



Sex differences in abnormal white matter development associated with conduct disorder in children



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ABSTRACT

Associations between white matter pathway abnormalities and antisocial personality disorder in adults are well replicated, and there is some evidence for an association of white matter abnormalities with conduct disorder (CD) in adolescents. In this study, white matter maturation using diffusion tensor imaging (DTI) was examined in 110 children aged 10.0 ± 0.8 years selected to vary widely in their numbers of CD symptoms. The results replicated age-related increases in fractional anisotropy (FA) found in previous studies. There was not a significant association between the number of CD symptoms and FA, but CD symptoms were found to be significantly associated with greater axial and radial diffusivity in a broad range of white matter tracts, particularly in girls. In complementary analyses, there were similar significant differences in axial and radial diffusivity between children who met diagnostic criteria for CD and healthy children with no symptoms of CD, particularly in girls. Brain structural abnormalities may contribute to the emergence of CD in childhood, perhaps playing a greater role in girls.

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1. Introduction

Conduct disorder (CD) is a disorder that often emerges in childhood, characterized by aggressive and antisocial behavior, which creates considerable societal cost (Romeo et al., 2006). It has been argued that amygdala and orbitofrontal cortex dysfunction in adolescents with CD and psychopathic traits disrupts emotion-based decision-making, including moral decision making (Viding, 2004; Kiehl, 2006; Decety et al., 2009; Lockwood et al., 2013; Decety and Cowell, 2014).

DTI can measure the microstructural integrity of white matter, quantified indirectly by fractional anisotropy (FA). Furthermore, distinctions in two aspects of white matter integrity can be made by measuring diffusion that is parallel (axial diffusivity) and perpendicular (radial diffusivity) to axonal tracts. Radial diffusivity has been used to assess myelination levels because it correlates with demyelination (Song et al., 2002, 2005; Klawiter et al., 2011). Conversely, axial diffusivity indexes axonal integrity (Budde et al., 2009). White matter abnormalities have consistently been found in adults with psychopathy or antisocial personality disorder (Sundram et al., 2012). In particular, antisocial adults, when

compared with healthy controls, exhibit reduced FA in the uncinate fasciculus (UF), which may indicate abnormally low structural connectivity of the amygdala and ventromedial prefrontal cortex, in forensic inpatients (Craig et al., 2009; Sundram et al., 2012) and incarcerated psychopaths (Motzkin et al., 2011; Hoppenbrouwers et al., 2013).

Studies of the UF in adolescents have yielded less consistent results. For instance, one study found no FA differences in the UF between healthy children and children with CD and other disruptive behavior disorder diagnoses (Finger et al., 2012). A difference study of 17–20 year olds found greater rather than lower FA in the UF in males with childhood-onset CD relative to healthy male controls (Passamonti et al., 2012). More recently, a study of male adolescents with aggressive CD and healthy male controls also found greater FA and lower radial diffusivity in the left UF in youth with CD (Sarkar et al., 2013). However, we are aware of no studies that have examined the association between CD and white matter abnormalities in childhood.

This gap in the literature is important for two reasons. First, CD that is present in childhood appears to be more impairing, persistent, and comorbid with attention-deficit/hyperactivity disorder (ADHD) (Moffitt et al., 1996). Second, previous studies may have ignored an important period of development. Normal development is characterized by increased total cortical white matter into early adulthood (Paus et al., 2001), and includes nonlinear increases in FA and nonlinear decreases in mean diffusivity from

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young childhood into an individual's twenties (Lebel and Beaulieu, 2011). It is entirely possible that antisocial personality disorder is associated with decreased FA in adulthood because of a disrupted developmental trajectory, characterized by white matter over-development early in life. Thus, the current study sought to characterize the association of CD with white matter development during childhood (9–11 year olds).

Furthermore, because there are marked sex differences in the prevalence of CD that must be understood to fully understand the nature of CD (Rutter et al., 2003; Moffitt et al., 2008), and because there are sex differences in brain development (Lenroot et al., 2007), special attention was paid in the current work to the interaction between CD and gender. The “gender paradox” hypothesis states that, to overcome gender-specific protective factors, persons of a given sex with a mental disorder that is less prevalent in that sex must exhibit greater dysfunction (Eme, 1992) and more comorbidity with other mental disorders (Loeber and Keenan, 1994). Thus, we will test for interactions with gender in all analyses.

2. Methods

2.1. Participants

A diverse sample of 110 children (10.0 ± 0.8 years; 53 males, 57 females; 49 White, 61 African American) were recruited using extreme groups sampling (Preacher et al., 2005). Families were recruited from both outpatient child mental health clinics (using flyers calling for children with behavior problems) and pediatric well-visit waiting rooms (using a flyer calling for well-behaved children). Based on a telephone screening interview, children were recruited into two strata at high or low risk for meeting DSM-IV diagnostic criteria for CD until approximately equal numbers were recruited in each stratum. In addition, within each of these two strata, children were preferentially recruited in approximately equal numbers of white girls, white boys, African American girls, and African American boys. The white stratum included both Hispanic and non-Hispanic white children. Parents and children were sequentially administered the DISC Predictive Scale (DPS) for CD, which predicts the full diagnosis of CD with high sensitivity and specificity (Lucas et al., 2001). The DPS consists of 8 “stem questions” from the reliable and valid Diagnostic Interview Schedule for Children (DISC-IV) CD module (Shaffer et al., 2000). Eight DPS questions refer to symptoms of CD and one to school expulsion. Children were selected for the high-risk stratum if the parent alone endorsed 2 or more DPS items, the child alone endorsed 3 or more items, or the parent and child collectively endorsed 3 or more separate items. Children were selected for the low-risk stratum if neither informant endorsed any DPS CD items. To spread the distribution of CD symptoms, children with intermediate scores of 1 on the DPS were not included in the study to allow the recruitment of children with more CD symptoms.

To disentangle severity of CD symptoms from the child's sex and race-ethnicity, selection continued until equal numbers of high- and low-risk children of each sex and race-ethnic category agreed to participate. Exclusion criteria included presence of a pervasive developmental disorder, history of head trauma with loss of consciousness exceeding 15 min, and safety contraindications for neuroimaging. On the day of scanning, the full DISC-IV (Shaffer et al., 2000) was administered in separate rooms to the primary caregiver and to the child by trained interviewers, including the module covering CD symptoms during the last 12 months. DTI data were obtained for 53 children with no symptoms of CD (27 males; 33 African American) and 57 children with at least one symptom of CD (26 males; 28 African American). All participants gave assent, and informed written consent was obtained from the child's parent or legal guardian. The study was approved by the Internal Review Board at the University of Chicago.

Scanning parameters. Images were acquired on a 3T Philips Achieva Quasar scanner equipped with an 8-channel SENSE head coil at the Brain Research Imaging Center at the University of Chicago. A single-shot echo planar imaging pulse sequence was used (TR/TE=12,572 ms/55 ms; 80 slices; voxel size=2 mm³; matrix size=112 × 112) with one zero-weighted image ($b=0$ s/mm²) and 32 diffusion sensitizing orientations ($b=1000$ s/mm²).

Diffusion-weighted images were processed and analyzed using the FMRIB Software Library v5.0 (FSL) (Jenkinson et al., 2012). First, images were skull-stripped (Smith, 2002) and head movement and eddy current corrections were performed. Next, fractional anisotropy (FA) images were calculated by fitting tensors to each voxel using FDT. Statistical analysis was then performed on the FA data using Tract-Based Spatial Statistics (TBSS) (Smith et al., 2006), using default parameters. Individual subjects' FA images were coregistered to standard space using a non-linear b-spline warp. These aligned images were then averaged and thresholded at

Table 1

Demographic characteristics of and the percent prevalence of each conduct disorder symptom as a function of the total number of conduct disorder symptoms in the 110 scanned children included in the analyses.

Number of CD symptoms	0	1	2	3	4	5	6+
<i>N</i>	53	18	18	5	4	7	5
<i>Demographic characteristics</i>							
Age (years)	9.9	10.3	9.9	9.8	10.0	10.3	9.8
Sex (% female)	50.9	44.4	66.7	20.0	100.0	42.9	40.0
<i>Race-ethnicity</i>							
%Afr-Am	52.8	50.0	66.7	60.0	25.0	57.1	80.0
%Hispanic	5.7	5.6	11.1	20.0	0.0	14.3	20.0
%Mother HS graduate	90.6	66.7	72.2	60.0	100.0	100.0	100.0
<i>Child's CD symptoms</i>							
Theft without confrontation	0.0	50.0	72.2	80.0	75.0	85.7	60.0
Vandalism	0.0	22.2	38.9	60.0	75.0	85.7	100.0
Bullying	0.0	11.1	16.7	20.0	100.0	71.4	100.0
Lying to con	0.0	5.6	27.8	20.0	75.0	71.4	80.0
Using a weapon	0.0	0.0	16.7	0.0	25.0	57.1	100.0
Starting physical fights	0.0	0.0	22.2	20.0	25.0	14.3	100.0
Cruel to people	0.0	0.0	0.0	40.0	0.0	42.9	80.0
Cruel to animals	0.0	5.6	0.0	60.0	0.0	28.6	20.0
Out late without permission	0.0	5.6	5.6	0.0	0.0	0.0	20.0
Theft with confrontation	0.0	0.0	0.0	0.0	25.0	14.3	20.0
Breaking and entering	0.0	0.0	0.0	0.0	0.0	14.3	0.0
Truancy	0.0	0.0	0.0	0.0	0.0	14.3	0.0

Note: CD=conduct disorder symptoms reported by parent and youth; no children were reported to engage in running away from home overnight, firesetting, or forced sex; children with 3 or more CD symptoms were said to meet diagnostic criteria for CD; children with 1 or 2 symptoms were said to exhibit subthreshold CD.

0.2 to create a mean FA skeleton onto which individual FA data were projected. Axial diffusivity (the primary diffusion eigenvariate) and radial diffusivity (average of secondary and tertiary eigenvariates) were also calculated and projected onto the same skeleton.

The association between CD and white matter integrity was tested using two complementary strategies within the same analytic framework. In the first strategy, we measured CD by counts of the number of CD symptoms. This was done because dichotomous classifications of mental disorders may be less biologically valid (Craddock and Owen, 2007) and dimensional analyses are often better suited to hypothesis testing (Kraemer et al., 2004). In the second strategy, we used DSM-IV criteria for the diagnosis of CD to conduct group comparisons.

2.2. Analyses of counts of CD symptoms

Three general linear models were used to estimate the influence of age, gender, race, number of CD symptoms, the gender-by-CD interaction, and race-by-CD symptoms interaction on FA, radial diffusivity, and axial diffusivity of the skeleton-projected data. In addition to these predictor variables of interest, each model also included maternal completion of high school as a covariate of no interest. This was included because it is robustly associated with the child's tested intelligence (Edwards and Roff, 2010; Bornstein et al., 2013; Ghassabian et al., 2014). The FSL function RANDOMISE (Winkler et al., 2014) was used to perform non-parametric statistical analyses, in which 5000 permutations were conducted to estimate the actual null distribution for comparison to obtained test statistics for significant positive and negative effects of each predictor variable. Threshold-Free Cluster Enhancement (TFCE) was used, rather than voxel-based thresholding, and corrected for multiple comparisons with family-wise error. All reported statistics are FWE-corrected $p < 0.05$. For viewing purposes, statistical images were “thickened” and are shown in radiological convention.

2.3. Analyses of the diagnosis of CD

To complement the analyses of symptom counts we also compared three nominal groups in planned comparisons: met DSM-IV criteria for CD ($n=39$), subthreshold CD (one or two symptoms of CD; $n=18$), and healthy control (HC) children with no symptoms of CD ($n=53$) groups. The same covariates and methods were used in these comparisons as in the analyses of symptom counts.

3. Results

Demographic characteristics of the scanned sample are shown

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