An MRI Study of the Corpus Callosum in Autism

Joseph Piven, M.D., James Bailey, B.S., Bonnie J. Ranson, B.A., and Stephan Arndt, Ph.D.

Objective: The purpose of this study was to examine the size of subregions of the corpus callosum in autistic individuals. Method: The areas of three subregions (anterior, body, and posterior) of the corpus callosum were examined on midsagittal magnetic resonance images of 35 autistic subjects whose mean age was 18 years and 36 healthy comparison subjects matched on age and IQ. Results: After controlling for total brain volume, gender, and performance IQ, the authors detected a significantly smaller size of the body and posterior subregions of the corpus callosum in the autistic individuals. Conclusions: In the context of recent reports of increased brain size in autism, several possible mechanisms are considered in exploring the significance of a smaller relative size of the corpus callosum in autism.
(Am J Psychiatry 1997; 154:1051–1056)

Although a number of studies have now documented that autism is a neurobiological disorder (1), the underlying brain mechanisms involved remain largely unknown. Structural imaging studies in autism have focused predominantly on assessing cerebral asymmetry (2–4) and on measuring the size of the ventricles (3, 5–7), posterior fossa (8–11), and brain stem (9, 10, 12, 13) structures. One recent report (14) suggested that the size of the posterior subregions of the corpus callosum may be reduced in autistic individuals, as seen on midsagittal magnetic resonance imaging (MRI).

For several reasons, further study of the corpus callosum in autism is warranted. First, the corpus callosum is the largest and most prominent axonal pathway in the mammalian brain. Involved in the interhemispheric transfer of information (15), it has become a paradigm for the study of cortical connectivity in the brain (16). Abnormal connectivity of the brain in autism has been hypothesized on the basis of data from several functional imaging (17, 18) and neuropsychological (19) studies. Further study of the size of the corpus callosum in autism may provide indirect insight into this hypothesized mechanism.

Second, examination of the size of subregions of the corpus callosum may contribute to our understanding of regional differences in cerebral cortical volume that have been suggested in autism. Using a semiautomated method of quantitative measurement, we recently reported increased volume of the parietal, temporal, and occipital (i.e., posterior) but not frontal lobes in 36 autistic subjects compared with 35 healthy volunteers (20). Viewed in comparison with the data from the healthy volunteers, these results could be interpreted to suggest that posterior brain enlargement in autistic individuals is abnormal. However, the fact that the frontal lobes were the only lobes where enlargement was not detected in the autistic subjects suggests an alternative interpretation: relative to the size of the rest of the autistic brain, it is the frontal lobes that should be viewed as most abnormal. This latter view is consistent with a number of reports suggesting the importance of the frontal lobe in understanding the deficits in autism (18, 21, 22).

The pattern of fibers traversing the corpus callosum has been shown to reflect the anterior-posterior topographical patterns of the cortical regions (23). Laboratory studies using a variety of staining techniques have demonstrated that cortical regions can be mapped to specific subregions of the corpus callosum (24, 25) and that in general, axons from anterior cortical regions project to the anterior corpus callosum and those from the posterior cortical regions project to the more posterior aspects of the corpus callosum. Further study of the size of the corpus callosum in autism may therefore provide insight into the nature of the anterior-posterior pattern of cortical enlargement in autistic individuals that has been suggested (20, 26).

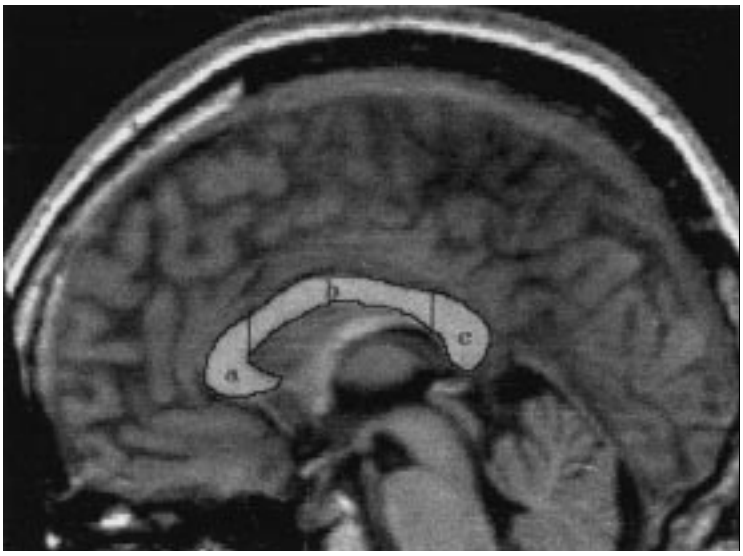
In this study we used detailed MRI to examine the size of the anterior, body, and posterior subregions of the corpus callosum in autistic individuals and comparison subjects. Reliable measurement of the corpus

Received April 12, 1996; revision received Dec. 27, 1996; accepted Jan. 30, 1997. From the Department of Psychiatry, University of Iowa. Address reprint requests to Dr. Piven, Child and Adolescent Psychiatry Clinic, University of Iowa Hospitals and Clinics, 1875 John Pappajohn Pavilion, Iowa City, IA 52242-1057.

This research was supported in part by a March of Dimes clinical research grant and NIMH grants MH-51217, MH-01028, MH-40856, and MH-43271.

The authors thank Michael Flaum, M.D., Peg Nopoulos, M.D., Nancy Andreasen, M.D., Ph.D., Michael Miller, Ph.D., and Anthony LaMantia, Ph.D., for their contributions to this manuscript.

FIGURE 1. Subregions of the Corpus Callosum on Midsagittal Magnetic Resonance Imaging[a]



[a]Based on a modification of the method of Witelson (42); a=anterior, b=middle, and c=posterior.

callosum has been demonstrated in previous studies using MRI (27). The study group was examined in a previous study reported by our group (20) in which regional brain enlargement (after adjustment for height, performance IQ, and gender) was demonstrated in autistic individuals.

METHOD

Thirty-five autistic subjects (26 male and nine female), previously diagnosed with autistic disorder at the Child Psychiatry Clinic of the University of Iowa Hospitals and Clinics, participated in this study. Subjects were selected for the study if they were age 12 years or older, were likely to complete a 20-minute MRI scan without requiring sedation, and had no history of a substantial medical or neurological disorder. The mean age of the autistic subjects was 18.0 years (SD=4.5, range=12–29).

Parental informants for all of the autistic subjects were interviewed with the Autism Diagnostic Interview (28). All subjects met both the DSM-III-R and the Autism Diagnostic Interview algorithm (ICD-10) criteria for autistic disorder. At the time of their initial evaluation in the Child Psychiatry Clinic, all autistic subjects received clinical physical examinations and were reported to be without evidence of substantial abnormality. Subjects were also tested during their clinic visits with the Wechsler Adult Intelligence Scale—Revised (WAIS-R) (29), the Wechsler Intelligence Scale for Children—III (WISC-III) (30), or the Leiter International Performance Scale (31) for measurement of nonverbal IQ. The results of these tests were obtained retrospectively from clinic records. Both the Leiter and the Wechsler performance IQ scales are commonly used for assessing nonverbal IQ in autistic individuals and have been shown to be well correlated (32). Verbal IQs were not consistently available for all subjects (i.e., often as a result of the verbal deficits characteristic of autism, nonverbal measures such as the Leiter scale are used preferentially) and thus were not included in this study. The mean IQ of the autistic subjects was 91.0 (SD=19.8, range=52–136). No autistic subject had a history of treatment for a seizure disorder. Around the time of their MRI scans, the autistic subjects were examined for neurocutaneous markings of tuberous sclerosis and neurofibromatosis and measured for head circumference and height.

The comparison group consisted of 36 healthy volunteers (20 male and 16 female) recruited from the community through newspaper advertisements. The comparison subjects were a subset of an MRI database of the Mental Health Clinical Research Center at the University of Iowa, enriched with individuals having nonverbal IQs of 70–90 and with younger individuals (12–17 years). They were selected from the database as most closely resembling the age and IQ composition of the group of autistic subjects in the study. No comparison subject had a history of treatment for a psychiatric disorder (including alcohol or drug abuse and attention deficit hyperactivity disorder), a history of a learning disability, or a substantial medical or neurological disorder, as determined by structured interview. The nonverbal IQ of all comparison subjects was assessed with the performance subscales of the WAIS-R or the WISC-III. The mean age of the comparison subjects was 20.2 years (SD=3.8, range=13–28), and the mean nonverbal IQ was 102.1 (SD=12.8, range=72–135).

After explanation of the MRI procedure, written informed consent was obtained from all subjects over 17 years of age and informed assent (as well as parental consent) was obtained from subjects under 18 years of age. MRI data were obtained with a T_1-weighted three-dimensional spoiled-gradient recall acquisition sequence on a 1.5-T scanner in the approximate coronal plane with use of the following parameters: 1.5-mm slices with no gap; flip angle=40°; TR=24 msec; TE=5 msec; two excitations; field of view=26 cm; matrix=256×192. This sequence yields approximately 124 contiguous slices through the entire brain and requires an acquisition time of approximately 20 minutes.

MRI data were processed with the locally developed family of software known as BRAINS (33–37) on a Silicon Graphics Personal Iris four-dimensional graphic work station by a technician blind to the identity of the subjects. The various components of this software have been validated with a variety of methods, including phantoms and postmortem tissue (33, 35–40).

Initially, the whole brain was "cut out" of the skull by manually tracing along the pial-arachnoid junction, in consecutive slices to include the cerebral hemispheres, cerebellum, and brain stem, down to the level of the vertebral arteries (i.e., the inferior boundary of the brain stem). The MRI data were then converted to a three-dimensional data set with the use of BRAINBLAST, a voxel-processing program that does surface and volume rendering. Before subsequent analysis, the data were realigned and resampled in this three-dimensional orientation to ensure comparability of head position across all subjects (41). Thus, for example, the coronal plane was aligned so that its axis was perpendicular to a line drawn between the anterior-posterior commissure and the interhemispheric fissure, and the sagittal plane was aligned so that its axis was parallel to the anterior-posterior commissure line and the interhemispheric fissure. Resampled images were interpolated to cubic voxels so that there was no distortion. At this stage of the processing, total brain volume was assessed. Blind intrarater and interrater reliability for the measurement of total brain volume was high (intraclass correlations were 0.99 and 0.95, respectively).

Segmentation of all regions of interest was performed by an individual who was blind to the subjects' status, after adequate interrater and intrarater reliability had been established. Segmentation was performed after resampling of images (interpolated to 1-mm voxels) in the midsagittal plane. With information from simultaneous visualization in three orthogonal planes, the average of the two most midline 1-mm sagittal slices (i.e., where the sylvian aqueduct and the septum pellucidum were most clearly visualized) was used to best approximate the midsagittal corpus callosum area.

Three subregions (anterior, body, and posterior) of the corpus callosum were outlined according to a modification of the method described by Witelson (42) (figure 1). The Witelson method divides the corpus callosum into seven subregions; however, in this study, the corpus callosum was subdivided into only three subregions. This lim-

ited the number of analyses performed and maximized reliability. After a line was drawn through the most anterior and the most posterior points of the corpus callosum (i.e., the length), the anterior region was defined by a perpendicular line drawn superiorly from the line through the most anterior point of the inner convexity of the corpus callosum. This subregion corresponds to Witelson's subregions 1 (rostrum) and 2 (genu) of the corpus callosum. A line drawn perpendicular to the line through a point at the posterior one-fifth of the line delineated the posterior subregion of the corpus callosum, corresponding to Witelson's subregion 7 (splenium). The remainder of the corpus callosum constituted the body of the corpus callosum and corresponds to Witelson's subregions 3 through 6 (body plus isthmus). Blind intrarater and interrater reliability for the measurement of all regions of interest was high (intraclass correlation ≥0.90, N=10).

In the statistical analysis we used multivariate analysis of covariance (MANCOVA) and analysis of covariance (ANCOVA) to test for case-control differences in the size of selected subcortical structures, after adjusting for gender, total brain volume, and performance IQ. Adjustment for total brain volume is important in this study to take into account differences in corpus callosum size that may be due to previously demonstrated differences in total brain volume in these same autistic and comparison subjects. Probability figures are noted only if they achieved significance at conventional levels ($p<0.05$). Adjustment for multiple comparisons was made with the Bonferroni correction.

TABLE 1. Results of Analysis of Covariance Comparing Areas of Subregions of the Corpus Callosum in Autistic and Healthy Comparison Subjects[a]

Subregion of the Corpus Callosum and Covariate	F (df=1, 66)	p
Anterior		
Diagnosis	1.60	0.21
Gender	0.01	0.91
Total brain volume	12.03	0.0009
Performance IQ	0.02	0.89
Middle (body)		
Diagnosis	15.05	0.0002[b]
Gender	1.99	0.16
Total brain volume	29.34	0.0001
Performance IQ	1.21	0.28
Posterior		
Diagnosis	6.13	0.02[b]
Gender	0.10	0.76
Total brain volume	20.35	0.0001
Performance IQ	0.22	0.64

[a]Analyses are adjusted for total brain volume, gender, and performance IQ.
[b]Significant after Bonferroni correction for multiple comparisons.

TABLE 2. Adjusted and Unadjusted Areas of Subregions of the Corpus Callosum in Autistic and Healthy Comparison Subjects

	Unadjusted Area (cm^2)				Adjusted Area (cm^2)[a]			
	Autistic Subjects (N=36)		Comparison Subjects (N=35)		Autistic Subjects (N=36)		Comparison Subjects (N=35)	
Subregion of the Corpus Callosum	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Anterior	1.65	0.35	1.70	0.25	1.65	0.20	1.70	0.10
Middle (body)	2.85	0.60	3.00	0.35	2.85	0.50	3.00	0.25
Posterior	1.65	0.40	1.70	0.25	1.65	0.30	1.70	0.10

[a]Adjusted for total brain volume, gender, and performance IQ.

RESULTS

The results of a MANCOVA including the dependent variables of size of the anterior, body (middle), and posterior corpus callosum subregions; total brain volume; performance IQ; and gender revealed a significant main effect of diagnosis ($F=2.96$, df=3, 57, $p<0.04$) but no significant second-order interactions. The results of a comparison of regions of interest in the autistic and comparison subjects appear in table 1. After adjustment for gender, performance IQ, and total brain volume, the body and posterior corpus callosum subregions were found to be significantly smaller in the autistic subjects than in the comparison subjects. The adjusted size of the anterior corpus callosum did not differ between the two groups. The mean unadjusted sizes of the anterior, body, and posterior subregions of the corpus callosum in the autistic subjects were not significantly different from those in the comparison subjects. All results regarding the effect of diagnosis (table 1) were consistent with nonparametric analyses. Adjusted and unadjusted sizes of the three corpus callosum subregions in the autistic and comparison subjects appear in table 2.

DISCUSSION

Relative to total brain size, regional differences in the size of the corpus callosum between the two subject groups were detected. With some qualifications, this result is in agreement with the few previous reports on MRI of the corpus callosum in autism. Egaas et al. (14) reported a smaller area of the posterior subregions of the corpus callosum; however, corpus callosum measurements were not adjusted for a measure of total brain size. In addition, our recalculation of the t test results from that study (based on published values for the means, standard deviations, and group sizes), revealed only marginal to small effect sizes; significant differences (at the uncorrected 0.05 level) were evident only with the use of a one-tailed t test. Filipek et al. (26) also noted that the corpus callosum was significantly smaller in autistic individuals after adjustment for brain size; however, no data are available on whether subregions of the corpus callosum were examined. Finally, Berthier (43), with MRI, noted posterior thinning of the corpus callosum in subjects with Asperger's syndrome; however, neuroanatomical assessments in that report were based on qualitative ratings only. And Guerin et al. (44) reported corpus callosum thinning in a single postmortem case study.

In the study by Egaas et al. (14), smaller absolute area of the posterior subregions of the corpus callosum was interpreted as being related to hypoplasia of the parietal lobes in autism, reported by those investigators in an earlier qualitative study of parietal lobe size. However, two recent quantitative MRI studies (20, and personal

communication from Filipek) have demonstrated enlargement of the parietal, temporal, and occipital lobes, consistent with a number of reports of increased head circumference (45–49) and increased brain size (9) in autism. The results of these studies suggest that an alternative hypothesis for the finding of a decrease in corpus callosum size must be considered.

The pattern of posterior abnormalities (i.e., in the body and posterior subregions) of the corpus callosum in the present study is consistent with previous reports of volume abnormalities in the posterior (i.e., temporal, parietal, and occipital but not frontal) lobes in autism. However, while the presence of a posterior pattern of abnormality in both the cortical lobes and the corpus callosum appears consistent, the direction of the size differences is the opposite of what might have been predicted on the basis of knowledge of the physiological relationship between these two structures. The pattern (and volume) of cortical-callosal fibers traversing the corpus callosum is generally thought to reflect the topographical patterns of the cortical regions. Enlargement in the posterior cortical lobes would typically be expected to be associated with parallel enlargement in the posterior corpus callosum, in the same way that smaller cortical volumes have been shown to be reflected in smaller cross-sectional area of the corpus callosum (50).

Several possible explanations should be considered in attempting to reconcile the finding of both a smaller size of the posterior corpus callosum and a larger size of the posterior cortical lobes in our autistic subjects. First, studies of nonhuman primates have demonstrated the loss of up to 70% of axonal projections from the cortex to the corpus callosum during brain development (51). Elimination of callosal axons is temporally related to increased cortical synaptogenesis and may be mediated by competition between neurons for trophic support (52). If excess brain enlargement in autism results from an increase in the number of cells in the cortex, it is possible that local (ipsilateral) cortical connections may outcompete more distant connections from the contralateral hemisphere for trophic factors, resulting in selective elimination of callosal projections and a decrease in callosal size. The decrease in hemispheric connectivity that might result from a decrease in callosal size in autism is consistent with hypotheses generated from previous functional imaging and neuropsychological studies (17–19) which suggest the possibility that abnormal cortical connectivity may underlie the deficits in autism. However, the strong and positive correlation between corpus callosum size and total brain volume detected in this and other studies (53, 54) argues against the likelihood that larger cortical size results in a decrease in axonal projections to the corpus callosum.

A second possible explanation is that the relatively smaller size of the corpus callosum after adjustment for total brain volume is the result of a greater volume of either nonneuronal cortical tissue or cortical neurons that do not project axons to the callosum. It is generally considered that in adult primates, only 2%–3% of cortical neurons send axons to the corpus callosum (55) and that the largest fraction of callosal neurons comes from only a few cortical layers (e.g., cortical layer III) (16, 56). Thus, the relative differences in callosal size we detected may be unrelated to callosal size differences but instead may be entirely the result of greater cortical volume.

A final consideration in interpreting the data from this study is the extent to which valid inferences about cortical connectivity can be made from knowledge of the cross-sectional area of the corpus callosum. In their quantitative study of the size and axonal composition of the corpus callosum in the macaque, LaMantia and Rakic (55) concluded that as a result of substantial regional differences in axon size and myelination, there was no evidence of a statistically significant relation between cross-sectional area and axon number. Recent histological findings from a postmortem study of human brains, however, lend some support to the assumption that midsagittal corpus callosum area is a reflection of the degree of anatomical connectivity between the cerebral hemispheres. Aboitiz et al. (57) examined 20 human brains and found a significant positive relation between corpus callosum area and the number of small-diameter but not large-diameter callosal fibers. However, the proportion of axons of differing size and myelination is known to vary throughout subregions of the corpus callosum (55, 57), and there exists the possibility that the proportion of small and large axons in autism differs from that in nonautistic individuals because of selective loss or reduction of a certain class of callosal axons. Taken together, these findings suggest that interpretations about the underlying significance of reduced callosal size in autism should be made with caution.

In conclusion, we report the results of an MRI study of the anterior, body, and posterior subregions of the corpus callosum in a group of autistic individuals in whom enlargement of the temporal, parietal, and occipital lobes had previously been demonstrated. Relative to total brain size, the cross-sectional area of the body and posterior subregions of the corpus callosum were found to be smaller in autistic individuals compared with healthy subjects. These results suggest several possibilities, including anomalous connectivity of the cerebral cortex in autism or an increase in brain volume that is unrelated to the size of the corpus callosum, and underscore the importance of taking into account potential confounding variables (e.g., total brain volume) in imaging studies of the brain. The finding of a dissociation between cortical and callosal size on MRI in autistic subjects suggests that further imaging studies of this phenomenon are warranted.

REFERENCES

1. Lainhart JE, Piven J: Diagnosis, treatment, and neurobiology of autism in children. Curr Opin Pediatr 1995; 7:392–400
2. Tsai LY, Jacoby CG, Stewart MA: Morphological cerebral asymmetries in autistic children. Biol Psychiatry 1983; 18:317–327
3. Campbell M, Rosenbloom S, Perry R, George AE, Kricheff II,

Anderson L, Small AM, Jennings SJ: Computerized axial tomography in young autistic children. Am J Psychiatry 1982; 139: 510–512
4. Creasey H, Rumsey JM, Schwartz M, Duara R, Rapoport JL, Rapoport SI: Brain morphometry in autistic men as measured by volummetric computed tomography. Arch Neurol 1986; 43: 669–672
5. Rosenbloom S, Campbell M, George AE: High resolution CT scanning in infantile autism: a quantitative approach. J Am Acad Child Psychiatry 1984; 23:72–77
6. Harcherik DF, Cohen DJ, Ort S, Paul R, Shaywitz BA, Volkmar FR, Rothman SLG, Leckman JF: Computed tomographic brain scanning in four neuropsychiatric disorders of childhood. Am J Psychiatry 1985; 142:731–734
7. Gaffney GR, Kuperman S, Tsai LY, Minchin S: Forebrain structure in infantile autism. J Am Acad Child Adolesc Psychiatry 1989; 28:534–537
8. Courchesne E, Yeung-Courchesne R, Press GA, Hesselink JR, Jernigan TL: Hypoplasia of cerebellar vermal lobules VI and VII in autism. N Engl J Med 1988; 318:1349–1354
9. Piven J, Nehme E, Simon J, Barta P, Pearlson G, Folstein SF: Magnetic resonance imaging in autism: measurement of the cerebellum, pons, and fourth ventricle. Biol Psychiatry 1992; 31: 491–504
10. Kleiman MD, Neff S, Rosman NP: The brain in infantile autism: is the cerebellum really abnormal? (abstract). Ann Neurol 1992; 28:422
11. Holttum JR, Minshew NJ, Sanders RS, Phillips NE: Magnetic resonance imaging of the posterior fossa in autism. Biol Psychiatry 1992; 32:1091–1101
12. Hsu M, Yeung-Courchesne R, Courchesne E, Press GA: Absence of magnetic resonance imaging evidence of pontine abnormality in infantile autism. Arch Neurol 1991; 48:1160–1163
13. Hashimoto T, Tayama M, Murakawa K, Tsutomu Y, Miyazaki M, Harada M, Kuroda Y: Development of the brainstem and cerebellum in autistic patients. J Autism Dev Disord 1995; 25:1–22
14. Egaas B, Courchesne E, Saitoh O: Reduced size of the corpus callosum in autism. Arch Neurol 1995; 52:794–801
15. Lassonde M: The facilitatory influence of the corpus callosum on interhemispheric processing, in Two Hemispheres—One Brain. Edited by Lepore F, Ptito M, Jasper H. New York, Alan R Liss, 1986, pp 385–401
16. Innocenti GM: General organization of callosal connections in the cerebral cortex, in Cerebral Cortex, Vol 5: Sensory-Motor Areas and Aspects of Cortical Connectivity, Edited by Jones E, Peters A. New York, Plenum Press, 1986
17. Horwitz B, Rumsey J, Grady C, Rapoport SI: The cerebral metabolic landscape in autism: intercorrelations of regional glucose utilization. Arch Neurol 1988; 45:749–755
18. Zilbovicius M, Garreau B, Samson Y, Remy P, Barthélémy C, Syrota A, Lelord G: Delayed maturation of the frontal cortex in childhood autism. Am J Psychiatry 1995; 152:248–252
19. Minshew NJ, Goldstein G, Siegel D: Neuropsychologic functioning in autism: profile of a complex information processing disorder. J Int Neuropsychological Society 1997; 3:303–316
20. Piven J, Arndt S, Bailey J, Andreasen N: Regional brain enlargement in autism: a magnetic resonance imaging study. J Am Acad Child Adolesc Psychiatry 1996; 35:530–536
21. Damasio H, Maurer RG, Damasio AR, Chuio HC: Computerized tomographic scan findings in patients with autistic behavior. Arch Neurol 1980; 37:504–510
22. Ozonoff S, Pennington BF, Rogers SJ: Executive function deficits in high-functioning autistic individuals: relationship to theory of mind. J Child Psychol Psychiatry 1991; 32:1081–1195
23. Innocenti GM, Manzoni T, Spidalieri G: Patterns of the somesthetic messages transferred through the corpus callosum. Exp Brain Res 1974; 19:447–466
24. Pandya DN, Seltzer B: The topography of commissural fibers, in Two Hemispheres—One Brain. Edited by Lepore F, Ptito M, Jasper H. New York, Alan R Liss, 1986, pp 47–73
25. Lacoste MC, Kirkpatrick JB, Ross ED: Topography of the human corpus callosum. J Neuropathol Exp Neurol 1985; 44:578–591
26. Filipek PA, Richelme C, Kennedy CN, Rademacher J, Pitcher DA, Zidel S, Caviness VS: Morphometric analysis of the brain in developmental language disorders and autism (abstract). Ann Neurol 1992; 32:475
27. Giedd JN, Castellanos FX, Casey BJ, Kozuch P, King AC, Hamburger SD, Rapoport JL: Quantitative morphology of the corpus callosum in attention deficit hyperactivity disorder. Am J Psychiatry 1994; 151:665–669
28. LeCouteur A, Rutter M, Lord C, Rios P, Robertson S, Holdgrafer M, McLennan J: Autism Diagnostic Interview: a standardized investigator-based instrument. J Autism Dev Disord 1989; 19:363–387
29. Wechsler D: Wechsler Adult Intelligence Scale—Revised (WAIS-R). San Antonio, Tex, Psychological Corp, 1981
30. Wechsler D: Wechsler Intelligence Scale for Children—III (WISC-III). San Antonio, Tex, Psychological Corp 1991
31. Arthur G: The Arthur Adaptation of the Leiter International Performance Scale. Chicago, Psychological Service Center Press, 1953
32. Phelps L, Branyan BJ: Correlations among the Hiskey, K-ABC Nonverbal Scale, Leiter, and WISC-R Performance Scale with public-school deaf children. J Psychoeducational Assessment 1988; 6:354–358
33. Cohen G, Andreasen NC, Alliger R, Arndt S, Kuan J, Yuh WTC, Ehrhardt J: Segmentation techniques for the classification of brain tissue using magnetic resonance imaging. Psychiatry Res: Neuroimaging 1992; 45:33–51
34. Andreasen NC, Flashman L, Flaum M, Arndt S, Swayze V II, O'Leary DS, Ehrhardt JC, Yuh WTC: Regional brain abnormalities in schizophrenia measured with magnetic resonance imaging. JAMA 1994; 272:1763–1769
35. Cizadlo T, Andreasen NC, Zeien G, Rajaprabhakaran R, Harris G, O'Leary DS, Swayze VW, Arndt S, Hichwa R, Ehrhardt J, Yuh WTC: Image registration issues in the analysis of multiple-injection $^{150}H_20$ PET studies: BRAINFIT. Society Photo-Optical Instrumentation Engineers, International Society for Optical Engineering 1994; 2168:423–430
36. Arndt S, Swayze V, Cizadlo T, O'Leary D, Cohen G, Yuh WTC, Ehrhardt JC, Andreasen NC: Evaluating and validating two methods for estimating brain structure volumes: tessellation and simple pixel counting. Neuroimage 1994; 1:191–198
37. Andreasen NC, Rajaprabhakaran R, Cizadlo T (eds): Automated Atlas-Based Dissection of Human Brain From MR Images. San Francisco, Society of Magnetic Resonance in Medicine, 1994
38. Andreasen NC, Cohen G, Harris G, Cizadlo T, Parkkinen J, Rezai K, Swayze VW II: Image processing for the study of brain structure and function: problems and programs. J Neuropsychiatry Clin Neurosci 1992; 4:125–133
39. Andreasen NC, Cizadlo T, Harris G, Swayze V II, O'Leary DS, Cohen G, Ehrhardt J, Yuh WTC: Voxel processing techniques for the antemortem study of neuroanatomy and neuropathology using magnetic resonance imaging. J Neuropsychiatry Clin Neurosci 1993; 5:121–130
40. Andreasen NC, Harris G, Cizadlo T, Arndt S, O'Leary D, Swayze V, Flaum M: Techniques for measuring sulcal/gyral patterns in the brain as visualized through magnetic resonance scanning: BRAINPLOT and BRAINMAP. Proc Natl Acad Sci USA 1994; 900:93–97
41. Rauch RA, Jinkins JR: Variability of corpus callosal area measurements from midsagittal MR images: effect of subject placement within the scanner. AJNR 1996; 17:27–28
42. Witelson SF: Hand and sex differences in the isthmus and genu of the human corpus callosum. Brain 1989; 112:799–835
43. Berthier ML: Corticocallosal anomalies in Asperger's syndrome (letter). AJR 1994; 162:236–237
44. Guerin P, Lyon G, Barthélémy C, Sostak E, Chevrollier V, Garreau B, Lelord G: Neuropathological study of a case of autistic syndrome with severe mental retardation. Dev Med Child Neurol 1996; 38:203–211
45. Steg JP, Rapoport JL: Minor physical anomalies in normal, neurotic, learning disabled, and severely disturbed children. J Autism Child Schizophr 1975; 5:299–307
46. Bailey A, LeCouteur A, Gottesman I, Bolton P, Simonoff E,

Yudza E, Rutter, M: Autism as a strongly genetic disorder: evidence from a British twin study. Psychol Med 1995; 25:63–77
47. Lainhart JE, Piven J, Wzorek MA, Landa R, Santangelo S, Coon H, Folstein S: Macrocephaly in children and adults with autism. J Am Acad Child Adolesc Psychiatry 1997; 36:282–289
48. Davidovitch M, Patterson B, Gartside P: Head circumference measurements in children with autism. J Child Neurol 1996; 11: 389–393
49. Woodhouse W, Bailey A, Rutter M, Bolton P, Baird G, LeCouteur A: Head circumference in autism and other pervasive developmental disorders. J Child Psychol Psychiatry 1996; 37:665–671
50. Barkovich AJ, Norman D: Anomalies of the corpus callosum: correlation with further anomalies of the brain. Am J Neuroradiol 1988; 9:493–501
51. LaMantia AS, Rakic P: Axon overproduction and elimination in the corpus callosum of the developing rhesus monkey. J Neurosci 1990; 10:2156–2175
52. Purves D, Lichtman JW: Elimination of synapses in the developing nervous system. Science 1980; 210:153–157
53. Rauch R, Jinkins JR: Analysis of cross-sectional area measurements of the corpus callosum adjusted for brain size in male and female subjects from childhood to adulthood. Behav Brain Res 1993; 64:65–78
54. Parashos IA, Wilkinson WE, Coffey CE: Magnetic resonance imaging of the corpus callosum: predictors of size in normal adults. J Neuropsychiatry Clin Neurosci 1995; 7:35–41
55. LaMantia AS, Rakic P: Cytological and quantitative characteristics of four cerebral commissures in the rhesus monkey. J Comp Neurol 1990; 291:520–537
56. Schwartz ML, Goldman-Rakic PS: Callosal and intrahemispheric connectivity of the prefrontal association cortex in rhesus monkey: relation between intraparietal and principal sulcal cortex. J Comp Neurol 1984; 226:403–420
57. Aboitiz F, Scheibel AB, Fisher RS, Zaidel E: Fiber composition of the human corpus callosum. Brain Res 1992; 598:143–153