence for a similar trend on the right CC body.

Discussion

The results of our study, in agreement with the previous literature, showed a smaller corpus callosum in autistic individuals when examined against a comparison group (Frazier & Hardan, 2009; Lainhart et al., 2005). The corpus callosum was significantly reduced in size throughout its extent (lengthwise) with a small area of possible increase at the level of the splenium. Although we did not attempt to parcellate the corpus callosum, the findings help explain those structural imaging studies that emphasize changes at the level of the genu and/or a severity of gradation involving the rostro-caudal axis of this structure (Frazier & Hardan, 2009). In effect, a focal overgrowth of fibers at the caudal pole of the corpus callosum may help conceal reductions in other parts of the splenium.

Our shape analysis suggests an overrepresentation of the shorter commissural fibers traversing the corpus callosum, i.e., those belonging to the occipital (visual) fiber bundles at the pole of the splenium (Hofer & Frahm, 2006). The cells of origin for these projections are located predominantly within the striate cortex (Kretz & Rager, 1990). The putative overabundance of fibers from the occipital cortex provides an explanatory mechanism for the superior abilities in visual search tasks exemplified by some autistic individuals (O’Riordan & Plaisted, 2001; O’Riordan et al., 2001) and suggest a model wherein altered processing of sensory input occurs within the cortex (Casanova et al., 2003).

Morphometric abnormalities of the corpus callosum provide an interesting clinicopathological correlate to autism due to this structure’s role in developmental integration and learning processes (Mihirshahi, 2006). The authors speculate that the distributed nature of the corpus callosum abnormality suggests a disturbance of both heterotopic and homotopic callosal connections. This would provide for a global callosal deficit manifested by abnormalities in the ability to establish those temporal relations essential to the integrative representation of sensory features (heterotopic connections), while simultaneously altering the topographical correspondence between right and left maps contributing to the generation of feature-selective receptive fields (Houzel & Milleret, 1999). It is therefore not surprising that patients with agenesis of the corpus callosum exhibit social and behavioral problems associated with autism (Badaruddin et al., 2007).

According to the homotopic callosal inhibitory theory of Cook (1984), the process of activation of cortical columns in the left hemisphere during verbal processing provides for surround inhibition, which in turn prevents activation of neighboring columns with their contiguous cognitive content. The genesis of this surround inhibition rests within the peripheral neuropil space of minicolumns where different anatomical elements provide a shower curtain of inhibition to pyramidal cells within the core of the cell minicolumn. In essence, gamma-aminobutyric acid (GABA) interneurons contribute to a circumferential zone of inhibitory and disinhibitory activity gating communication of the central minicolumnar core with surrounding areas (Casanova et al., 2003). Both anatomical and functional studies suggest abnormalities of surround inhibition in autism (Casanova et al., 2002a; Tommerdahl et al., 2007), which may be due, in turn, to faulty homotopic callosal inhibition (Cook, 1984).

The callosal findings reported in this study appears related to neuropathological findings of a minicolumnopathy in subjects with autism (Casanova et al., 2002b; Casanova et al., 2006). The cerebral cortex is composed of elementary processing units arranged in columnar fashion (Hofman, 1985). Rakic has proposed that the size of the neocortex (i.e., the number of columnar arrangements) is the product of supernumerary mitotic activity within the germinal cells of the periventricular zone and their longevity during individual embryonic development (Rakic & Kornack, 2001). A series of asymmetrical divisions involving these cells provides for clones which migrate to the cortex under the guidance of a glial scaffolding (Casanova et al., 2009). With each generated minicolumn there is an increased need for creating supporting interconnections. It has been calculated that each minicolumn is associated to approximately 10^3 other minicolumns (Casanova, 2004). The overall increase in minicolumns seen during corticalization therefore provides for bigger brains and a biased gray/white matter ratio (Casanova et al., 2002a). In essence, the bigger brains within an encephalization plot have more white matter than expected when considering size alone (Hofman, 2001). This white matter increase is made primarily of short arcuate projections at the expense of longer corticocortical connections including the commissural tracks (Casanova, 2004). Across species, those with bigger brains have smaller corpora callosa (Olivares et al., 2000; Rilling & Insel, 1999). This finding is the putative mechanism underlying cerebral dominance and providing for the emergence of higher cognitive functions such as language (Casanova & Tillquist, 2008). Many of the reported morphometric abnormalities in autism may therefore be interdependent. In essence, abnormalities of both corpus callosum size and cerebral dominance have been implicated in psychiatric conditions, such as autism, that are characterized by increased brain size and the presence of language disorder (Herbert et al., 2005; Johnson & Casanova, 2009; Williams & Casanova, 2009).

Results from our study indicate a generalized reduction of the corpora callosa in autistic individuals. The findings acquire relevance from previous neuroimaging studies that varied among themselves in regards to a preferred anatomical subdivision (e.g., genu, body, splenium). Generalized findings, involving the rostro-caudal extent of the corpus callosum, is expected from a mitotic event affecting periventricular germinal cells and the total number of cortical minicolumns. This suggests a pathocclisis during early development as symmetrical division of periventricular germinal cells in human and non-human primates occurs during the first 40 days of gestation (Rakic & Kornack, 2001). Furthermore, since the commissural fibers that transverse the different anatomical compartments of the corpus callosum originate in disparate brain regions our results suggests the presence of widely distributed cortical abnormalities in autistic individuals.

It is worthwhile noticing that completely opposite morphometric findings have now been reported in developmental dyslexia. Both dyslexia and autism appear to fall at opposite ends of a minicolumnar spectrum which is manifested by divergent findings in regards to measurements for total brain volume, gyral window, white matter parcellation, and size of the corpus callosum (Williams & Casanova, 2009). Although a pervasive disorder may affect, by definition, learning abilities, our findings suggest that the underlying substratum for this deficit is different for both autistic and developmental dyslexic individuals.

Acknowledgments

Funding

Funding for this work was provided by NIH grants R01 NS39538, R01 NS52470, R01 MH86784, and R01 MH88893, by Autism Speaks grant AS03799, and by the Nancy Lurie Marks Family Foundation.

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Figure 1.

Mapping the surface of the corpus callosum. In the pseudocylindrical coordinate system, the z coordinate is the arc length along the centerline from the splenium (left). Radius and polar angle are then measured within the plane orthogonal to the centerline at z .

Figure 2.

The map of $\Delta\rho = \rho_{\text{autism}}(\phi, z) - \rho_{\text{control}}(\phi, z)$, i.e. the mean deficit or excess in $\rho(\phi, z)$ in the autistic cases compared with controls. Differences are statistically significant (for $q^* = 0.05$) in the outlined areas.

Figure 3.

Regions where autistic and control CC appear to differ, as in Figure 2, projected back into anatomical space and viewed from above and from below. The CC in those with autism is significantly larger (resp. smaller, insignificantly different) than the CC in comparison clients where $\Delta\rho > 0$ (resp. $\Delta\rho < 0$, $\Delta\rho \approx 0$).

Figure 4.

Mean $\Delta\rho$ as a function of z , averaging over ϕ , within sections of the CC body encompassing those regions where $\Delta\rho$ was significantly less than 0. These sections are outlined in the inset, upper left (compare Figure 2). On the left body (L), as z increases toward the genu, so does mean $\Delta\rho$ (95 % confidence interval on the slope of the line: $[-0.004, 0.045]$). There is no evidence of such a trend on the right (R), where the slope is consistent with zero (95 % confidence interval $[-0.017, 0.025]$). Confidence intervals were estimated via bootstrap resampling of autism/comparison client case pairs.

Table 1

Demographics of study participants. See also Conturo et al. (2008).

Case	Age	Sex	Ethnicity	Hand.	IQ	VIQ	PIQ	Medications
A1	22.2	M	Caucasian	R	108	107	108	<i>atomoxetine</i> (Strattera) none
C1	24.1	M	Caucasian	R	115	111	116	
A2	22.1	M	Caucasian	R	100	97	102	<i>paroxetine</i>
C2	24.8	M	Caucasian	R	109	105	112	none
A3	25.7	M	Caucasian	R	118	116	116	none <i>methotrexate^d, chloroquine^d, ranitidine</i>
C3	23.1	M	Caucasian	R	111	107	114	
A4	20.0	M	Caucasian	R	95	95	95	<i>quetiapine</i> (Seroquel)
C4	20.6	M	Caucasian	R	103	102	103	none
A5	22.3	M	Caucasian	R	105	83	132	<i>carbamazepine; duloxetine</i> (Cymbalta) none
C5	19.8	M	Caucasian	R	105	93	117	
A6	21.9	F	Caucasian	R	101	96	106	<i>fexofenadine</i> (Allegra); <i>cetirizine</i> (Zyrtec); <i>loratadine</i> (Claritin); <i>naproxen</i>
C6	19.4	F	Caucasian	R	92	95	109	none
A7	23.8	M	Caucasian	R	99	93	105	none
C7	23.7	M	Caucasian	R	99	89	109	none
A8	32.9	M	Caucasian	L	110	104	116	none
C8	32.4	M	Caucasian	L	105	94	116	none
A9	39.6	F	Caucasian	R	94	109	80	none
C9	36.6	F	Caucasian	R	108	119	96	none
A10	53.4	F	Caucasian	R	110	110	107	unspecified thyroid medication none
C10	50.9	F	Caucasian	R	116	115	112	
A11	22.5	M	Caucasian	R	116	112	117	<i>methylphenidate; mirtazapine</i> none
C11	22.6	M	Caucasian	R	117	116	114	
A12	18.2	M	Caucasian	R	118	111	121	none

Case	Age	Sex	Ethnicity	Hand.	IQ	VIQ	PIQ	Medications
C12	19.8	M	Caucasian	R	113	105	120	none
A13	17.7	M	Caucasian	R	98	95	101	none <i>sulfacetamide; clindamycin; tazarotene; azeleic acid</i>
C13	16.5	M	Caucasian	R	86	88	88	
A14	49.2	M	Caucasian	R	96	88	103	none
C14	51.8	M	Caucasian	R	93	97	91	none
A15	22.7	M	Caucasian	R	96	83	110	<i>citalopram; multivitamin; vitamin E</i> <i>minocycline</i>
C15	21.7	M	Caucasian	R	101	96	106	
A16	19.2	M	Caucasian	R	99	109	88	none
C16	17.2	M	Caucasian	R	99	96	102	none
A17	16.5	M	Asian	R	112	104	119	<i>fluoxetine</i>
C17	18.5	M	Asian	R	117	119	111	none

Notes:

^aTaken for arthritis

A_n/C_n: matched autistic/control pair *n*; Age: years of age at time of scan; Hand.: handedness; IQ: full-scale IQ; VIQ: verbal IQ; PIQ: performance IQ; Medications: taken within three years prior to MRI scan.