Volumetric Analysis of the Corpus Callosum in Early-Onset Bipolar Disorder

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Introduction: Abnormalities in the area of the corpus callosum (CC) have been reported in magnetic resonance imaging (MRI) studies of adults with bipolar disorder (BPD), including reduced area and absence of typical age-related decline when compared to healthy controls (HC). To date, only one study has evaluated CC area in youths with BPD (Yasar), and found no differences except reduced circularity of the splenium. Here, we use a volumetric parcellation system to extract multiple callosal subregions with functional and connectional relevance, and then correlate these findings with cortical regions to which they are structurally related. We provide a comparison of this volumetric method with that of the more commonly performed cross-sectional area. This work represents the first application of this novel, comprehensive set of callosal measures in this patient population.

Method: MRI scans with 1.5 mm slice thickness were obtained and analyzed from right-handed youths with DSM-IV BPD and HC (group-matched for age and gender) on a 1.5T GE scanner. *Gray and White Matter Segmentation*: Brain images were positionally normalized to overcome variations in head position by using a standard 3-dimensional coordinate system. The image sets were then segmented into gray, white, and CSF tissue classes using a semi-automated intensity contour algorithm for external border definition and signal intensity histogram distributions for delineation of gray-white borders. This technique yielded separate components of neocortex, subcortical gray nuclei, white matter (WM), and ventricular system subdivisions that correspond to the natural tissue boundaries distinguished by signal intensities on T1-weighted images (Filipek). Total cerebral volume **(**TCV) was defined as all gray matter (GM) and WM, and did not include CSF, cerebellum or brainstem. *Parcellation of the neocortex:* The neocortex was divided into 48 parcellation units (PUs) per hemisphere, based on the system described by Rademacher and modified by Caviness. This comprehensive system approximates architectonic and functional subdivisions (Sanides). *White Matter Parcellation & Corpus Callosum Division:* The WM parcellation is an automatic rule-based (i.e. operator-independent) routine following segmentation and GM parcellation. It subdivides cerebral WM into peripheral and deep divisions based upon a set of topographic relationships derived from anatomy and described by Witelson. The CC is divided into seven distinct subregions: rostrum (CC1), genu (CC2), anterior body (CC3), anterior midbody (CC4), posterior body (CC5), isthmus (CC6) and splenium (CC7) (Figure 1). In addition, length and area measurements of the CC and its subdivisions were made based on the midsagittal slice in order to compare with the volumetric findings. *Statistical Analysis:* A series of backward-selection linear regression models were performed on CC1-CC7 and total CC as dependent variables with diagnosis, sex, age, and TCV as predictor variables. Bivariate correlations were tested between significant callosal regions and (1) their connections to cortical (GM) PUs, and (2) clinical measures in the BPD group. All tests were two-tailed with alpha=0.05.

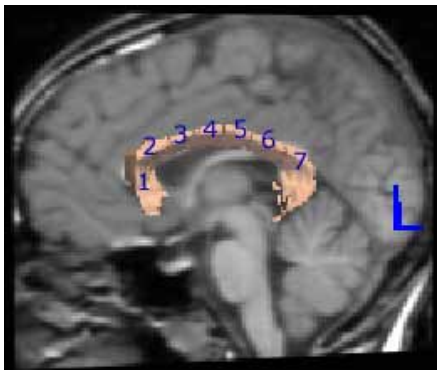

Figure 1: Mid-Sagittal MRI showing CC Subdivisions.

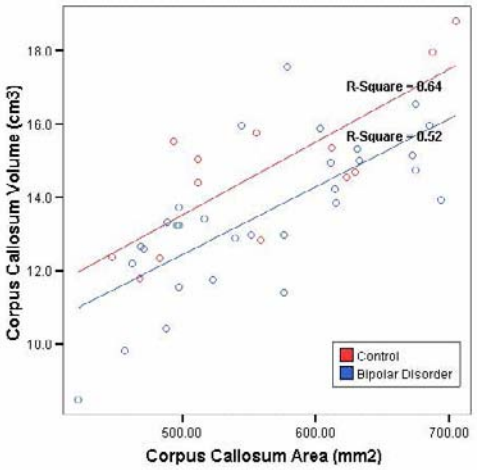

Figure 2: Regression fits of CC Area-Volume Correlations.

Results: Data are presented from 30 youths with BPD (aged 11.3 ± 2.8) and 13 HC (10.8 ± 2.9). *Regression models:* BPD was associated with smaller CC2 and CC5 volumes, while CC7 showed an age-by-diagnosis interaction, with HC aged 12 and older having larger volumes than their BPD counterparts. *Clinical Variables:* In youths with BPD, CC5 and CC7 were positively correlated with current mood stabilizer treatment, and CC5 was negatively correlated with current stimulant treatment. There were no correlations with number of psychoactive medications, or with chlorpromazine equivalent dosages among those (*n*=27) taking antipsychotics. *Cortical Correlations*: In BPD, CC2 volumes correlated significantly with frontal pole and middle frontal gyrus, while CC5 correlated with insular cortex. CC7 correlated significantly with inferior temporal gyrus, temporo-occipital part, lateral occipital cortex, superior division, temporal frontal cortex, posterior division, and temporal occipital fusiform cortex. For HC, no significant correlations were found between CC2, CC5, and CC7 and any associated PU. *Callosal Area Measurements:* Linear regression models were repeated using the traditional cross-sectional area measurements for CC subregions, and no between-group differences were found. The correlation coefficients for the area and volume measurements for each region were moderately strong (mean Pearson *r*=0.58; *p*s<0.05; see Figure 2), and the coefficients of variation (COV) were comparable between the two methods (area: mean COV=0.219; volume: mean COV=0.287).

Conclusions: These findings suggest CC volumetric abnormalities exist in youths with BPD, which may lead to impaired interhemispheric communication between cerebral regions connected by the genu, posterior body, and splenium. The early appearance of CC abnormalities in youths with BPD suggests an underlying neurodevelopmental process in the pathophysiology of BPD. Given that CC differences were detected using volumetric but not cross-sectional area methods suggests that the former is a more sensitive method for evaluating callosal subregions. Further investigations of the CC should include both area and volumetric measurements to further explore the differences in these techniques, and to permit comparisons between prior studies that have reported CC area.

References

Caviness VS et al, 1996. MRI-based topographic parcellation of human neocortex. J Cogn Neurosci 8, 566-88.

Filipek PA et al. 1989. MRI-based morphometry: development and applications to normal controls. Ann Neurol 25, 61-7.

Frazier JA et al. 2005. Cortical gray matter differences identified by structural magnetic resonance imaging in pediatric BPD. Bipolar Disord 7, 555-69.

Makris N et al. 1999. MRI-based topographic parcellation of human cerebral white matter and nuclei II. Neuroimage 9, 18-45.

Meyer JW et al. 1999. MRI-based topographic parcellation of human cerebral white matter. Neuroimage 9, 1-17.

Rademacher J et al. 1992. Human cerebral cortex: localization, parcellation, and morphometry with MRI. J Cogn Neurosci 4, 353-73.

Sanides F, 1971. Functional architecture of motor and sensory cortices in primates in the light of a new concept of neocortex development. In: Noback CR, Montana W, eds. Advances in Primatology. Academic Press, New York, pp 137-208.

Witelson SF, 1989. Hand and sex differences in the isthmus and genu of the human corpus callosum. Brain 112, 799-835.

Yasar AS et al. 2006. MRI study of corpus callosum in children and adolescents with bipolar disorder. Psychiatry Res 146, 83-5.