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Original Article

Macrocephaly, Corpus Callosum Morphology, and Autism

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ABSTRACT

Although the cause of autism is undetermined, a general consensus has been that some type of early aberrant neural development underlies the disorder. Given the increased prevalence of macrocephaly in autism, one theory of abnormal neural development implicates early brain growth resulting in larger brain and head size in autism. Surface area measurements of the midsagittal section of the corpus callosum can be used as an index of neural development and white-matter integrity because the corpus callosum is the major white-matter structure that interconnects the two cerebral hemispheres. The purpose of this study was to obtain corpus callosum surface area, shape, and contour in a sample of non–mentally retarded autistic subjects with macrocephaly (n = 12) and compare them with those of matched (n = 8), typically developing control subjects with benign macrocephaly. No significant differences were found in surface area, shape, or contour between groups, nor did corpus callosum surface area relate to measures of IQ or picture vocabulary. These findings suggest no unique difference in overall regional corpus callosum surface area in autism with macrocephaly. (*J Child Neurol* 2005;20:34–41).

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Autism, with a prevalence rate of about 1.6 per 1000,[1] is a pervasive developmental disorder with qualitative impairments in social interaction and communication, along with restricted, repetitive, and stereotyped patterns of behavior.[2] These core features of autism are expressed early in the child's development, and autism is typically diagnosed before the age of 5 years, often by 2 or 3 years of age. Autism is viewed as a spectrum disorder in which symptoms can manifest on a continuum from mild to profound. Despite its well-documented symptomatology,[2–5] the cause of autism is undetermined.

Although the etiology remains undetermined, a general consensus has been that some type of aberrant neural development underlies the disorder of autism.[5,6] For example, one theory of abnormal neural development implicates early brain growth that results in larger brain and hence head size in autism.[7–14] Indeed, one of the most replicated findings in autism is the increased prevalence of macrocephaly, defined as head circumference greater than the 97th percentile for age and sex. By definition, using standardized head circumference norms,[15] less than 3% of the normal population would have macrocephaly, but about 20% of individuals diagnosed with autism meet the criteria for macrocephaly.[7,16] Even Kanner, in his original description of the disorder, noted the preponderance of "large heads" in the group of patients he described.[17]

One index of normal brain growth and morphology is the size of the corpus callosum, the white-matter structure formed by axons projecting between the two hemispheres.[18–21] Abnormalities in the size, shape, and regional development of the corpus callosum have characteristic associations with a variety of errors in neural development.[22–24]

The corpus callosum has been the focus of a number of studies in autism in an attempt to demonstrate aberrant neural development.[25–29] The results from these studies have often found differences with subjects with autism possessing a smaller corpus callosum surface area, but no consistent pattern across all studies has been found. For example, in a sample of 35 autistic and 36 control subjects, Piven et al examined regional and total corpus callosum surface area.[28] They found a significantly smaller size of the body and posterior subregions in autistic subjects. Egaas et al examined the corpus callosum surface area in a sample of 51 autistic subjects, including both those with IQ scores greater than 70, mentally retarded subjects, and 51 age- and sex-matched controls.[26] They found decreased size of the corpus callosum, concentrated in posterior subregions, in subjects with autism. Hardan et al, in a sample of 22 non–mentally retarded autistic and 22 age- and intelligence-matched controls, found decreased anterior surface area of the corpus callosum in subjects with autism.[27] Saitoh et al found reduced size of the posterior corpus callosum in 33 subjects with autism and 23 normal controls,[30] whereas Elia et al found no difference in the corpus callosum surface area between 22 subjects with autism with mental retardation and 11 control subjects.[31] Courchesne et al analyzed the corpus callosum and observed smaller anterior surface area in 43% of their sample.[32] However, none of these studies specifically examined subjects with autism with macrocephaly, and significant differences in IQ between the subjects with autism and control subjects were often present.

Postmortem studies in autism have also found abnormal corpus callosum development. Bailey et al found a thinning in corpus callosum width just posterior to the genu in one of six subjects with autism with mental retardation.[33]

There are at least two confounding factors in past studies examining corpus callosum morphology and morphometrics in autism that limit the interpretation of past research: (1) lack of control for increased prevalence of macrocephaly in autism and/or (2) lack of control over the level of intellectual functioning in the autism or comparison sample. The issue with regard to intellectual function is that autism has a markedly different prevalence rate for mental retardation, up to 70% compared with that for the normal population.[1] The presence of mental retardation increases the likelihood of neuroimaging abnormalities, and corpus callosum size has a modest but positive relationship with IQ.[14,34,35] Thus, any inclusion of cases with mental retardation would more likely be associated with smaller corpus callosum values.

Taking these issues into consideration, detailed corpus callosum morphometrics were undertaken on non–mentally retarded subjects with autism with macrocephaly compared with age- and sex-matched control subjects with benign macrocephaly. We concentrated exclusively on those subjects with autism with macrocephaly and normal intelligence because they might be the subjects with autism with the greatest likelihood of detectable signs of early aberrant neural development, and corpus callosum surface area has not been specifically analyzed in this subset of subjects with autism.

One of the most widely accepted measurements of the corpus callosum was developed by Witelson, in which the corpus callosum can be divided into seven arbitrary surface areas.[36,37] As shown in Figure 1, this protocol allows regional surface area investigation of the corpus callosum, including rostrum (1), genu (2), anterior midbody (3), posterior midbody (4), isthmus (5 and 6), and splenium (7) measurements.

As mentioned above, corpus callosum surface area is influenced by total head and brain size.[35] In addition to statistical control of head size, the brain and regions of interest such as the corpus callosum can be placed in standardized space using the Talairach and Tournoux method,[38] commonly referred to as the Talairach space. Accordingly, using such methods, a composite single corpus callosum measure of subjects with autism can be compared with that of controls and the Witelson protocol.[36,37] Standardizing each corpus callosum in the Talairach space also provides another method to control for potential head size differences between typically developing individuals and those with autism.

In addition, the shape and contour of the corpus callosum are important in functionality, which the Witelson method[36,37] does not address. Gabrielli et al developed a series of midsagittal angle measurements that isolate the specific contours of the corpus callosum.[23] This angle-based protocol allows the examination of potential contour and shape differences in the corpus callosum that can be evident between autism and benign macrocephaly. The composite single corpus callosum measure mentioned above is invaluable in subjectively comparing overall shape and contour differences between groups.

The corpus callosum is regionally organized (ie, pathways in the genu represent predominantly frontal lobe interhemispheric fibers),[36,39] and by performing regional analyses in addition to whole corpus callosum surface area, it is possible to test regional versus whole corpus callosum surface area differences and their relationship, if any, with neuropsychologic performance. Accordingly, given the increased possibility of neuroimaging abnormalities in mentally retarded subjects, we excluded subjects with a Wechsler Performance IQ < 69. Therefore, all subjects were administered either the Wechsler Adult Intelligence Scale-III[40] or the Wechsler Intelligence Scale for Children-III[41] and the Peabody Picture Vocabulary Test, III,[42] a measure of verbal abilities.

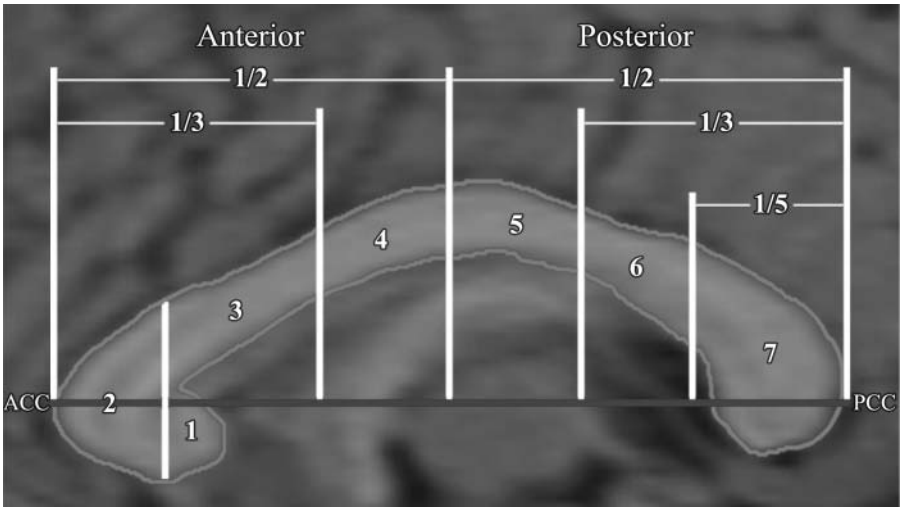

Figure 1. AT_1-weighted, midsagittal view of the human corpus callosum (left to right, anterior [ACC] to posterior [PCC]) using regional divisions based on the Witelson protocol.[36] To obtain these areas, the anterior posterior maximum distance is manually determined using the National Institutes of Health IMAGE program and a computer macro is used to insert perpendiculars to this axis.[53] These perpendiculars divide the corpus callosum into halves, or the anterior and posterior portions, and then into thirds to create anterior, middle, and posterior portion.[53] Finally, the corpus callosum is divided into fifths to create the anteriormost portion of the corpus callosum, or genu, and the posteriormost portion of the corpus callosum, or splenium. Seven corpus callosum areas were created delineating the rostrum (1), genu (2), anterior midbody (3), posterior midbody (4), isthmus (5 and 6), and splenium (7).

In the current study, 12 subjects with autism with macrocephaly were compared with eight head circumference–matched controls with benign macrocephaly. We examined whole midsagittal surface area and shape, the standard seven surface areas from the Witelson method,[36,37] and then examined contour and shape differences between subjects with autism and control subjects using the method outlined by Gabrielli et al.[23] Lastly, through morphing techniques,[43] a composite corpus callosum from all subjects with autism was compared with that of controls.[38]

METHODS

Subjects

Subjects were recruited from community sources, particularly parent support groups, social skills groups, and schools as part of an institutional review board–approved prospective, cross-sectional study. Two subject groups were studied: subjects with autism selected for macrocephaly (head circumference > 97th percentile for age and sex) and typically developing subjects with benign macrocephaly (head circumference > 97th percentile for age and sex) ranging from 7 through 19 years of age.

Autism associated with high versus low IQ can differ in etiology and neuroanatomy.[6,12,14,44–47] The same is true for autism in male versus female individuals. Because the autism and comparison samples should be as homogeneous as possible in regard to IQ and gender, all subjects in this study were boys with Wechsler Performance IQs of 69 or higher based on either the Wechsler Intelligence Scale for Children-III[41] or the Wechsler Adult Intelligence Scale-III.[40] The comparison group consisted of normal (typically developing) subjects with head circumference–defined macrocephaly, group-matched by age to the autism subjects. Subjects from the autism and benign macrocephaly groups were part of a large cohort of approximately 100 children and adults participating in an ongoing study of autism.[48] Demographic variables are summarized in Table 1.

Subjects with Autism

Autism was diagnosed by interviewing the subject's mother with the Autism Diagnostic Interview-Revised.[49] In addition, autistic subjects were directly assessed using the Autism Diagnostic Observation Schedule-Generic,[50] a semistructured play and interview session designed to elicit social, communication, and stereotyped repetitive behaviors characteristic of autism. All autistic subjects met Autism Diagnostic Interview-Revised,[49] Autism Diagnostic Observation Schedule-Generic,[50] and *Diagnostic and Statistical Manual of Mental Disorders-IV*[51] criteria for autism. History, physical examination, fragile X gene testing, and karyotype excluded medical causes of autism.

Comparison Subjects

The typically developing subjects, normal controls with benign macrocephaly, were selected with no developmental, neurologic, or clinically significant psychiatric disorders based on history, IQ and reading and language tests, physical examination, and structured psychiatric assessment. Pervasive developmental disorders were excluded in all comparison subjects by history, direct observation, and interview of the mother using the Family History Interview for Disorders of Social Development and Cognition.[52] The Family History Interview is a measure specifically designed to detect signs of autism spectrum disorders and milder, isolated autism-like features using the family history method.[52]

Neuropsychologic Testing

All subjects were administered the Wechsler Intelligence Scale for Children-III[41] or Wechsler Adult Intelligence Scale-III[40] depending on age at testing.

Table 1. Demographic Variables and Group Comparisons

	Autism Macrocephaly (n = 12)			*Benign Macrocephaly (n = 8)*			*Group Comparisons*	
Assessments Used	*Mean*	*SD*	*Range*	*Mean*	*SD*	*Range*	*F*	*Significance*
Wechsler Verbal IQ	106.00	33.01	46–142	123.25	10.90	111–138	2.01	.17
Wechsler Performance IQ	107.83	17.66	69–125	120.38	10.08	106–136	3.28	.09
Wechsler Full-Scale IQ	107.33	26.06	55–135	124.00	11.28	109–139	2.87	.11
Peabody Picture Vocabulary Test	108.00	29.61	53–136	122.13	7.97	111–132	1.71	.21
Age at time of scan (years)	12.42	4.32	7–19	12.50	3.46	8–16	0.00	.96
Total intracranial volume (cm^3)	1656.15	129.45	1451.66–1874.98	1720.90	97.23	1608.52–1926.77	0.20	.66
Total brain volume (cm^3)	1533.42	124.63	1348.01–1713.69	1567.95	93.41	1452.43–1762.20	0.01	.92
Head circumference (cm^3)	58.49	2.10	55.40–61.00	58.69	1.96	56.45–62.30	0.40	.54

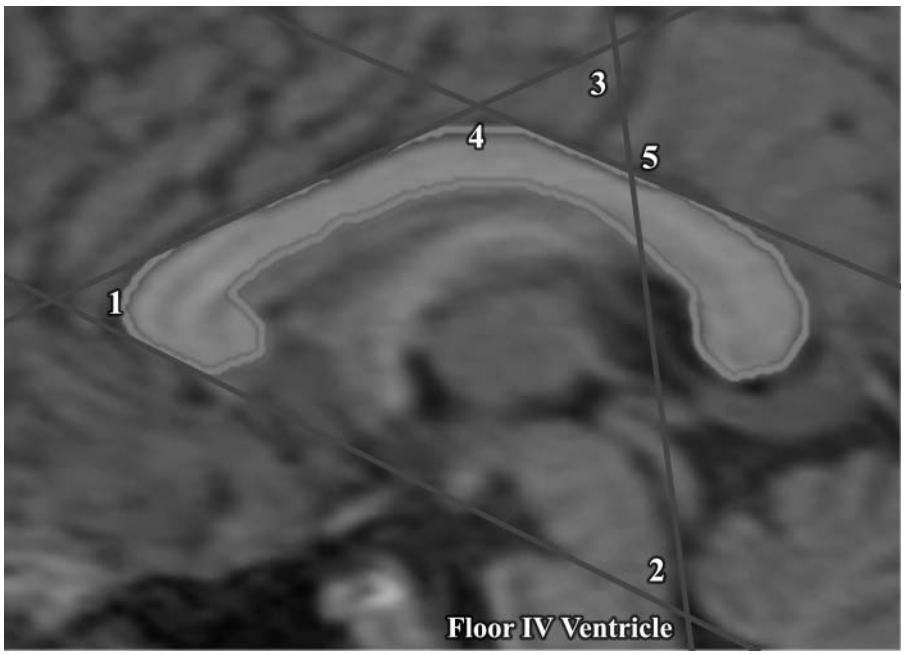

Figure 2. Shape and contour angle measurements of the corpus callosum based on those developed by Gabrielli et al.[24] These measurements were made using the National Institutes of Health IMAGE program[53] after correction for variation in head placement in the scanner was made in MEDx.[54] Each angle was manually determined in the sagittal plane using the angle tool in the IMAGE program.[53] The midsagittal slice of each scan was selected based on the clearest view of the corpus callosum, aqueduct, tectum, septum pellucidum, and falx along the midline of the brain. Angle 1 is between a line crossing the anterior commissure and touching the inferior margin of the genu of the corpus callosum and a second one tangential to the upper surface of the anterior portion of its body. Angle 2 is between a line crossing the anterior commissure and touching the inferior margin of the genu of the corpus callosum and one tangential to the floor of the fourth ventricle. Angle 3 is between a line tangential to the floor of the fourth ventricle and one tangential to the convexity of the anterior portion of the body of the corpus callosum. Angle 4 is between the lines tangential to the convexity of the anterior and posterior portions of the body of the corpus callosum. Angle 5 is between the lines tangential to the floor of the fourth ventricle and the convexity of the posterior portion of the body of the corpus callosum.

In addition, the Peabody Picture Vocabulary Test-III,[42] a measure of object identification and verbal abilities, was administered.

Head Circumference and Height

Head circumference and height were measured in all subjects using the standardized methods and reference data described by Farkas et al.[15]

Neuroimaging

Magnetic resonance images were acquired on a Marconi 1.5 Tesla Scanner. Multiple protocols were run (ie, T_1, T_2, proton density, and fluid-attenuated inversion recovery) and were used for the clinical review. For quantitative analysis of this investigation, the three-dimensional T_1 (TE = 4.47 milliseconds, TR = 13 milliseconds, flip angle = 20 degrees, slice thickness = 1.2 mm, field of view = 25.6 cm) sequence was used for identification of the midsagittal slice. In some cases, sedation was necessary and followed a strict clinical protocol approved by the institutional review board of the University of Utah and performed by an on-site anesthesiologist in conjunction with the radiologist. The procedure was clearly explained, as best as possible, to the subject and parent or guardian. In several situations, rehearsal was used to "practice" lying in the scanner. In all cases written, informed consent was obtained prior to any imaging. No complications or untoward effects were encountered. All scans were reviewed by a clinical radiologist with special competence in neuroradiology, but no significant clinical abnormalities were found (see Bigler et al[48]).

Image Analyses

Quantitative analyses followed the corpus callosum measurement protocol developed by Witelson[36,37] (see Figure 1), and shape and contour analyses followed the protocol developed by Gabrielli et al[23,24] (Figure 2). Using the National Institutes of Health IMAGE program,[53] the seven area measurements of the midsagittal area of the corpus callosum defined by Witelson[36,37] were obtained. As demonstrated in Figure 1, one genu, one rostrum, one splenium, and two isthmus measurements were investigated with the remaining two measurements making up the anterior and posterior midbody of the corpus callosum. To obtain these areas, the anterior-posterior maximum distance was manually determined and a computer macro was used to insert perpendiculars to this axis. These perpendiculars divide the corpus callosum into halves and the anterior and posterior portions and then into thirds to create an anterior, middle, and posterior portion.[53] Finally, the corpus callosum is divided into fifths to create the anteriormost portion of the corpus callosum, or genu, and the posterior-

Table 2. Summary of the Anatomic Description* of Midsagittal Surface Area in Standard Scans of the Autism Macrocephalic and Benign Macrocephalic Groups in cm² and Multivariate Analysis Findings

	Autism Macrocephaly (n = 12)			*Benign Macrocephaly (n = 8)*			*Group Comparisons*	
Anatomic Classification	*Mean*	*SD*	*Range*	*Mean*	*SD*	*Range*	*F*	*Significance*
Rostrum	0.35	0.10	0.18–0.54	0.36	0.10	0.25–0.57	0.01	.92
Genu	1.60	0.35	1.06–2.44	1.82	0.47	1.37–2.60	1.02	.33
Anterior midbody	1.05	0.21	0.67–1.38	1.09	0.24	0.86–1.47	0.23	.64
Posterior midbody	0.87	0.17	0.59–1.12	0.91	0.17	0.66–1.15	0.00	.98
Isthmus	2.00	0.31	1.47–2.53	2.08	0.19	1.84–2.33	0.20	.67
Splenium	1.47	0.26	1.09–1.82	1.49	0.26	1.15–1.85	0.01	.91
Total corpus callosum	7.34	0.91	6.08–8.89	7.75	0.99	6.36–9.43	0.20	.66

*Anatomic description based on classification schemata of Witelson[36] and Carpenter and Sutin.[39]

Table 3. Summary of the Anatomic Description* of Midsagittal Surface Area Talairach-Adjusted Scans of the Autism Macrocephalic and Benign Macrocephalic Groups in cm² and One-Way ANOVA Findings

Talairach Adjusted Anatomic Classification	*Autism Macrocephaly (n = 12)*			*Benign Macrocephaly (n = 8)*			*Group Comparisons*	
	Mean	*SD*	*Range*	*Mean*	*SD*	*Range*	*F*	*Significance*
Rostrum	0.32	0.09	0.19–0.51	0.29	0.09	0.15–0.46	0.76	.39
Genu	1.20	0.33	0.81–1.83	1.22	0.29	0.85–1.83	0.02	.88
Anterior midbody	1.02	0.14	0.80–1.34	0.94	0.14	0.73–1.15	1.72	.21
Posterior midbody	0.82	0.19	0.55–1.20	0.76	0.13	0.56–0.94	0.69	.42
Isthmus	1.65	0.30	1.16–2.14	1.62	0.15	1.42–1.90	0.07	.80
Splenium	1.26	0.27	0.81–1.63	1.18	0.16	0.91–1.37	0.60	.45
Total corpus callosum	6.28	0.98	4.85–8.01	6.01	0.48	5.41–7.00	0.52	.48

ANOVA = analysis of variance.
*Anatomic description based on classification schemata of Witelson[36] and Carpenter and Sutin.[39]

most portion of the corpus callosum, or splenium. The midsagittal slice of each scan was selected based on the clearest view of the corpus callosum, aqueduct, tectum, septum pellucidum, and falx along the midline of the brain.

Scans were interactively conformed to Talairach dimensions in MEDx[54] using an affine 12-parameter transformation within the automated image registration module embedded in MEDx.[54,55] This embedded module allows for the rotation of scans to develop a composite corpus callosum image to compare subjects with autism with macrocephaly and subjects with benign macrocephaly. This procedure ensured that the corpus callosum was level and area division was consistent across scans.

In addition, five angle measurements using the procedure established by Gabrielli et al[23,24] were made using the National Institutes of Health IMAGE program[53] after correction for variation in head placement in the scanner had been made in MEDx,[54] as mentioned above (see Figure 2). Each angle was manually determined in the sagittal plane using the angle tool in the National Institutes of Health IMAGE program.[53] An initial line crossing the anterior commissure and touching the inferior margin of the genu of the corpus callosum and a second one tangential to the upper surface of the anterior portion of the body completed the first angle. The second angle was between the first line described above and one tangential to the floor of the fourth ventricle. The third was between the line tangential to the floor of the fourth ventricle and tangential to the convexity of the anterior portion of the body of the corpus callosum. Angle 4 was between the lines tangential to the convexity of the anterior and posterior parts of the corpus callosum. Angle 5 was between the lines tangential to the floor of the fourth ventricle and the convexity of the posterior portion of the body of the corpus callosum.

Quantitative analysis of total brain volume and total intracranial volume had already been calculated as part of an early study.[48] These values were used as part of the statistical analysis to control for volume of differences for some of the comparisons.

All analyses were based on the average of two measures done separately and at different times. Inter- and intrarater reliability of the seven corpus callosum divisions[36,37] and angle measurements[23,24] exceeded $r = .95$ for all cases. Raters were blind to diagnosis.

Statistical Analyses

Between-group differences in intelligence and picture vocabulary were analyzed with one-way analysis of variance (ANOVA) with intelligence and vocabulary measures as dependent variables and diagnosis (autism macrocephaly vs benign macrocephaly) as the independent variable. Analyses were performed with and without controlling for age, IQ, total brain volume, and total intracranial volume. Between-group differences in total brain volume, total intracranial volume, and head circumference were analyzed with multivariate analysis with total brain volume, total intracranial volume, and head circumference as independent variables; diagnosis as the fixed factor; and age and Wechsler Performance IQ as covariates. Group differences in surface area, contour, and shape in Talairach-converted scans were analyzed with one-way ANOVA with each angle and surface area measurement as dependent variables and diagnosis as the independent variable. In standard scans, regional surface area and shape and contour differences were analyzed with a multivariate analysis of variance with angle measurements and corpus callosum surface area measurements as dependent variables; total intracranial volume, Wechsler Performance IQ, and age as controls; and diagnosis as the fixed factor. IQ, picture vocabulary, and regional surface area relationships were examined with partial correlations in standard scans, with total intracranial volume and age as controls. The relationship between neuropsychologic function, shape and contour, and regional surface area was examined with bivariate correlations in Talairach-adjusted scans. Bonferroni corrections were applied to bivariate and partial correlations to account for familywise statistical error owing to multiple comparisons.

Table 4. Summary of the Angulation of Non–Talairach-Adjusted Scans and Multivariate Findings and Summary of the Angulation of Talairach-Adjusted Scans and One-Way ANOVA Findings

Corpus Callosum Measurement	*Autism Macrocephaly (n = 12)*			*Benign Macrocephaly (n = 8)*			*Group Comparisons*	
	Mean	*SD*	*Range*	*Mean*	*SD*	*Range*	*F*	*Significance*
Angle 1	48.40	8.49	40.83–68.77	48.99	7.55	43.98–65.92	0.01	.93
Angle 2	73.65	3.93	65.59–78.95	72.63	4.50	65.23–78.60	0.72	.41
Angle 3	63.39	4.76	56.07–70.51	61.58	7.16	48.45–70.89	0.05	.83
Angle 4	126.51	4.48	116.16–132.42	123.92	11.46	98.72–133.53	0.01	.92
Angle 5	110.77	6.47	99.29–120.87	114.02	7.54	102.18–127.70	1.06	.32
Talairach angle 1	54.08	7.12	41.31–67.31	53.91	12.08	34.30–67.54	0.00	.97
Talairach angle 2	78.71	3.98	71.81–82.84	79.56	4.46	73.01–85.70	0.20	.66
Talairach angle 3	54.53	7.72	42.30–69.22	56.32	7.88	43.39–63.92	0.26	.62
Talairach angle 4	116.89	7.27	106.19–130.44	119.67	12.37	95.70–130.65	0.41	.53
Talairach angle 5	112.53	7.58	99.78–122.16	119.14	6.66	109.01–128.00	3.99	.06

ANOVA = analysis of variance.

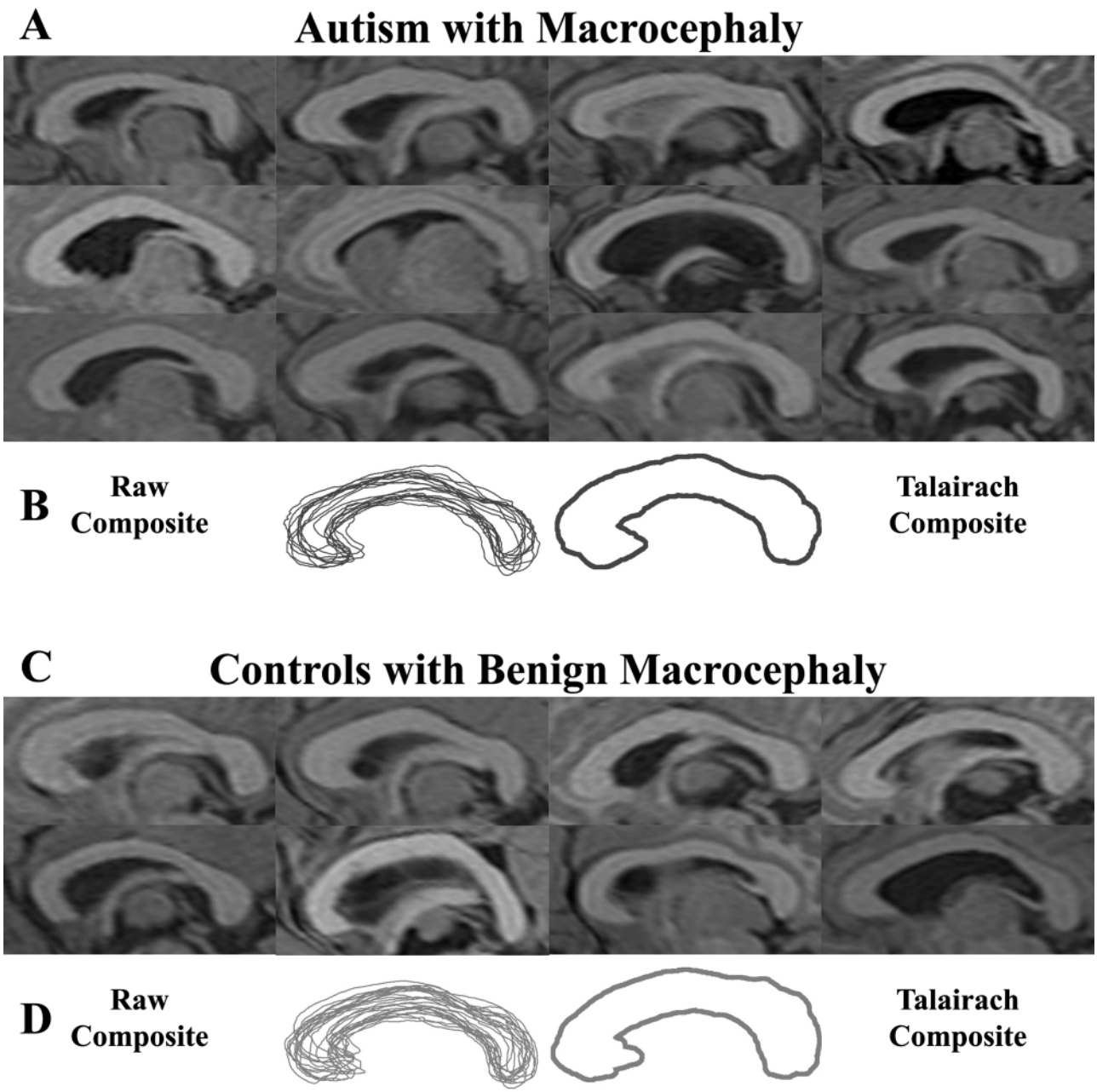

Figure 3. Subjects with autism with macrocephaly (*A*) are compared with the control subjects with macrocephaly (*C*) using non–Talairach-converted, T_1-weighted midsagittal views of the corpus callosum (anterior to posterior, left to right). The midsagittal slice of each scan was selected based on the clearest view of the corpus callosum, aqueduct, tectum, septum pellucidum, and falx along the midline of the brain. All images had been rotated into the same anterior-posterior plane. Corpus callosum images (*B*) are midsagittal composites of the autism group with macrocephaly. On the left are raw, non–Talairach-converted, corpora callosa and on the right are Talairach-converted corpora callosa. Talairach scans were interactively conformed to Talairach dimensions in MEDx[54] using an affine 12-parameter transformation within the automated image registration module embedded in MEDx.[54,55] Corpus callosum images (*D*) are midsagittal composites of controls with benign macrocephaly. On the left are raw, non–Talairach-converted corpora callosa and on the right are Talairach-converted corpora callosa.

RESULTS

Table 1 presents the demographic data comparing the autism macrocephaly group with the benign macrocephaly controls. Although the subjects with autism and the control subjects had almost identical head circumference (see Table 1), the control subjects with benign macrocephaly were somewhat older, had larger total intracranial volume and total brain volume, and also exhibited better performance on measures of intelligence and picture vocabulary. None of the differences were significant, although the Wechsler Performance IQ difference approached significance. Accordingly, in all analyses, statistical comparisons were per-

formed controlling for age, Wechsler Performance IQ, and total intracranial and/or total brain volume.

Absolute corpus callosum surface area and Talairach-adjusted values are shown in Tables 2 and 3. Table 4 summarizes the analyses involving angulation of the corpus callosum. Figure 3 provides the midsagittal view of the corpus callosum for all subjects, a tracing overlay of each corpus callosum outline, and a composite, "morphed" view of all corpus callosum outlines between the autism macrocephaly and benign macrocephaly groups, creating a single image for each group.

When total intracranial volume, Wechsler Performance IQ, and age were controlled, no significant regional or total surface area differences were found between subjects with autism macrocephaly and subjects with benign macrocephaly in standard or Talairach-converted comparisons. Likewise, no significant shape and contour differences were found in standard or Talairach-converted images between groups.

No significant relationship between regional surface area, shape, or contour and IQ or picture vocabulary performance was found in either group.

DISCUSSION

Several studies examining corpus callosum surface area, both quantitatively and qualitatively, have found smaller area in subjects with autism.[26–28,56] However, none of these studies specifically examined subjects with autism with macrocephaly compared with a control group that did not differ in head circumference. Additionally, we examined so-called high-functioning[57] subjects with autism for whom the lowest Wechsler Performance IQ was 69. The current findings demonstrate no significant differences in overall corpus callosum surface area, shape, or contour between subjects with benign macrocephaly and control subjects with benign macrocephaly after controlling for age, head size, and Wechsler Performance IQ. These findings suggest no unique relationship of the overall surface area and shape of the corpus callosum in autism associated with macrocephaly in individuals 7 years and older.

Because a number of studies suggest some type of white-matter pathology and impaired interhemispheric transfer of information in autism,[4–6,58,59] these current findings suggest that the overall size or shape might not be the key factor in defining corpus callosum abnormalities after controlling for head size and IQ. A number of studies have hypothesized abnormal white-matter connectivity rather than specific neuroanatomic dysmorphology in subjects with autism .[3,6] For example, some studies have found that subjects with autism have significantly larger occipital, parietal, and temporal lobes (without controlling for macrocephaly) and significantly larger brain size and have hypothesized that increased brain size might be the result of decreased neuronal death, increased development of neurons, or increased genesis of non-neuronal cells, directly related to the issue of white-matter connectivity.[9,11,58,59] The current study indicates that if these anomalies are part of the disorder of autism, they are not reflected in the gross morphology of the corpus callosum.

Although the small sample size of this study results in insufficient statistical power to be fully confident that no unique overall corpus callosum surface area differences accompany corpus callosum area and general morphology in autism with macrocephaly, inspection of Figure 3, in which the actual midsagittal views can be seen, shows no major differences. Accordingly, no specific gross morphology characteristics of the corpus callosum in subjects with autism are present in this sample with macrocephaly when compared with controls with macrocephaly.

These findings suggest no unique role of an overall size difference in the corpus callosum associated with macrocephaly in autism. The lack of gross morphology differences suggests that this approach to morphometric analysis of the corpus callosum might lack specificity in autism. Newer methods to assess white-matter integrity, such as spectroscopy,[60] diffusion tensor imaging,[61] and magnetization transfer,[62] might be helpful to further elucidate the role of corpus callosum abnormalities in autism.

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