Increased Structural Connectivity in Corpus Callosum in Adolescent Males With Conduct Disorder

Jibiao Zhang, PhD, Xueling Zhu, PhD, Xiang Wang, MD, PhD, Junling Gao, MD, PhD, Huqing Shi, PhD, Bingsheng Huang, MD, PhD, Weijun Situ, MS, Jinyao Yi, MD, PhD, Xiongzhao Zhu, MD, PhD, Shuqiao Yao, MD, PhD

Objective: Adolescents with conduct disorder (CD) are at high risk for developing adult antisocial personality disorder. However, the underlying neuropathophysiology of CD remains poorly understood. We hypothesized that the microstructure of white matter (WM) of males with CD may differ from that of healthy control subjects (HCs). **Method:** Tract-based spatial statistics (TBSS) and quantitative tractography were used to assess WM microstructural differences between 36 teenaged boys with CD and 33 demographically matched HCs. **Results:** The CD group behavioral scale scores were significantly higher than those of the HCs on the Barratt Impulsivity Scale, the Strength and Difficulties Questionnaire, and the Antisocial Process Screening Device total scales. TBSS revealed that, relative to HCs, the CD group had higher fractional anisotropy (FA) in the corpus callosum (CC) region, bilaterally, including the genu and body of the CC, as well as in some projection fibers in the region of the left anterior coronal radiate and right superior coronal radiate. Tractography confirmed higher FA of fibers passing through the regions with significant differences in the TBSS results. Exploratory analysis revealed that impulsivity associated positively with the FA of these fibers in the CD group. **Conclusions:** Maturation of WM microstructure in CD subjects differed from that in HCs, mainly in the CC. The abnormal maturation of WM structures may play an important role in the impulsivity and aggression of teenagers with CD. J. Am. Acad. Child Adolesc. Psychiatry, 2014;53(4):466–475. **Key Words:** conduct disorder (CD), white matter (WM), diffusion tensor imaging (DTI), tract-based spatial statistics (TBSS), impulsivity

Conduct disorder (CD) is an impulse-control–related disorder characterized by impulsivity, aggression toward people or animals, property destruction, deceptiveness or theft, and serious rule violation before 18 years of age.[1] CD has been reported to occur in about 16% of otherwise normal preadolescents[2] and may co-exist with other disorders, such as attention-deficit/hyperactivity disorder (ADHD),[3] oppositional-defiant disorder (ODD),[4] and substance abuse.[5]

A few previous studies have documented abnormalities in the structure of CD brains, such as reduced prefrontal cortex (PFC), anterior insular, and amygdalar volume,[6-9] reduced thickness and gray matter (GM) density of the cingulate cortex,[8] and reduced cortical folding of anterior brain regions.[10] Consistent with the notion of there being functional dysregulation in CD, some functional imaging studies have shown pronounced deactivation of the anterior cingulate cortex (ACC) and reduced functional connectivity between the rostral ACC and the amygdala.[11-13] Others have reported dysfunction of the orbitofrontal cortex (OFC) in CD.[14,15] Such findings are consistent with evidence from structural studies. Indeed, converging evidence points to the involvement of white matter (WM) abnormalities in psychiatric and behavioral disorders such as ADHD,[16] antisocial personality disorder (APD),[8] and schizophrenia.[17] The etiology of conduct problems may not be attributable solely to variations within brain regions, but may also involve the fiber pathways that connect them.

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Diffusion tensor imaging (DTI) is an advanced noninvasive technique used to examine subtle changes in WM microstructural organization of major neuronal fiber pathways.[18] There have been only 2 studies that have focused exclusively on WM microstructure in CD. In 1 study, the researchers found abnormal WM microstructure in the left uncinate fasciculus (UF), connecting the lateral OFC to the anterior temporal lobes,[19] and in the other, the researchers reported an abnormality in the right UF characterized by higher fractional anisotropy (FA) and lower radial diffusivity (RD) than in healthy controls (HC).[20,21] In addition, there have been 2 studies reported that focused mainly on disruptive behavior disorder (DBD, composed of both CD and ODD).[13,22] Wang *et al.* documented reduced FA in the CC and bilateral anterior corona radiata (ACR) in DBD brains.[22] However, Finger *et al.* did not find any significant differences in WM microstructure between adolescents with DBD versus HCs.[13]

The aforementioned DTI studies had several limitations in terms of sample constitution and analysis methodology. First, the samples in the DBD studies were heterogenous in that both groups were made up of males and females with CD or ODD, with or without ADHD or psychopathic traits.[13,22] To enable clear interpretation, CD and ODD, which have distinct features, should be analyzed separately from each other, as well as from ADHD.[4] In addition, maturation of WM may differ temporally between males and females,[23] and such differences could have led to the negative finding by Finger *et al.*[13] Second, the work by Sarkar *et al.*[20] was based on Craig *et al.*'s reports[24] about APD in adults, and, like the studies by Craig *et al.*, they used region-of-interest (ROI) analysis with prior knowledge of APD. ROI analysis is a hypothesis-driven method of regional brain analysis but is sensitive only to that specific region.[25] Traditional ROI methodology is focused mainly on the selection of specific areas that may not be very representative of fiber delineations at the macrostructural level.[26] In contrast, tractography can provide macroscopic information of anatomical fiber pathways in vivo, rather than assessments of limited ROIs.[26] The traditional voxel-based analysis (VBA) method is an operator-independent and data-driven analysis technique applied to the whole brain without an a priori hypothesis, but it has been criticized for smoothing issues.[25] In addition, most of the studies mentioned above, with the exception of the study by Sarkar et al.,[20] involved 15 or fewer individuals with CD.

Overall, differences in WM between CD and HC brains remain poorly understood. There is a need to clarify these issues in studies that have large, homogenous samples and that use more prudent analysis methods. TBSS is based on a nonlinear registration algorithm and on an alignment invariant tract representation in which the data can be projected to and de-projected from the "mean FA skeleton"; thus, data are less susceptible to anatomical deformations as compared with a voxel-based morphometry (VBM) approach.[27] Here we used TBSS together with tractography in a large sample of adolescent boys to overcome the weaknesses of traditional VBA and ROI methods. We hypothesized that there would be significant WM aberrations beyond the UF in the CD group relative to HCs.

METHOD

Sample

A total of 36 male adolescents with CD were recruited from outpatient clinics affiliated with the Second Xiangya Hospital of Central South University in Changsha, Hunan, China. To constitute the HC group, 33 age-, gender-, and IQ-matched volunteers were recruited from a regular school in the same city. The study was approved by the Ethics Committee of the Second Xiangya Hospital of Central South University. All subjects and their parents were made aware of the purpose of the study and gave informed written consent.

Diagnoses of CD were made independently by 2 well-trained psychiatrists based on the Structured Clinical Interview for the *DSM-IV-TR* Axis I Disorders–Patient Edition (SCID-I/P).[28] Psychiatrists rated each symptom item as absent (0), subclinical (1), or clinically present (2), based on the SCID-I/P users' guide, which has been translated into Chinese and adapted for use in both patients and healthy individuals.[29] We did not diagnose CD based solely on information from the adolescent per se, but rather also interviewed a parent of each subject to obtain detailed information. Specifically, it was up to the psychiatrists to make the final judgment if the information that the patients and parents offered was not consistent.

For HC recruitment, 2 investigators gave a detailed explanation of the aim and procedure of this research to the headmaster and teachers of the school, in person. Upon obtaining permission from the school administration, students who matched the CD subjects' ages and genders were selected randomly from class rosters. Volunteers who agreed to be interviewed by the psychiatrists were subjected to an SCID-I/P and