Published in final edited form as:

J Autism Dev Disord. 2009 June ; 39(6): 834–841. doi:10.1007/s10803-009-0689-4.

Corpus callosum volume and neurocognition in autism

Christopher J. Keary, Nancy J. Minshew, Rahul Bansal, Dhruman Goradia, Serguei Fedorov, Matcheri S. Keshavan, and Antonio Y. Hardan

A. Y. Hardan is now at the Department of Psychiatry and Behavioral Sciences, Stanford University of Medicine, Stanford, California. R. Bansal and S. Federov are at the Department of Psychiatry, Wayne State University, Detroit, Michigan. M.S Keshavan is now at the Department of Psychiatry, Beth Israel and Deaconess Medical Center, Harvard Medical School, Boston, MA. All authors, with the exception of SF, were affiliated with the Department of Psychiatry Institute and Clinic, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania at the time that the work was done

Abstract

The corpus callosum has recently been considered as an index of interhemispheric connectivity. This study applied a novel volumetric method to examine the size of the corpus callosum in 32 individuals with autism and 34 age-, gender- and IQ-matched controls and to investigate the relationship between this structure and cognitive measures linked to interhemispheric functioning. Participants with autism displayed reductions in total corpus callosum volume and in several of its subdivisions. Relationships were also observed between volumetric alterations and performance on several cognitive tests including the Tower of Hanoi test. These findings provide further evidence for volumetric alterations in the corpus callosum in autism, but warrant additional studies examining the relationship of this structure and specific measures of interhemispheric connectivity.

Keywords

Autism; corpus callosum; volume; MRI; connectivity; neuropsychological tests

Introduction

Emerging theories of autism include the characterization of this disorder by poor connectivity between different cortical regions resulting in impaired integrative processing and deficient higher order cognitive abilities (Just, Cherkassky, Keller, & Minshew, 2004). Evidence for this theory has come from new innovative fMRI methodologies assessing “functional connectivity,” a measure of synchrony of activation in related brain regions during task completion. Decreased coordination between brain regions has been found during performance on tasks of sentence comprehension (Kana, Keller, Cherkassky, Minshew, & Just, 2006) and executive planning (Just, Cherkassky, Keller, Kana, & Minshew, 2007). These studies are driving new strategies of looking at “normal

The address of the corresponding author is: Antonio Y. Hardan, M.D., Department of Psychiatry and Behavioral Sciences, Stanford University, 401 Quarry Road, Stanford, CA 94305, Phone: (650) 724-8919, Fax: (650) 724-0829, hardanay@stanford.edu.. All authors, with the exception SF, were affiliated with the Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania at the time the study was performed. Serguei Federov is affiliated with the Department of Psychiatry, Wayne State University, Detroit, Michigan. Dr. Hardan is now at the Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA. Dr. Keshavan is now at Beth Israel and Deaconess Medical Center, Harvard Medical School. Dr. Bansal is now at the Department of Psychiatry, Wayne State University, Detroit, Michigan.

functioning” in brain activity where instead of focusing on specific regions of interest the brain is seen as an *integrated system* of regions of interest that must collaborate to achieve normal functioning (Just, Cherkassky, Keller, Kana, & Minshew, 2007). This pattern of aberrant connectivity is consistent with theories of autism as a complex information processing disorder wherein impaired integration of information drives impaired concept formation and complex sensory, language and motor skills but leaves comparable simple tasks and basic rule learning undisturbed (Minshew, Goldstein, & Siegel, 1997).

Establishing the anatomical correlate of this reduced connectivity is a major goal of current structural imaging studies which have implicated both white matter (specifically abnormal between-region white matter tracts) and gray matter architecture. Volumetric differences in white matter regions have been consistently found in younger autistic individuals (Carper & Courchesne, 2005) and key volumetric studies have found that these volumetric differences may affect outer radiate compartments, carrying within region fibers, differently than inner radiate compartments, carrying between region fibers (Herbert et al., 2004). In addition, diffusion tensor imaging studies have found reduced fractional anisotropy (a measure of coherent fiber tract directionality) in white matter regions including the corpus callosum (Barnea-Goraly et al., 2004). Although these findings implicate white matter tract abnormalities in autism, it is unlikely that these findings exist in the absence of cortical grey matter abnormalities. Abnormally narrow cortical minicolumn architecture has been a well documented finding in autism and it is hypothesized that such an architecture could result in fewer long distance connecting fibers in comparison to abundant short distance connections (Casanova et al., 2006). Establishing which between region connections are deficient, if any, remains an important research goal and imaging studies are an important method to establish which connections are of particular interest.

The corpus callosum, as a structure composed entirely of long distance connecting fibers, has been the focus of many studies in autism which hypothesize that the poor connectivity of the brain in autism would be reflected in this structure. While several neuroimaging studies have found decreases in CC size (Manes et al., 1999; Hardan, Minshew, & Keshavan, 2000; Vidal et al., 2006), caution is necessary in drawing inferences of overall connectivity based purely on morphometric volume (Piven, Bailey, Ranson, & Arndt, 1997). Current studies are responding to this issue by exploring the significance of CC size measurements in individuals with autism as they relate to findings from novel imaging methodologies and performance on cognitive tasks. Relationships have been found between smaller CC size in individuals with autism and decreased “functional connectivity” in specific CC subregions (Just, Cherkassky, Keller, Kana, & Minshew, 2007). In addition, current DTI studies in autism have established links between low fractional anisotropy/mean diffusivity in CC subregions and slower processing speed (Alexander et al., 2007). However, studies have yet to link abnormal CC features to specific cognitive deficits that might implicate decreased CC size as part of the pathophysiology of autism and the clinical ramifications of smaller CC size remain an important topic of research.

The purpose of the present study is to better characterize the volumetric differences of CC subregions in autism and to assess the clinical significance of these findings. Although reductions in CC size have been found in previous studies, discrepancies still remain as to which subregions of the CC are affected (Brambilla et al., 2003). Existing studies have used mid-sagittal surface to measure the size of the CC and differences have been reported in the anterior regions of the CC (Hardan, Minshew, & Keshavan, 2000; Vidal et al., 2006), posterior regions (Egaas, Courchesne, & Saitoh, 1995), or subsections from both regions (Piven, Bailey, Ranson, & Arndt, 1997; Manes et al., 1999). Localizing CC volumetric differences to specific subregions is an important research goal as callosal regions carry fibers from specific cortical areas (Pandya & Seltzer, 1986) and deficiencies in a subregion

may implicate abnormalities to corresponding cortical lobes. This study aims to better localize any observed reductions while applying a volumetric measurement of the CC allowing a higher sensitivity than cross-sectional measurements. Additionally, this study examines the relationships between these structural abnormalities and functionally significant clinical measures assessing several cognitive abilities including interhemispheric communication.

Method

Participants

Subjects were 32 non-mentally retarded individuals with autism between the ages of 8 and 45 years and 34 healthy controls between 9 and 43 years of age. The participants with autism represented all consecutive referrals to a research clinic who met criteria for participation in the study. The diagnosis of autism was established through expert clinical evaluation in accordance with published clinical descriptions of high functioning individuals with autism (Minshew, Goldstein, & Siegel, 1997) and two structured research diagnostic instruments, the Autism Diagnostic Interview-Revised (ADI-R) (Lord, Rutter, & LeCouteur, 1994) and Autism Diagnostic Observation Schedule (ADOS) (LeCouteur, Rutter, & Lord, 1989). Controls were children, adolescents, and young adults recruited from the community through advertisements in areas socioeconomically comparable to those of the families of origin of the participants with autism. Potential control subjects were screened by questionnaire, telephone, face-to face interview, and observation during screening psychometric tests. All subjects were medically healthy and had a full scale IQ of 70 or higher. Controls were group-matched with individuals with autism with regard to age, socioeconomic status and full scale, verbal and performance IQ.

Potential participants with autism were excluded if found to have evidence of an associated infectious, genetic, or metabolic disorder, such as Fragile X syndrome or tuberous sclerosis. Potential subjects were excluded if found to have evidence of birth asphyxia, head injury, or a seizure disorder. Exclusions were based on neurologic history and examination, physical examination, and chromosomal analysis or metabolic testing if indicated. Potential control subjects were also screened to exclude those with family history of autism, developmental cognitive disorder, learning disability, affective disorder, anxiety disorder, schizophrenia, obsessive-compulsive disorder, or other neurologic or psychiatric disorders thought to have a genetic component. The socioeconomic status of the family of origin was assessed using the Hollingshead method (Hollingshead, 1975). The age-appropriate version of the Wechsler Intelligence scale (WAIS-R or WISC-R) was administered to measure Full Scale IQ, Performance IQ and Verbal IQ. Methodology of the study, including MRI scanning for minors, was approved by the Institutional Review Board. Procedures were fully explained to all subjects and, when appropriate, to their parent or legal guardian. Written informed consent was obtained from subjects or their guardians.

Procedures

Neuropsychological Tests—Each participant received the Wisconsin Card Sorting Test (WCST), the Tower of Hanoi test (ToH), the Tactile Finger Recognition test (as part of the Reitan Klove exam), and the Tactual Performance Test (TPT). Testing was done by trained neuropsychology technicians under the supervision of professional psychologists. In the WCST, a frontal lobe associated rule changing test, dependent variables included the number of perseverative, nonperseverative, and total errors. The ToH test protocol in this study involved the movement of four disks in increasing size between two of three pegs without stacking a larger disk upon a smaller disk. The task was repeated four times to assess planning skills; the number of moves required and time taken were dependent

variables for all four trials. The Tactile Finger Recognition test asked participants to identify, by sensation only, which finger was touched and errors were measured for each hand individually. Finally, the TPT had participants insert shaped pegs into a board while blindfolded over three trials: first just using the non-dominant hand, then dominant hand, then bimanually. Speed of task completion is the variable of interest.

These four tests assess a variety of cognitive abilities from planning to sensory-motor processing. These neuropsychological tests were also selected to act as a clinical index of interhemispheric communication with evidence, although limited, from lesion studies implicating both hemispheres in the execution of some of these tasks (Tarnok, Barsi, Gadoros, & Halasz, 2006). Although few clinical tests exist that measure exclusively CC function, the WCST and ToH test both show bilateral frontal cortical activation during task performance in normal individuals (Smith, Taylor, Brammer, & Rubia, 2004; Newman, Carpenter, Varma, & Just, 2003). Poor performance on perseverative perseverate error measures of the WCST, displaying an underlying deficit in concept formation and plasticity, is characteristic of individuals with autism (Minshew, Meyer, & Goldstein, 2002) as is inferior performance on executive function tasks, such as the ToH (Hughes, Russell, & Robbins, 1994). In a recent fMRI study, abnormal synchronization was observed between different brain areas including the frontal, parietal and corpus callosal in a group of high functioning individuals with autism while performing the Tower of London test (a comparable frontal lobe task) (Just, Cherkassky, Keller, Kana, & Minshew, 2007). In addition, the tactile finger recognition test and the TPT, measures of sensory-motor processing (Quinn & Geffen, 1986) and tactile form perception and spatial learning and memory (Thompson & Parsons, 1985) respectively, were chosen as both tests have been used previously to assess interhemispheric communication in individuals with CC lesions (Nyden, Carlsson, Carlsson, & Gillberg, 2004; Brown, 2003).

MRI scans—All scans were obtained on a General Electric (Milwaukee) 1.5 Tesla Signa scanner. The imaging protocol consisted of two T₁-weighted (TR=500, TE=20) series: a sagittal series of 3 mm slice thickness parallel to the midline structure, and an axial series of 5 mm slice thickness. An additional 1.5 mm SPGR (spoiled gradient recalled echo in steady state) coronal series (TR = 35; TE = 5, NEX = 1, flip angle = 45°) was collected, which was used for all the measurements reported in this study. All images were transferred from the acquisition facility to the image analysis laboratory via File Transfer Protocol and archived on CD-ROM disks. 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 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. 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.

Corpus Callosum Measurements—The volume of the CC was generated by tracing the CC on the mid-sagittal slice and the 6 adjacent para-sagittal slices on each side. The boundaries of the different CC subdivisions (genu, rostrum, rostral body, anterior mid-body,

posterior mid-body, isthmus, and splenium) were determined on each slice based on the organization developed by Witelson and used in previous studies (Hardan, Minshew, & Keshavan, 2000; Witelson, 1989). The number of parasagittal slices was determined by the ability to reliably determine the CC contours on each slice. After determining the boundaries of the different subdivisions on each slice (total 13), vertical lines were established dividing each slice into 7 different regions. 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 and inter-rater reliability ($ICC > 0.93$).

Data Analysis

A Student's t-test was used to compare all the demographic data. To examine group differences in CC volumes, a multivariate analysis of covariance was applied. Between-group differences in performance measures from neuropsychological test dependent variables were analyzed with two tailed student t-tests for equality of means. Spearman's and when applicable Pearson's correlations coefficients were used to examine the relationships between CC volumes and 1) age, 2) TBV, and 3) performance on neuropsychological tests. The false discovery rate approach was used to correct for multiple comparisons (Benjamini & Hochberg, 1995, 2000). Probability figures were considered significant if they achieved significance at conventional levels (i.e., $p < 0.05$).

RESULTS

The complete demographic information of this sample was previously published (Hardan, Kilpatrick, Keshavan, & Minshew, 2003). Neuropsychological tests and good quality MRI scans were available on a subgroup of the original sample and no demographic characteristics were observed between participants with autism and controls (Table 1). No differences were found between the two groups based on gender (Autism group: Male: 29, female 2; Controls: Male: 31, Female: 2; $\chi^2 = 0.949$; $df = 1$; $p = 0.669$) or handedness (Autism group: Right: 26, left 5; Controls: right: 29, left: 4; $\chi^2 = 1.124$; $df = 1$; $p = 0.570$). To examine diagnostic group differences in corpus callosum volumes, a multivariate analysis of covariance was computed with diagnosis (autism vs. healthy controls) as the between-subjects independent variable and total brain white matter volume as the covariate. Total corpus callosum, Witelson subdivisions, and anterior and posterior regions volumes were the dependent variables. Results indicated a significant overall multivariate effect (Wilks' $\Lambda = 0.629$, $F(8,54) = 3.99$, $p = .001$). Tests of between-subjects effects are summarized in Table 2 and showed smaller total CC ($p = .031$), rostrum ($p = .001$), genu ($p = .026$), anterior body ($p = .015$), and anterior region volumes ($p = .011$) in individuals with autisms. Effect sizes for significant findings ranged from medium (Cohen's $d = .57$) for total CC volume and splenium ($d = .45$) to large for the rostrum ($d = .91$). Effect sizes for non-significant findings were negligible (isthmus $d = .05$) to small (posterior CC $d = .35$).

Results from performance on the neuropsychological tests are summarized in Table 3. Participants with autism made significantly more perseverative and total errors on the WCST with no difference in non-perseverative errors. On the ToH test, participants with autism took significantly longer and made significantly more mistakes in most trials. Finally, participants with autism performed slower on the TPT, however no differences were observed between the two groups on the Finger Recognition test.

The relationships between CC volumes and age and TBV were examined and no associations were found in the autism and control groups. Correlations were examined

between CC structures and performance on neuropsychological tests and relationships were observed only in the autism group. An association was observed between the isthmus volume and the total number of moves on the TOH ($R = -0.410$; $df = 29$; $p = 0.027$). A similar relationship was observed between the isthmus and total errors ($R = -0.524$; $df = 18$; $p = 0.026$) on the WCST. Correlations were also found between errors in the left hand while performing the finger recognition test and several CC volumes including the genu ($R = -0.507$; $df = 24$; $p = 0.011$), posterior body ($R = -0.637$; $df = 24$; $p = 0.001$), and splenium ($R = -0.490$; $df = 24$; $p = 0.015$). These relationships were found in all individuals with autism including the ones who were right handed. No associations were found between CC volumes and performance on the TPT in the autism group. Finally, the false discovery approach was applied in light of the number of multiple comparisons and only the correlations between errors in the left hand while performing the FRT and the posterior body and splenium remained significant.

DISCUSSION

Reductions in the size of the CC in individuals with autism were observed in this study, involving mostly anterior regions. These observations are consistent with previous neuroimaging studies in autism, but it remains unclear if these abnormalities are specific to autism since alterations of the CC size have been reported in several others neuropsychiatric disorders such as schizophrenia, attention deficit disorders and Tourette's disorder (Paul et al., 2007). In the present study, the anterior body, genu, and rostrum were all found to be smaller in size in individuals with autism. A tendency toward size reduction in the splenium was also observed which is consistent with previous reports (Vidal et al., 2006; Just, Cherkassky, Keller, Kana, & Minshew, 2007). Although the total CC volume was found to be smaller in participants with autism, a decrease in the size of the anterior regions appears to be the main contributor to this overall decrease. Findings in previous cross-sectional measurements of the CC support the presence of reductions in the anterior region (Piven, Bailey, Ranson, & Arndt, 1997; Manes et al., 1999; Hardan, Minshew, & Keshavan, 2000; Vidal et al., 2006). These results highlight the need to conduct measurements not only to examine the total size of the corpus callosum but also its subdivisions.

In light of the topographic distribution of white matter fibers in the CC, regional alterations of this structure can help identify abnormalities in corresponding cortical brain areas. Anterior CC subregions carry fibers largely from the frontal cortex (Pandya & Seltzer, 1986) and reduction in these subdivisions is consistent with theories of poor connectivity between the frontal cortex and other brain regions. These observations are supported by several studies implicating the frontal lobe in the pathophysiology of autism including neuropsychological investigations describing executive function (Ozonoff, Pennington, & Rogers, 1991) and complex language and reasoning deficits (Minshew, Goldstein, & Siegel, 1997), a post-mortem study pointing to abnormal minicolumnar architecture in frontal regions (Casanova, Buxhoeveden, Switala, & Roy, 2002), a DTI report of reduced fractional anisotropy in pre-frontal cortices (Barnea-Goraly et al. 2004), and abnormalities associated with frontal lobe functioning involving theory of mind (Frith, & Frith, 2006). Findings from the current study implicate further the frontal lobe in autism, but it remains unclear whether these volumetric alterations are causing frontal lobe deficits or just associated with these deficits. Lesion and neurosurgical studies of individuals with acquired anterior CC damage have reported effects on verbal fluency and memory (Pozzili et al., 1991; D'Angelo et al., 1997) and age related reduction in anterior CC volume has been linked to impairment in inhibitory processes in selective attention (Muller-Oehring, Schulte, Raassi, Pfefferbaum, & Sullivan, 2007). However, it is not known if cognitive deficits observed in these studies are similar to the ones observed in autism. Finally, individuals with agenesis of the CC exhibit several cognitive and clinical characteristics that are similar to the ones observed in autism,

such as impairment in abstract reasoning, problem solving, generalization and social deficits (Paul et al., 2007). Hence, the examination of individuals affected with this disorder will be instrumental in shedding light on the contribution of the CC to the overall deficits observed in autism.

The largest difference in performance on the selected neuropsychological tests was observed in tests associated with frontal lobe function. The most robust performance difference between participants with autism and controls was found on perseverative errors of the WCST reflecting an underlying deficit in concept flexibility (concept formation and plasticity) that is characteristic of individuals with autism (Minshew, Meyer, & Goldstein, 2002). Poor performance among individuals with autism was also observed on measures from the ToH test which is consistent with reported deficiencies on comparable executive function tests (Hughes, Russell, & Robbins, 1994). Additionally, performance between the two groups became increasingly significant over time. This pattern indicates that control participants improved with planning and practicing while autism participants did not. Performance on the TPT and the Tactile Finger Recognition test is consistent with current neurological profiles of autism documenting deficits in complex motor tasks but not in sensory perception tasks (Minshew, Goldstein, & Siegel, 1997).

Correlations between several neuropsychological test performance and CC measurements were observed in this investigation. CC volume reductions were correlated with poor performance on several neurocognitive tests as reflected in a higher number of errors on the TOH and finger recognition test. These observations are consistent with a previous DTI study in autism reporting a relationship between radial diffusivity and processing speed measured during PIQ testing (Alexander et al., 2007). They are also concordant with findings from other studies implicating the CC in interhemispheric and functional connectivity (Quigley et al., 2003; Madden et al., 2004). These findings support the role of the CC in the pathophysiology of autism and emphasize further its role in interhemispheric connectivity in autism. However, additional functional neuroimaging studies are warranted to provide direct evidence of these cognitive-structural relationships and to help determine whether they are associative or causative in nature. This is particularly important since most of the associations observed in the present study between volumetric measurements and performance on neuropsychological tests were not observed when controlling for multiple comparisons.

This study provides additional evidence of CC abnormalities in autism and implicates this structure further in the pathophysiology of this disorder. However, this investigation has several limitations including participants' characteristics who were essentially high functioning individuals with a wide age range. Additionally, adjustment of the p-value might be needed in light of the number of comparisons conducted. However, while p-value adjustments reduce the risk of making type I errors, they increase the chance of making type II errors, or necessitate the increase of the sample size (Feise, 2002). Future studies should apply novel imaging methods, such as DTI and fMRI, while assessing cognitive functioning using more specific neuropsychological tests of interhemispheric connectivity. These studies will elucidate the contribution of the CC to autism symptomatology and will help determine whether these structural alterations are related to the disorder itself or a consequence of its clinical features (Sanchez, Hearn, Do, Rilling, & Herndon, 1998).

Acknowledgments

This work was supported in part by NIMH grant MH 64027 to Dr. Hardan, and NICHD grant HD 35469, and NICHD grant HD 35469 to Dr. Minshew. The authors thank Diane L Williams, PhD, for assistance in study design. The efforts and commitment of the participants and their families in this study are gratefully acknowledged.

References

- Alexander AL, Lee JE, Lazar M, Boudos R, DuBray MB, Oakes TR, Miller JN, Lu J, Jeong EK, McMahon WM, Bigler ED, Lainhart JE. Diffusion tensor imaging of the corpus callosum in autism. *Neuroimage*. 2007; 34:61–73. [PubMed: 17023185]
- Barnea-Goraly N, Kwon H, Menon V, Eliez S, Lotspeich L, Reiss AL. White matter structure in autism: Preliminary evidence from diffusion tensor imaging. *Biological Psychiatry*. 2004; 55:323–326. [PubMed: 14744477]
- Benjamini Y, Hochberg T. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society*. 1995; 85:289–300.
- Benjamini Y, Hochberg T. On the adaptive control of the false discovery rate in multiple testing with independent statistics. *Journal of Educational and Behavioral Statistics*. 2000; 26:60–83.
- Brambilla P, Hardan AY, di Nemi SU, Perez J, Soares JC, Barale F. Brain anatomy and development in autism: Review of structural MRI studies. *Brain Research Bulletin*. 2003; 61:557–569. [PubMed: 14519452]
- Brown, WS. Clinical neuropsychological assessment of callosal dysfunction: Multiple sclerosis and dyslexia. In: Zaidel, E.; Iacoboni, M., editors. *The parallel brain: The cognitive neuroscience of the corpus callosum*. The MIT Press; Cambridge, Massachusetts: 2003. p. 391–406.
- Carper RA, Courchesne E. Localized enlargement of the frontal cortex in early autism. *Biological Psychiatry*. 2005; 57:126–133. [PubMed: 15652870]
- Casanova MF, Buxhoeveden DP, Switala AE, Roy E. Minicolumnar pathology in autism. *Neurology*. 2002; 58:428–432. [PubMed: 11839843]
- Casanova MF, van Kooten IA, Switala AE, van Engeland H, Heinsen H, Steinbusch HW, Hof PR, Trippe J, Stone J, Schmitz C. Minicolumnar abnormalities in autism. *Acta Neuropathol*. 2006; 112:287–303. [PubMed: 16819561]
- D'Angelo V, Napolitano M, Gorgogliione L, Scarabino T, Latino R, Simone P, Bisceglia M. Surgical treatment of anterior callosal tumors. *Journal of Neurosurgical Science*. 1997; 41:117–122.
- Egaas B, Courchesne E, Saitoh O. Reduced size of corpus callosum in autism. *Archives of Neurology*. 1995; 52:794–801. [PubMed: 7639631]
- Feise RJ. Do multiple outcome measures require p-value adjustment? *BMC Med Res Methodol*. 2002; 2:8. [PubMed: 12069695]
- Frith CD, Frith U. The neural basis of mentalizing. *Neuron*. 2006; 18:531–534. [PubMed: 16701204]
- Hardan AY, Minshew NJ, Keshavan MS. Corpus callosum size in autism. *Neurology*. 2000; 55:1033–1036. [PubMed: 11061265]
- Hardan AY, Kilpatrick M, Keshavan MS, Minshew NJ. Motor performance and anatomic magnetic resonance imaging (MRI) of the basal ganglia in autism. *Journal of Child Neurology*. 2003; 18:317–324. [PubMed: 12822815]
- Herbert MR, Ziegler DA, Makris N, Filipek PA, Kemper TL, Normandin LL, Sanders HA, Kennedy DN, Caviness VS Jr. Localization of white matter volume increase in autism and developmental language disorder. *Annals of Neurology*. 2004; 55:530–540. [PubMed: 15048892]
- Hollingshead, AB. Four Factor Index of Social Status. Yale University Department of Sociology; New Haven, CT: 1975.
- Hughes C, Russell J, Robbins TW. Evidence for executive dysfunction in autism. *Neuropsychologia*. 1994; 32:477–492. [PubMed: 8047253]
- Just MA, Cherkassky VL, Keller TA, Minshew NJ. Cortical activation and synchronization during sentence comprehension in high-functioning autism: Evidence of underconnectivity. *Brain*. 2004; 127:1811–1821. [PubMed: 15215213]
- Just MA, Cherkassky VL, Keller TA, Kana RK, Minshew NJ. Functional and anatomical cortical underconnectivity in autism: Evidence from an fMRI study of an executive function task and corpus callosum morphometry. *Cerebral Cortex*. 2007; 17:951–961. [PubMed: 16772313]
- Kana RK, Keller TA, Cherkassky VL, Minshew NJ, Just MA. Sentence comprehension in autism: Thinking in pictures with decreased functional connectivity. *Brain*. 2006; 129:2484–2493. [PubMed: 16835247]

- LeCouteur A, Rutter M, Lord C, Rios P, Robertson S, Holdgrafer M, McLennan J. Autism diagnostic interview: A standardized investigator-based instrument. *Journal of Autism and Developmental Disorders*. 1989; 19:363–387. [PubMed: 2793783]
- Lord C, Rutter M, LeCouteur A. Autism Diagnostic Interview-Revised: A revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *Journal of Autism and Developmental Disorders*. 1994; 24:659–685. [PubMed: 7814313]
- Madden DJ, Whiting WL, Huettel SA, White LE, MacFall JR, Provenzale JM. Diffusion tensor imaging of adult age differences in cerebral white matter: Relation to response time. *Neuroimage*. 2004; 21:1174–1181. [PubMed: 15006684]
- Magnotta VA, Harris G, Andreasen NC, O'Leary DS, Yuh WT, Heckel D. Structural MR image processing using the BRAINS2 toolbox. *Computerized Medical Imaging and Graphics*. 2002; 26:251–264. [PubMed: 12074920]
- Manes F, Piven J, Vrancic D, Nanclares V, Plebst C, Starkstein SE. An MRI study of the corpus callosum and cerebellum in mentally retarded autistic individuals. *Journal of Neuropsychiatry and Clinical Neurosciences*. 1999; 11:470–474. [PubMed: 10570760]
- Minshew NJ, Goldstein G, Siegel DJ. Neuropsychologic functioning in autism: Profile of a complex information processing disorder. *Journal of the International Neuropsychological Society*. 1997; 3:303–316. [PubMed: 9260440]
- Minshew NJ, Meyer J, Goldstein G. Abstract reasoning in autism: A dissociation between concept formation and concept identification. *Neuropsychology*. 2002; 16:327–334. [PubMed: 12146680]
- Muller-Oehring EM, Schulte T, Raassi C, Pfefferbaum A, Sullivan EV. Local-global interference is modulated by age, sex and anterior corpus callosum size. *Brain Research*. 2007; 1142:189–205. [PubMed: 17335783]
- Newman SD, Capenter PA, Varma S, Just MA. Frontal and parietal participation in problem solving in the Tower of London: fMRI and computational modeling of planning and high-level perception. *Neuropsychologia*. 2003; 41:1668–1682. [PubMed: 12887991]
- Nyden A, Carlsson M, Carlsson A, Gillberg C. Interhemispheric transfer in high-functioning children and adolescents with autism spectrum disorders: A controlled pilot study. *Developmental Medicine and Child Neurology*. 2004; 46:448–454. [PubMed: 15230457]
- Ozonoff S, Pennington BF, Rogers SJ. Executive function deficits in high-functioning autistic individuals: Relationship to theory of mind. *Journal of Child Psychology and Psychiatry*. 1991; 32:1081–1105. [PubMed: 1787138]
- Pandya, DN.; Seltzer, B. The topography of commissioned fibers. In: Lepore, F.; Ptito, M.; Jasper, HH., editors. *Two hemispheres—one brain: Functions of the corpus callosum*. Liss; New York: 1986. p. 44–73.
- Paul LK, Brown WS, Adolphs R, Tyszka JM, Richards LJ, Mukherjee P, Sherr EH. Agenesis of the corpus callosum: genetic, developmental and functional aspects of connectivity. *Nat Rev Neurosci*. 2007; 8:287–99. [PubMed: 17375041]
- Piven J, Bailey J, Ranson BJ, Arndt S. An MRI study of the corpus callosum in autism. *American Journal of Psychiatry*. 1997; 154:1051–1056. [PubMed: 9247388]
- Pozzilli C, Bastianello S, Padovani A, Passafiume D, Millefiorini E, Bozzao L, Fieschi C. Anterior corpus callosum atrophy and verbal fluency in multiple sclerosis. *Cortex*. 1991; 27:441–445. [PubMed: 1743039]
- Quigley M, Cordes D, Turski P, Moritz C, Haughton V, Seth R, Meyerand ME. Role of the corpus callosum in functional connectivity. *American Journal of Neuroradiology*. 2003; 24:208–212. [PubMed: 12591635]
- Quinn K, Geffen G. The development of tactile transfer of information. *Neuropsychologia*. 1986; 24:793–804. [PubMed: 3808287]
- Sánchez MM, Hearn EF, Do D, Rilling JK, Herndon JG. Differential rearing affects corpus callosum size and cognitive function of rhesus monkeys. *Brain Research*. 1998; 812:38–49. [PubMed: 9813233]
- Smith AB, Taylor E, Brammer M, Rubia K. Neural correlates of switching set as measured in fast, event-related functional magnetic resonance imaging. *Human Brain Mapping*. 2004; 21:247–256. [PubMed: 15038006]

- Tárnok Z, Barsi P, Gáboros J, Halász P. Executive dysfunction in frontal lesions and frontal epilepsy. *Ideggyogy.* 2006; Sz 20:269–280.
- Thompson LL, Parsons OA. Contribution of the TPT to adult neuropsychological assessment: A review. *Journal of Clinical Experimental Neuropsychology.* 1985; 7:430–444.
- Vidal CN, Nicholsen R, DeVito TJ, Hayashi KM, Geaga JA, Drost DJ, Williamson PC, Rajakumar N, Sui Y, Dutton RA, Toda RW, Thompson PM. Mapping corpus callosum deficits in autism: An index of aberrant cortical connectivity. *Biological Psychiatry.* 2006; 60:218–225. [PubMed: 16460701]
- Witelson SF. Hand and sex differences in the isthmus and genu of the human corpus callosum: A postmortem morphological study. *Brain.* 1989; 112:799–835. [PubMed: 2731030]

Figure 1.
Seven volumetric corpus callosum subdivisions, lower left to back: rostrum; genu; rostral body; anterior body; posterior body; isthmus; splenium

Figure 2. The relationship between the isthmus' volume and the number of total moves on the Tower of Hanoi in participants with autism ($R = -0.410$; $df\ 29$; $p = 0.027$).

Table 1

Demographic Information

	Autistics			Controls		
	N=32			N=34		
	M	SD	Range	M	SD	Range
Age (years)	19.8	10.2	8.8-45.7	18.6	9.06	9.2-43.9
Full Scale IQ	102.9	13.6	75-135	104.0	10.5	86-121
Verbal IQ	106.9	15.6	75-140	104.7	10.4	88-124
Performance IQ	97.8	12.5	78-137	102.6	10.0	86-121
Socioeconomic Status	3.88	1.67	1-7	3.52	1.24	1-7

No significant differences

Table 2
Volumetric Measurements (cm³) and Multivariate Analysis of Covariance

Corpus Callosum	Autism N = 32		Control N = 34		TWM as covariate		
	Mean	SD	Mean	SD	F (1,61)	P	
Total	6.3	1.2	6.8	1.0	4.1	0.03*	
Rostrum	0.11	0.05	0.17	0.09	12.7	<0.01*	
Genu	1.6	0.38	1.8	0.28	4.3	0.026*	
Rostral body	0.87	0.16	0.91	0.17	1.03	0.32	
Anterior Body	0.70	0.15	0.77	0.13	6.3	0.015*	
Posterior Body	0.62	0.12	0.63	0.11	0.15	0.70	
Isthmus	0.59	0.13	0.58	0.17	0.04	0.84	
Splenium	1.7	0.41	1.9	0.46	3.1	0.08	
Anterior CC	3.3	0.68	3.7	0.56	6.8	0.011*	
Posterior CC	2.9	0.59	3.1	0.55	1.9	0.17	

TWM: Total White Matter; Anterior CC = Rostrum + Genu + Rostral body + anterior mid-body; Posterior CC = Posterior mid body + isthmus + splenium

Table 3
Performance of participants on neuropsychological tests (all times in sec)

	PDD		Control		t	df	p
	N = 32	N = 34	M	SD			
Tower of Hanoi Test							
Trial 1 -- Moves	49	27	37	23	1.8	60	0.08
Trial 1 -- Time	251	287	144	107	1.9	35	0.07
Trial 2 -- Moves	44	30	28	12	2.6	37	0.01*
Trial 2 -- Time	215	203	110	47	2.7	31	0.01*
Trial 3 -- Moves	37	22	24	11	2.9	39	<0.01*
Trial 3 -- Time	172	168	92	33	2.5	30	0.02*
Trial 4 -- Moves	37	22	26	15	2.2	50	0.03*
Trial 4 -- Time	150	117	92	52	2.4	38	0.02*
Total Trials -- Moves	166	62	115	47	3.7	59	<0.01*
Total Trials -- Time	788	616	438	187	2.9	33	<0.01*
WCST							
Perseverative Errors	17	11	8.4	6.4	3.0	24	<0.01*
Nonpersev Errors	15	9.4	9.8	10	1.7	28	0.09
Total Errors	32	19	18	15	2.5	29	0.02*
FRT							
Errors, Right Hand	0.67	1.3	0.30	0.81	1.2	36	0.23
Errors, Left Hand	0.63	1.2	0.24	0.50	1.4	28	0.16
Tactile Perception Test							
Trial 1 -- Time	437	162	324	115	2.9	50	<0.01*
Trial 2 -- Time	272	125	210	111	1.8	49	0.08
Trial 3 -- Time	201	181	121	70	1.8	20	0.09
Total Trials -- Time	894	363	656	268	2.7	49	0.01*
WCST: Wisconsin Card Sorting Test; FRT: Finger Recognition Test							

Table 4
Correlations between corpus callosum volumes and performance on neuropsychological tests

	Tower of Hanoi		WCST		Finger Recognition Test		TPT	
	N= 27		N= 18		N=24		N=18	
	Moves	Time	Total errors		Right	Left	Trials	
Genu	-0.02	0.04	-0.47*		0.23	-0.51*	-0.11	
Rostral body	-0.41	0.05	-0.25		0.29	-0.37	-0.17	
Anterior Body	-0.04	0.14	-0.43		0.26	-0.42*	-0.16	
Posterior Body	-0.19	-0.06	-0.17		-0.50	-0.63*	-0.22	
Isthmus	-0.41*	-0.28	-0.52*		0.02	-0.36	-0.21	
Splenium	-0.26	0.002	-0.25		0.13	-0.49*	-0.06	

WCST: Wisconsin card sorting test; TPT: Tactile perception test; Moves; Total trials/moves; Time: Total trials-time; Right: Errors with right hand; Left: Errors with left hand; Trials: Total trials

* p < 0.05

^ p < 0.05 when controlling for multiple comparisons.