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White Matter Microstructure in Youths With Conduct Disorder: Effects of Sex and Variation in Callous Traits

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Objective: Studies using diffusion tensor imaging (DTI) to investigate white matter (WM) microstructure in youths with conduct disorder (CD) have reported disparate findings. We investigated WM alterations in a large sample of youths with CD, and examined the influence of sex and callous-unemotional (CU) traits.

Method: DTI data were acquired from 124 youths with CD (59 female) and 174 typically developing (TD) youths (103 female) 9 to 18 years of age. Tract-based spatial statistics tested for effects of diagnosis and sex-by-diagnosis interactions. Associations with CD symptoms, CU traits, a task measuring impulsivity, and the impact of comorbidity, and age- and puberty-related effects were examined.

Results: Youths with CD exhibited higher axial diffusivity in the corpus callosum and lower radial diffusivity and mean diffusivity in the anterior thalamic radiation relative to TD youths. Female and male youths with CD exhibited opposite changes in the left hemisphere within the internal capsule, fornix, posterior thalamic radiation, and uncinate fasciculus. Within the CD group, CD symptoms and callous traits exerted opposing influences on corpus callosum axial diffusivity, with callous traits identified as the unique clinical feature predicting higher axial diffusivity and lower radial diffusivity within the corpus callosum and anterior thalamic radiation, respectively. In an exploratory analysis, corpus callosum axial diffusivity partially mediated the association between callous traits and impulsive responses to emotional faces. Results were not influenced by symptoms of comorbid disorders, and no age- or puberty-related interactions were observed.

Conclusion: WM alterations within the corpus callosum represent a reliable neuroimaging marker of CD. Sex and callous traits are important factors to consider when examining WM in CD.

Key words: conduct disorder, callous-unemotional traits, diffusion tensor imaging (DTI), sex differences, FemNAT-CD

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Conduct disorder (CD) is characterized by aggressive, antisocial, and oppositional/defiant behaviors during childhood and adolescence,[1] as well as impairments across social, cognitive, and affective domains.[2] Meta-analytic evidence from functional (fMRI) and structural (sMRI) MRI studies has shown abnormal neural responses[3] and volume reductions[4] across a number of cortical and subcortical regions critical for emotion processing and regulation, decision making, executive functions, and empathy. However, diffusion tensor imaging (DTI) findings on white matter (WM) microstructure in youths with antisocial behavior have been inconsistent in both the nature and loci of reported effects.[5] Methodological factors, as well as demographic and clinical features of the samples, may have contributed to the inconsistent findings and lack of replication.[5]

The current study used DTI to investigate WM microstructure in the largest sample of female and male youths with CD recruited to date, and compared them to age- and puberty-matched, typically developing (TD) female and male youths. Tract-based spatial statistics (TBSS)[6] were used to examine WM microstructure at the whole-brain level and within specific regions-of-interest (ROIs). We adopted this approach because we had a priori hypotheses regarding the loci of expected group differences, and wanted to compare our results to those in existing DTI literature on CD in which both approaches have been used. However, we also sought to identify previously undetected

effects owing to our large and mixed sex sample. To measure diffusion within WM tracts, fractional anisotropy (FA) was computed, reflecting differences in microstructural properties such as axon density and degree of myelination.[7] FA is a function of axial diffusivity (AD) and radial diffusivity (RD) values, such that FA increases when AD increases and/or RD decreases, and vice versa. When observing changes/differences in FA, the changes in AD and/or RD can help with the biological interpretation. For example, greater axon density will manifest as increased FA and decreased RD. Axonal breakdown will lead to decreased FA and decreased AD, whereas demyelination will show up as decreased FA and increased RD.[7] Mean diffusivity (MD) is the rate of diffusion averaged over all orientations and is thought to provide a marker of neuronal damage in cell bodies and axonal fibers.[8] We used these four indices to characterize differences in microstructure across WM tracts between CD and TD groups.

The primary aim of the study was to test for effects of CD diagnosis on these DTI indices. Recent studies[9-13] have reported increased FA or AD within the uncinate fasciculus and/or corpus callosum in youths with CD compared to TD youths. Lower RD within the uncinate fasciculus[12] and the corpus callosum[13] has been reported in male youths with CD. Finally, decreased MD within the right uncinate fasciculus (defined as an ROI) was also reported for female youths with CD[11] compared to TD controls. As such, we predicted higher FA or AD and reduced RD or MD (believed to reflect increased microstructural integrity[7]) within the uncinate fasciculus and corpus callosum in youths with CD compared to TD youths. However, we note that several studies have also reported the opposite pattern of results (ie, reduced FA and AD, and increased RD and MD) across a number of other WM tracts.[14,15] Therefore, we also predicted differences in FA, AD, RD, and MD within other association, commissural, projection, and thalamic tracts but did not make predictions regarding the direction of these effects.

Our second aim was to test for sex-by-diagnosis interactions. Given known sex differences in the CD phenotype,[16] its etiology,[17] as well as rates of WM maturation in TD youths,[18] WM diffusivity may differ between female and male youths with CD. To date, however, most studies on CD have focused only on male youths[9,10,13,19] or female youths alone.[11] Three studies[12,14,20] have included mixed-sex samples but were underpowered to test for sex-by-diagnosis interactions, thereby contributing to the inconsistencies in the literature. These data highlight the need to investigate similarities across the sexes as well as testing for potential sex-specific effects.[5] In this context, we made no a priori hypotheses regarding differences between male and female youths with CD in terms of the location or direction of changes across the DTI indices.

Our third aim was to examine the impact of callous-unemotional (CU) traits (ie, reduced empathy and guilt, combined with shallow emotions and the callous use of others; see the "limited prosocial emotions" specifier for CD in *DSM-5*[1]) on WM alterations associated with CD. Indeed, several studies[14,20] have failed to account for heterogeneity within CD in relation to CU traits, which might have contributed to inconsistent findings across studies. Two recent studies showed that CU traits influenced the pattern of WM differences in youths with CD.[21,22] Furthermore, fMRI and sMRI studies have revealed that the unique variance associated with CD symptoms and CU traits shows opposing relationships with neural activity and gray matter volume in cortical[23] and subcortical structures.[24,25] Interestingly, two recent fMRI studies of empathy in youths reported that the callous subcomponent of CU traits was the strongest predictor of group differences in neural response[26] and connectivity.[27] Hence, we hypothesized that CD symptoms and CU traits (or the callous subcomponent) might show opposing associations with WM microstructure in youths with CD.

In addition to our three central aims, we conducted two follow-up analyses and one exploratory analysis. First, disorders that frequently co-occur with CD (eg, attention-deficit/hyperactivity disorder (ADHD), mood and anxiety disorders and substance abuse) are also associated with WM alterations in the corpus callosum and the uncinate fasciculus.[28-31] We therefore systematically assessed the impact of symptoms of comorbid disorders in our sample, predicting that group differences in WM microstructure might be partly explained by these symptoms. Second, given the large age range of our sample (9−18 years) and suggestions that relationships between CD and WM may differ by age[5,9,20] or pubertal stage,[32] we tested for age-by-diagnosis and puberty-by-diagnosis interactions. Finally, given that self-reported impulsivity has been shown to positively correlate with FA within the corpus callosum in CD youths,[13] we conducted an exploratory analysis aiming to extend this finding by relating WM microstructure to performance on an objective, laboratory-based measure of impulsivity: the emotional Go/No-Go task.[33] We hypothesized that in youths with CD, corpus callosum FA or AD would be positively correlated with impulsive responses on this task.

METHOD

Participants and Measures

A total of 124 (59 female) youths with CD and 174 (103 female) TD youths 9 to 18 years of age were included as

part of the Neurobiology and Treatment of Adolescent Female Conduct Disorder study (FemNAT-CD), a European multi-site study investigating sex differences in CD (https://www.femnat-cd.eu/). A total of 30 participants (16 with CD) were included in a previous DTI study comparing CD and TD female youths.[11] However, excluding those participants (n = 30) did not alter the main effects (data available upon request). Participants and their parents or main caregivers were interviewed separately using the Kiddie-Schedule for Affective Disorders and Schizophrenia—Present and Lifetime version (K-SADS-PL).[34] Interviews were conducted by trained staff at each site to assess for CD and other common comorbid disorders using *DSM-IV-TR* criteria.[35] Further details regarding participant demographics, socioeconomic status, inclusion/exclusion criteria, and interrater reliability of diagnoses are provided in Supplement 1, available online.

CU traits were assessed using the parent-report Inventory of Callous–Unemotional traits (ICU),[36] a standardized measure including callous ($\alpha = 0.74$), uncaring ($\alpha = 0.79$), and unemotional subscales ($\alpha = 0.85$). An estimate of full-scale IQ was obtained using the two-subtest (vocabulary and matrix reasoning) version of the Wechsler Abbreviated Scale of Intelligence[37] or the same subtests from the Wechsler Intelligence Scale for Children.[38] Participants were classified as either pre/early or mid/late/post pubertal using the Pubertal Development Scale.[39] Across all sites, written informed consent/assent was obtained from all participants and their parents according to site-specific ethical requirements (see Supplements 2 and 3, available online, for information on imputation procedures for missing data and ethical approvals).

Emotional Go/No-Go Task

Impulsivity was operationalized using the number of commission errors (false-alarm rates expressed as a percentage) on an emotional Go/No-Go task[33] (see Supplement 4 and Figure S1, available online, for further details regarding task design, response coding, convergent validity check, and testing procedures).

DTI Data Acquisition and Pre-processing

Diffusion-weighted images were acquired across four sites (see Tables S1 and S2, available online) and subsequently pre-processed using the FMRIB Software Library (FSL) diffusion toolkit[40] (see Supplements 5 and 6, available online, for details regarding site qualification procedures, acquisition parameters, image processing, and movement and distortion correction).

Statistical Analyses

We used analyses of variance (post hoc pairwise comparisons with Bonferroni correction, $p < .05$) and χ^2 tests to compare diagnostic groups (CD versus TD) on demographic and clinical variables (Table 1 and Supplement 1, available online).

Within FSL,[40] separate general linear models with a two (diagnosis: CD versus TD) by two (sex: male versus female) factorial design were fitted to the FA, AD, RD, and MD diffusion indices to test for main effects of diagnosis and sex-by-diagnosis interactions. Age and IQ were included as covariates of no interest (see Supplement 7, available online, for results of analyses without including IQ as a covariate of no interest and for an IQ-matched subsample). Additional factorial analyses were conducted entering mean-centered age as continuous covariates into the GLM. This enabled investigation of age-related differences between CD and TD youths (age-by-diagnosis interactions) as well as potential interactions with sex (age-by-diagnosis-by-sex interactions). Finally, in separate analyses, puberty scores were included as continuous covariates enabling investigation of potential puberty-related differences between youths with CD and TD youths and potential interactions with sex. For the models testing for age and puberty effects, IQ was included as a covariate of no interest (see Supplement 8, available online, for further details). Details of how between-site variability was accounted for within all statistical models are provided in Supplement 9, available online. All analyses (whole-brain and region-of-interest) were also conducted on mode of anisotropy, but no significant effects were observed (see Table S3).

At a whole-brain level, areas showing significant differences were identified using threshold-free cluster enhancement (TFCE; $p < .05$, familywise error [FWE] corrected for multiple comparisons; 5,000 permutations). We note that for our weakest effect (the observed sex-by-diagnosis interaction in the left internal capsule), we reran the analysis with 10,000 permutations to ensure that the p value still fell within the 95% CIs around $\alpha = 0.05$ of 0.0459–0.0544.

Two WM atlases[41,42] were used to label significant results. We also tested for differences in FA, AD, RD and MD within specific fiber tracts previously implicated in CD.[5] These masks were created using the JHU-ICBM-DTI-81 WM atlas[41] and included association, commissural, and projection pathways identified by Waller *et al.*[5] (see Table S4, available online, for full list of tracts). The same threshold was used for the voxelwise permutation-based ROI analyses (see also Table S3, available online, for false discovery rate–corrected and uncorrected ROI

TABLE 1 Demographic and Clinical Characteristics of Youths With Conduct Disorder (CD) and Typically Developing (TD) Participants

									Statistical analysis					
	Female Youth CD (n = 59)		Female Youth TD (n = 103)		Male Youth CD (n = 65)		Male Youth TD (n = 71)		Group (CD/TD) Effects		Sex (M/F) Effects		Group × Sex Interactions	
Characteristic/Variable	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	***F***	***p***	***F***	***p***	***F***	***p***
Age (y)	15.1	1.9	14.1	2.6	14.7	2.2	14.5	2.4	3.5	.07	<1	.94	1.4	.24
Full Scale IQ	97.6	13.1	102.5[a]	11.0	93.4[b]	11.8	102.5[a]	10.6	26.4	.001	2.3	.13	2.3	.13
SES	−0.4[a]	0.8	0.09	0.9	−0.17	0.6	0.24[b]	0.7	13.5	.001	2.37	.13	0.1	.7
Lifetime CD symptoms	5.5[a]	2.5	0.2[b]	0.4	6.2[a]	2.5	0.3[b]	0.6	814.5	.001	4.3	.04	2.2	.14
Lifetime ODD symptoms	6.1[a]	2.7	0.2[b]	0.6	5.8[a]	2.8	0.1[b]	0.4	742.7	.001	<1	.6	<1	.7
Lifetime ADHD symptoms	6.1[b]	6.3	0.1[c]	0.3	9.4[a]	6.4	0.1[c]	0.2	241.9	.001	12.1	.001	12.0	.001
Lifetime GAD symptoms	1.3[a]	1.7	0.1[c]	0.4	0.8[b]	1.4	0.04[c]	0.2	63.1	.001	7.3	.007	4.4	.04
Lifetime MDD symptoms	8.8[a]	7.9	0.4[c]	1.9	5.0[b]	6.4	0.2[c]	1.0	135.6	.001	12.4	.001	10.6	.001
Total ICU	32.5[b]	12.6	16.4[c]	8.0	37.5[a]	12.7	19.3[c]	7.8	202.3	.001	10.8	.01	<1	.4
Callous subscale of ICU	11.3[b]	6.2	4.2[c]	3.4	13.7[a]	6.5	4.7[c]	2.5	202.6	.001	6.9	.01	2.8	.1
Uncaring subscale of ICU	14.1[a]	5.0	7.9[b]	4.3	15.8[a]	5.0	8.9[b]	4.3	140.9	.001	6.1	.01	<1	.5
Unemotional subscale of ICU	7.2[a]	3.9	4.2[b]	2.5	8.0[a]	3.2	5.6[b]	2.9	52.5	.001	9.6	.01	<1	.5
Current *DSM-IV* Diagnoses	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	χ^2	***p***	χ^2	***p***	χ^2	***p***
ODD	41	70	0	0	48	74	0	0	178.1	.001	3.5	.06	<1	.6
ADHD	26[b]	44	0	0	39[a]	60	0	0	123.6	.001	11.1	.01	5.3	.02
GAD	12[a]	20	0	0	4[b]	6	0	0	23.7	.001	2.9	.09	5.5	.02
MDD	22	37	0	0	18	28	0	0	64.8	.001	<1	.9	1.3	.3
Alcohol abuse	2	3	0	0	1	2	0	0	4.3	.05	<1	.7	5.3	.2
Drug abuse (cannabis)	3	5	0	0	4	6	0	0	10.1	.01	<1	.5	<1	.8
Medication	17	29	0	0	13	20	0	0	43.3	.001	<1	.7	1.3	.3
PDS	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	χ^2	***p***	χ^2	***p***	χ^2	***p***
Pre/Early (stages I and II)	3	5	7	7	12	18	17	24	6.5	.2	31.2	.001	3.0	.6
Mid/Late/Post (stages III–V)	56[b]	95	96[a]	93	53[b]	82	54[b]	76						
Age of onset[d]														
Childhood	17	33	0	0	34	54	0	0			2.7	.1		
Adolescent	27	53	0	0	28	44	0	0						
Missing	7	14	0	0	1	2	0	0						
Handedness														

(*continued*)

TABLE 1 Continued

PDS	n	%	n	%	n	%	n	%	χ^2	p	χ^2	p	χ^2	p
Right	49	83	91	88	51	78	66	93	4.9	.08	<1	.9	3.9	.1
Left	4	7	11	11	11	17	3	4						
Ambidextrous	3	5	0	0	1	1.5	1	1						
Missing	3	5	1	0.9	2	3	1	1						

Note: Where appropriate, group (CD/TD) and sex (male/female) differences, sex-by-diagnosis interactions, and subsequent post hoc tests were computed using analyses of variance and χ^2 tests. Means with different superscript letters (a, b, and c) denote significant differences (pairwise comparisons with Bonferroni-adjusted p values are shown, p < .05). In addition to the commonly comorbid disorders currently listed in Table 1 that were present in our sample, the following disorders were also screened for as part of the K-SADS assessment: psychosis, mania, schizophrenia, autism spectrum disorder, bipolar disorder, panic disorder, separation anxiety disorder, phobia (simple/social/agoraphobia), obsessive compulsive disorder, posttraumatic stress disorder, enuresis, encopresis. Further information regarding the presence of those disorders in our sample is available upon request. Diagnoses of CD and comorbid disorders were made using the Kiddie-Schedule for Affective Disorders and Schizophrenia–Present and Lifetime version. ADHD = attention-deficit/hyperactivity disorder; F = female; GAD = generalized anxiety disorder; ICU = Inventory of Callous-Unemotional traits; M = male; MDD = major depressive disorder; ODD = oppositional defiant disorder; PDS = Pubertal Development Scale; SES = socioeconomic status.

[d]*Not including the 10 participants with ODD plus CD symptoms.*

results). Contrastwise FA, AD, RD, and MD values at a whole-brain and ROI level were extracted using the *fslmeants* tool in FSL, enabling cluster-based statistical analysis and multiple regression analyses. Cohen's *d* effect sizes based on group means and standard deviations are reported for the main effects and sex-by-diagnosis interactions.

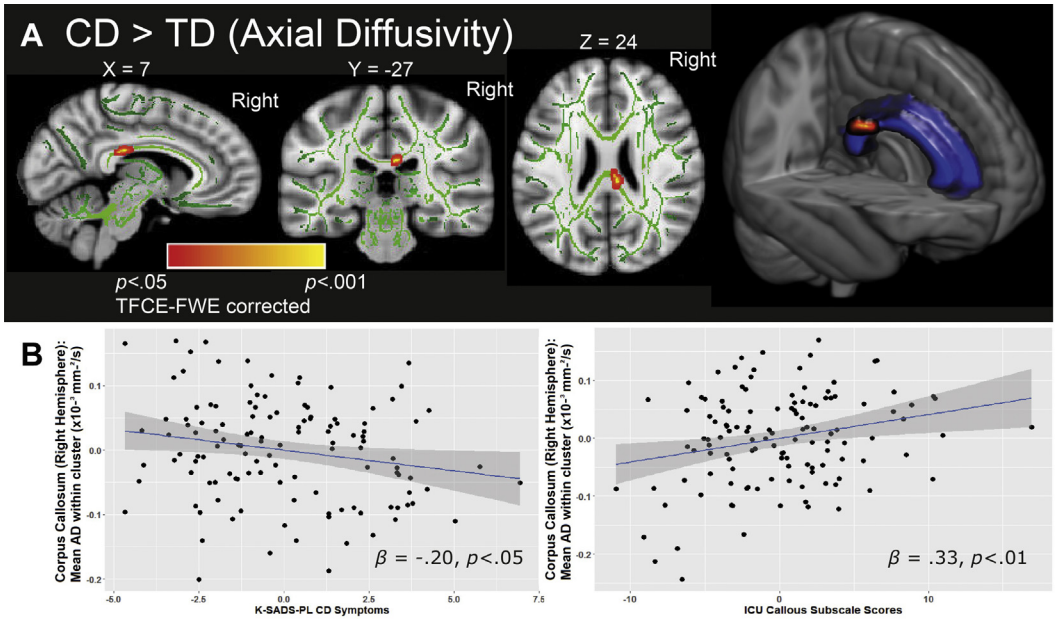
Consistent with previous work,[25] bivariate correlations (see Table S5, available online) and regression analyses were conducted for the CD group only within regions showing main effects of diagnosis or sex-by-diagnosis interactions. Multiple regression analyses were conducted in two steps to investigate the association between significant clusterwise differences and dimensional measures. First, CD symptoms (derived from the K-SADS-PL[34]) and CU traits (ICU total score) or ICU subscales (Callousness, Uncaring, Unemotional) were entered. Second, symptom counts of comorbid ADHD, oppositional defiant disorder, generalized anxiety disorder and major depressive disorder, alcohol use/abuse and substance use/abuse, as well as a measure of handedness, were added to assess their influence. Zero-order correlation coefficients were calculated to estimate associations between WM differences observed between groups (CD and TD) and impulsivity, as measured using the emotional Go/No-Go task.[33]

RESULTS

Whole-Brain Results

Youths with CD exhibited significantly higher AD (p = .02) within the body of the corpus callosum (posterior aspect) in the right hemisphere compared to TD youths (Figure 1A). No areas of reduced AD and no sex-by-diagnosis interactions were identified. Youths with CD also showed lower RD in bilateral anterior thalamic radiation (left, $p < .01$; right, $p = .01$) compared to TD youths (Figure 2A) and lower MD in the left anterior thalamic radiation ($p = .01$) (Figure 2B). No areas showing higher RD or MD were identified, but a sex-by-diagnosis interaction in RD was observed within the left internal capsule (posterior limb; $p = .04$), bordering the corticospinal tract (Figure 3A). Underlying this interaction, CD female youths showed higher RD than TD female youths, whereas CD male youths had lower RD than TD male youths (Figure 3A). No significant main effects or sex-by-diagnosis interactions were observed for FA. Finally, no significant two-way or three-way interactions were observed between age, diagnosis, and sex or for puberty, diagnosis and sex for any DTI index (all p values >.19; see Supplement 8 and Figure S2, available online).

FIGURE 1 White Matter Microstructure in Corpus Callosum: Youths With Conduct Disorder (CD) Compared With Typically Developing (TD) Youths



Note: (A) Voxels within the body of the corpus callosum (coordinates, x = 7, y = −27, z = 24; p = .02; k = 41; d = .59) where axial diffusivity (AD) differed between groups (CD > TD). All voxels (shown in red–yellow) are thresholded at p < .05, threshold-free cluster enhancement (TFCE); familywise error (FWE) corrected for multiple comparisons. Findings overlaid onto mean fractional anisotropy (FA) skeleton (green) in Montreal Neurological Institute (MNI) space (x, y, z). Corpus callosum shown in blue overlaid on to a 3D MNI152_T1_1mm template. For viewing purposes, statistical images were "thickened." (B) Partial regression plots showing unique associations between CD symptoms and mean AD in the corpus callosum (left) and ICU callous subscale scores and mean AD in the corpus callosum (right) in CD youths only (n = 124). The p and β values reflect the level of statistical significance and the standardized regression coefficients, respectively. Shaded error bars reflect 95% CIs. K-SADS-PL = Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime version; ICU = Inventory of Callous-Unemotional traits.

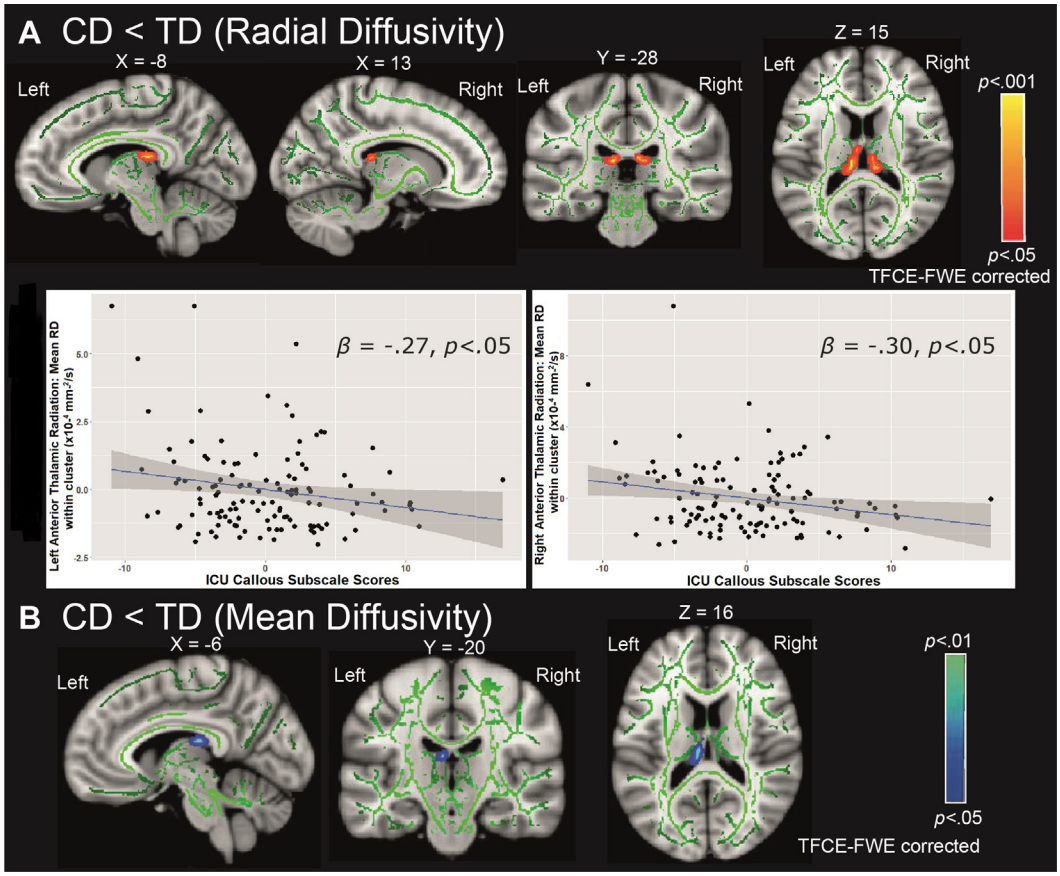
Regression Analyses: Effects of CD Symptoms, CU Traits, and Comorbid Symptoms

In the corpus callosum, unique variance associated with CD symptoms, after controlling for ICU total score, negatively predicted AD ($\beta = -0.21$, $p = .02$), whereas unique variance associated with CU traits did not significantly predict AD in this region after controlling for CD symptoms ($\beta = .15$, $p = .12$; Table S6, available online). After controlling for CD symptoms, and the uncaring and unemotional subscales of the ICU, unique variance associated with callous traits positively predicted AD ($\beta = 0.33$, $p < .01$; Figure 1B and Table S7, available online). CD symptoms still negatively predicted AD when controlling for ICU subscale scores ($\beta = -0.20$, $p = .03$) (Figure 1B and Table S7, available online). Controlling for symptoms of comorbid disorders did not alter these results, and the unique variance of those symptoms did not significantly predict AD (all $p > .13$; Tables S6 and S7, available online).

In the anterior thalamic radiation, neither CD symptoms nor total ICU scores predicted RD (all $p > .07$; Table S8, available online). After controlling for CD symptoms, and the uncaring and unemotional subscales of the ICU, unique variance associated with callous traits negatively predicted RD (left: $\beta = -0.27$, $p = .03$; right: $\beta = -0.30$, $p = .01$; Figure 2A and Table S9, available online). Adding comorbid disorder symptoms did not alter these results, and the unique variance of those symptoms did not significantly predict RD (Tables S8 and S9, available online). In the left anterior thalamic radiation, neither CD symptoms nor ICU total or ICU subscale scores significantly predicted MD (all $p > .06$; Tables S10 and S11, available online). Controlling for symptoms of comorbid disorders did not alter these results, and the unique variance of those symptoms did not significantly predict RD (all $p > .12$; Tables S10 and S11, available online).

To explore the sex-by-diagnosis interaction observed within the posterior limb of the left internal capsule, regression analyses were conducted on female and male youths with CD separately. A significant negative relationship was found between unique variance associated with CD symptoms and RD ($\beta = -0.21$, $p = .04$) for male youths with CD, but not for female youths ($\beta = 0.22$, $p = .1$) when controlling for ICU total score (Table S12, available online). After controlling for ICU subscale scores, unique variance associated with CD symptoms and RD was

FIGURE 2 White Matter Microstructure in Anterior Thalamic Radiation: Youths With Conduct Disorder (CD) Compared With Typically Developing (TD) Youths



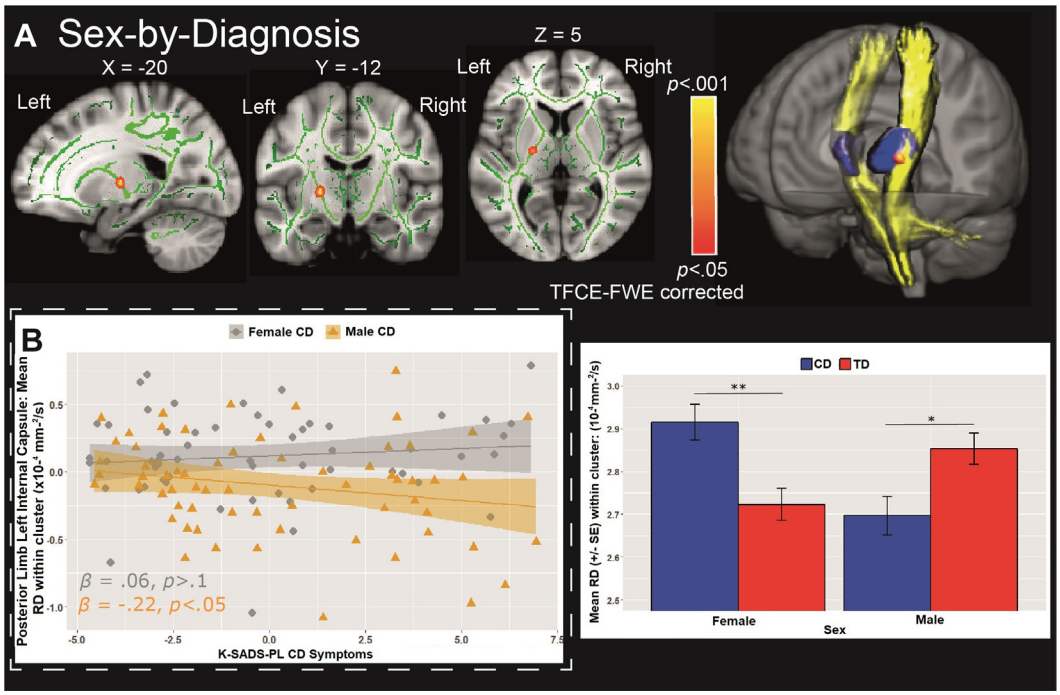
Note: (A) Voxels within the anterior thalamic radiation (left anterior thalamic radiation: x = −8, y = −28, z = 15; p < .01; k = 140; d =0.41: right anterior thalamic radiation: x = 13, y = −28, z = 15; p = .01; k = 80; d = 0.27) where radial diffusivity (RD) differed between groups (CD < TD). Partial regression plots show unique associations between ICU callous subscale scores and mean RD within the left (left graph) and right (right graph) anterior thalamic radiation in CD youths only (n = 124). The p and β values reflect the level of statistical significance and the standardized regression coefficients, respectively. Shaded error bars reflect 95% CIs. (B) Voxels within the left anterior thalamic radiation (x = −6 y = −20, z = 16; p = .03; k = 52; d = .31) where mean diffusivity (MD) differed between groups (CD < TD). All voxels (shown in red–yellow [top] and blue–light-blue [bottom]) are thresholded at p < .05, threshold-free cluster enhancement (TFCE); familywise error (FWE) corrected for multiple comparisons. Findings are overlaid onto the mean fractional anisotropy (FA) skeleton (green).

also observed for male youths ($\beta = -0.22$, $p = .04$) but not for female youths ($\beta = 0.06$, $p = .66$) with CD (Figure 3B and Table S13, available online). Controlling for symptoms of comorbid disorders did not alter these results, and the unique variance of those symptoms did not significantly predict RD in male youths (all $p > .15$; Tables S12 and S13, available online).

ROI Results

Sex-by-diagnosis interactions were observed in AD within the left fornix and the left posterior thalamic radiation (Figure 4A and 4B, respectively). Female youths with CD showed lower AD in the fornix compared to TD female youths, whereas male youths with CD showed a nonsignificant increase in AD compared to TD male youths; the opposite pattern (TD female youths < CD female youths; TD male youths > CD male youths) was observed within the left posterior thalamic radiation. A significant sex-by-diagnosis interaction was also observed for left uncinate fasciculus MD (CD female youths > TD female youths; CD male youths < TD male youths; Figure 4C). No further main effects or interactions were observed in the other ROIs for any DTI index (Table S4, available online). No associations were detected between CD symptoms, CU traits, or the ICU subscale scores, or any of the comorbid disorder symptoms and WM microstructure within the left fornix, left posterior thalamic radiation, or left uncinate fasciculus.

FIGURE 3 Sex-by-Diagnosis Interaction in Posterior Limb of Internal Capsule



Note: *(A) Voxels within the left internal capsule (x = −20, y = −12, z = 5; p = .04; k = 8; d = 1.35) revealing a sex-by-diagnosis interaction in radial diffusivity (RD). All voxels (shown in red–yellow) are thresholded at p < .05, threshold-free cluster enhancement (TFCE); familywise error (FWE) corrected for multiple comparisons. Findings are overlaid onto the mean fractional anisotropy (FA) skeleton (green). The internal capsule (bilateral) is shown in blue and the corticospinal tract (bilateral) is shown in yellow overlaid onto a 3D MNI152_T1_1mm template. Bar graph shows white-matter differences in the left internal capsule cluster for female youth (t = 3.26, df = 160, p = .005) and male youth (t = −2.71, df = 134, p = .04) with CD compared to TD controls. (B)* Inset *(dashed line) partial regression plot shows unique associations between CD symptoms for female and male youth with CD and mean RD within the left internal capsule cluster. The p and β values reflect the level of statistical significance and the standardized regression coefficients, respectively. Shaded error bars reflect 95% CIs. SE = standard error.*
*p < .05; **p < .01 (Bonferroni corrected; p <.05).

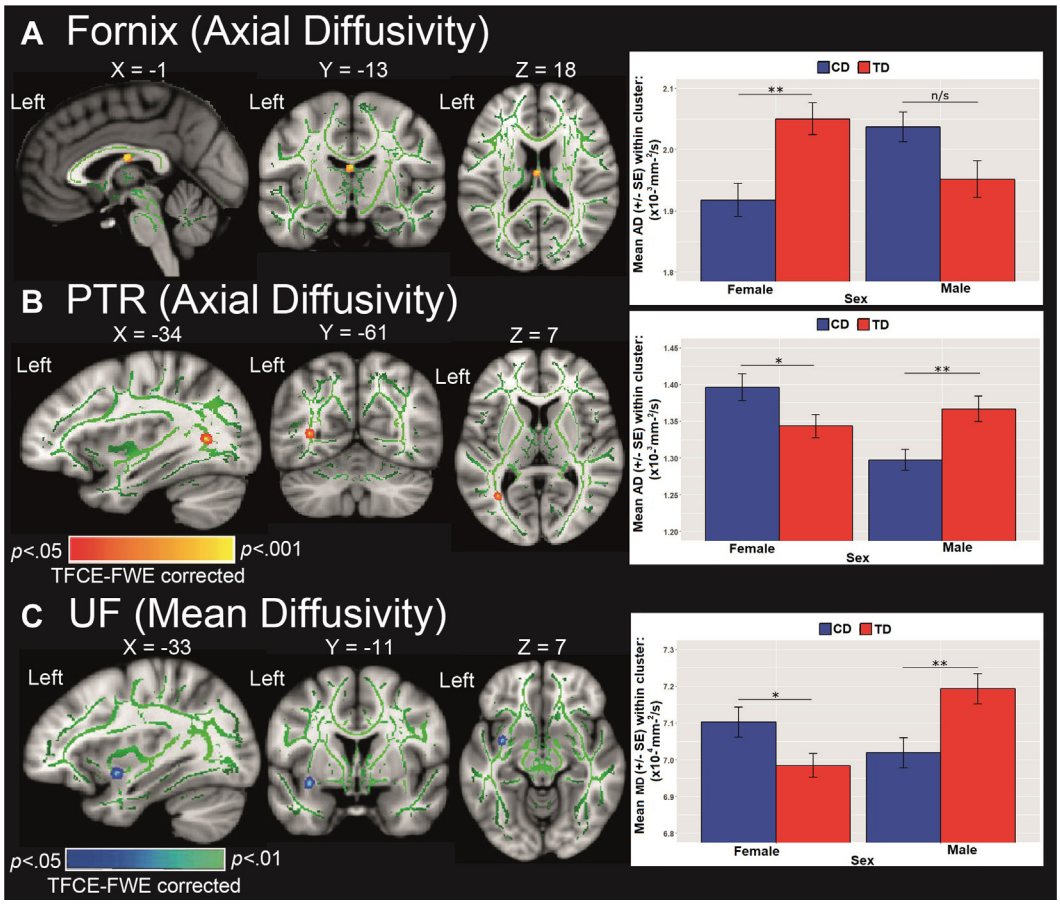
Associations Between WM Microstructure and Impulsivity

In a subset of the CD group for whom data were available (n = 107), commission errors to emotional "no-go" stimuli on the "Go/No-Go" task were positively correlated with AD in the corpus callosum (r = 0.24, p = .01) (Figure S3, available online). Furthermore, callous traits were positively correlated with commission errors to emotional no-go stimuli (r = 0.18, p = .05; Figure S3, available online). Given this pattern of results and evidence linking the corpus callosum to impulsivity in CD,[13] an exploratory post hoc mediation analysis was conducted to assess whether, in CD youths, corpus callosum AD values mediated the relationship between callous traits and impulsive responses (commission errors) to emotional faces. Callous traits, corpus callosum AD values, and commission errors to emotional no-go stimuli were modeled as the independent, mediating, and dependent variables, respectively. Given that CD symptoms negatively predicted AD in the corpus callosum when controlling for ICU subscale scores, CD symptoms were included as a covariate (see Lozier *et al.*[43] for a similar approach). Bootstrap-mediation analysis (with 5,000 bootstrap resamples of the data with replacement) was implemented with the SPSS PROCESS macro.[44] Rather than providing formal p values, statistical significance with α set at 0.05 is indicated by the 95% CIs not crossing zero. Corpus callosum AD partially mediated the relationship between callous traits and impulsive responses to emotional faces, but this effect was small (indirect effect = 0.14, 95% CI = 0.0019−0.3734; Figure S3, available online).

DISCUSSION

This study extends our understanding of WM microstructure in youths with CD in several important ways. First, consistent with our predictions, we demonstrated that compared to TD youths, female and male youths with CD showed higher AD within the body of the corpus callosum and lower RD bilaterally (plus lower MD on the left) in the anterior thalamic radiation. Our whole-brain and ROI analyses also revealed that female and male youths with CD exhibited opposite changes in WM microstructure within

FIGURE 4 Region of Interest (ROI) Analysis: Youths With Conduct Disorder (CD) Compared to Typically Developing (TD) Youths



Note: *(A) Voxels within the left fornix (x = −1, y = −13, z = 18; p = .02; k = 6; d = 1.15) revealing a sex-by-diagnosis interaction in axial diffusivity (AD). Bar graph shows white matter differences for female youth (t = 3.27, df = 160, p < .01) and male youth (t = 2.1, df = 134, p = .22). (B) Voxels within the left posterior thalamic radiation (x = −34, y = −61, z = 7; p = .03; k = 7; d = 1.5) revealing a sex-by-diagnosis interaction in AD. Bar graph shows white matter differences for female youth (t = 2.35, df = 160, p = .04) and male youth (t = 3.41, df = 134, p < .01). (C) Voxels within the left uncinate fasciculus (x = −33, y = −11, z = 7; p = .01; k = 9; d = 0.81) revealing a sex-by-diagnosis interaction in mean diffusivity. Bar graph shows white matter differences for female youth (t = 1.97, df = 160, p = .03) and male youth (t = 1.98, df = 134, p < .01). All voxels (shown in red–yellow [A and B] and blue-light-blue [C]) are thresholded at p < .05, threshold-free cluster enhancement (TFCE); familywise error (FWE) corrected for multiple comparisons. Findings are overlaid onto the mean fractional anisotropy (FA) skeleton (green). n/s = not significant; PTR = posterior thalamic radiation; SE = standard error; UF = uncinate fasciculus.*
*p < .05; **p < .01.

the left uncinate fasciculus and multiple projection pathways in the left hemisphere. Second, partially supporting our predictions, we demonstrated that callous traits and CD symptoms exerted opposite effects on AD within the corpus callosum, with callous traits identified as the unique clinical feature predicting higher AD and lower RD within the corpus callosum and anterior thalamic radiation, respectively. Furthermore, higher AD values in the corpus callosum were associated with higher levels of impulsive responses to emotional faces and partially mediated the association between callous traits and impulsive responses, although this effect was small. Finally, no age-by-diagnosis or puberty-by-diagnosis interactions were observed. In addition, contrary to predictions, no significant group differences or sex-by-diagnosis interaction in FA was observed, and none of the findings were influenced by symptoms of comorbid disorders.

This study is the first to show that female and male adolescents with CD exhibit common alterations in WM microstructure within the body of the corpus callosum and the anterior thalamic radiation. For the corpus callosum, consistent with the results of previous studies on CD with male only,[13,21] female only,[11] or mixed-sex samples,[12,14] we observed higher AD values (lower diffusivity) within this tract across sexes. The corpus callosum, which connects homologous regions across the hemispheres, is the largest WM tract and commissural pathway in the brain, and is thus central to interhemispheric communication.[45]

Disrupted interhemispheric communication has been associated with anger and aggression,[46] behaviors that are characteristic of CD individuals. Importantly, the corpus callosum is structurally and functionally heterogeneous across its three subdivisions: the genu, body, and splenium.[47] The observed group difference was located centrally in the posterior part of the body of the corpus callosum, which connects precentral regions (premotor area, supplementary motor area), as well as the insular, mid-posterior cingulate, and somatosensory cortices.[47] As such, that subdivision connects regions involved in response inhibition and socio-emotional processing,[46,48] consistent with the observed association between corpus callosum AD and commission errors to emotional faces in the CD group. Interestingly, our exploratory analysis revealed that higher AD within the corpus callosum partially mediated the relationship between callous traits and the number of commission errors to emotional no-go stimuli, implicating corpus callosum alterations in the association between callous traits and impulsive responses to emotional faces in youths with CD. We note, however, that previous research using the Go/No-Go task has identified commission errors to emotional no-go stimuli as an index of emotion (dys) regulation.[33]

Youths with CD also exhibited lower RD (lower diffusivity) bilaterally within the anterior thalamic radiation, a result consistent with just one study using a mixed-sex sample, in which greater CD severity was associated with increased FA (lower diffusivity) within this tract.[14] The anterior thalamic radiation forms part of the limbic system and connects the mediodorsal and anterior thalamic nuclei with the dorsolateral, ventrolateral, orbitofrontal, and anterior cingulate cortices.[49] These prefrontal regions are implicated in working memory, affective decision making, and empathy; notably, youths with CD also show impairments in these domains.[2] Given our results and the prominent role of the thalamus as a "relay station" and "gatekeeper" of sensory information between subcortical and cortical regions,[50] future studies should clarify to what extent impairments observed in CD and structural/functional alterations within those prefrontal regions might reflect "downward consequences" of WM differences within the anterior thalamic radiation.

The observed sex-by-diagnosis interactions were restricted to association (uncinate fasciculus) and projection pathways (posterior limb of the internal capsule, the fornix, and the posterior thalamic radiation) in the left hemisphere. The MD effect in the left uncinate fasciculus is consistent with those observed in previous studies that reported increased FA in male youths with CD[9,10,13] and one study in a mixed-sex sample.[12] Taken together, these results reinforce the view that the orbitofrontal cortex–amygdala circuitry might be central to the pathophysiology of CD and to some of its associated emotional and decision-making impairments, as suggested by a neurocognitive model of CD.[2] Most previous studies of CD have not observed group differences in the projection tracts that we identified (but see[11,14,19]). The internal capsule contains both ascending (from thalamus to cortex) and descending fibers (from fronto-parietal cortex to basal ganglia and corticospinal tract) and is considered a "neuroanatomical backbone" supporting perceptual, motor and higher-order cognitive functions.[45] The fornix forms part of the limbic system and connects the medial temporal lobe and hippocampus to the mammillary bodies and hypothalamus, thereby playing a central role in memory formation and retrieval.[45] Finally, the posterior thalamic radiation, which connects the posterior parts of the thalamus with the occipital and the parietal cortices, is a critical component of the visual system. Our results, along with those of two previous studies,[12,20] provide novel evidence that the relationship between CD and WM microstructure partly differs by sex; however, given the novelty of these findings, future studies should seek to replicate them and to investigate their origins and functional significance.

Building on, and extending, previous behavioral and neuroimaging studies,[2] we demonstrated that among youths with CD, the unique variance associated with CD symptoms and callous traits exhibited opposing associations with corpus callosum WM microstructure, with callous traits identified as the unique clinical feature predicting the group differences in AD observed within the corpus callosum and in RD in the bilateral anterior thalamic radiation. From a theoretical stance, these results: (1) identify novel WM correlates of CD, supporting the view that youths with CD constitute a heterogeneous group with different neurocognitive profiles[25,26]; and (2) could help to explain some of the inconsistent results reported in previous DTI studies.[5] Finally, our finding that callous traits were the strongest predictor of the group differences is consistent with two fMRI studies examining neural responses to others' pain in youths with conduct problems. The first showed that callous traits predicted lower anterior insula and anterior cingulate cortex responses,[26] whereas the second reported that callous traits predicted reduced functional connectivity of the amygdala and insula with the anterior cingulate cortex.[27] These results, together with recent psychometric, experimental, behavioral, genetic, and meta-analytic evidence demonstrating that the ICU subscales are each associated with distinct phenotypic and etiological characteristics as well as external correlates,[51-53] highlight the importance of considering the distinct dimensions

underlying the CU traits construct as operationalized by the ICU.[36] This line of research may inform future research and clinical work. Future studies should also examine how different clinical presentations of CD (eg, aggressive versus nonaggressive) might relate to WM differences.

Some neurodevelopmental considerations should be noted. Despite the fact that CD is considered by some to be a neurodevelopmental disorder,[54] and despite the hypothesis that the relationship between CD and WM microstructure might differ with age,[5,9,20] no age- or puberty-related interactions were observed. This tentatively suggests that the magnitude of differences between groups that we report here reflects similar developmental trajectories across the age range (9−18 years) for both CD and TD youths. Thus, it is possible that any neurodevelopmental changes might have already occurred by age 9 years. In any case, this developmental trend is different from the deviant and age-related trajectories reported for autism spectrum disorders,[55] another childhood psychiatric disorder. However, cross-sectional or correlational designs preclude drawing any valid inferences regarding (neuro)developmental processes,[56] highlighting the pressing need for prospective longitudinal studies of CD. Second, our results and those of previous studies suggest that CD might be characterized by a unique pattern of lower diffusivity (higher AD, lower RD and MD as reported here) compared to other childhood psychiatric disorders such as ADHD (lower FA with TBSS[28]) and autism spectrum disorders (lower FA, higher MD[57]) where meta-analyses have identified higher WM diffusivity.[28,58] DTI studies in youths with depression,[29] generalized anxiety disorder,[30] and substance misuse[31] have also consistently reported higher diffusivity (lower FA) in those clinical groups across a range of WM tracts that includes the uncinate fasciculus and corpus callosum. The fact that these results are in the opposite direction to those reported here may explain why the unique pattern of findings in CD youths was not influenced by symptoms of comorbid disorders. Finally, the adult condition of antisocial personality disorder, for which a diagnosis of CD by age 15 years is required,[1] has also been associated with WM differences in the same tracts that we identified. However, in contrast to our findings, there is a consistent pattern of higher diffusivity (eg, lower AD[59]) in adults with antisocial personality disorder[5,59] and those with psychopathy.[5] Interestingly, a recent study in adults with antisocial personality disorder found a negative correlation between AD in the corpus callosum and self-reported impulsivity.[60] Taken together, these data highlight the need for prospective longitudinal studies to clarify the association between WM microstructure and the developmental course of severe antisocial behavior and associated personality traits.

Despite the strengths of our study, which include the use of a much larger sample than has been included in previous DTI studies of CD, groups matched on pubertal status, and a systematic examination of the influence of of age, puberty, IQ, and clinical variables on the findings, some limitations should be noted. As with all previous DTI studies of CD, the cross-sectional design prevents us from inferring whether WM differences are a cause or a consequence of the disorder.[56] In addition, until replicated, the results of our exploratory mediation analysis should be interpreted as preliminary, given that the observed effect was small and mediation analyses are more suited to longitudinal data.[61] We also note that, because faces are the targets in the Go/No-Go task used here,[33] this paradigm might conflate emotional processing (known to be impaired in CD[2]) with impulsivity. However, because corpus callosum AD values did not correlate with any performance indices (accuracy or reaction time) on the Emotion Hexagon task,[62] in which participants have to identify emotional facial expressions (see Supplement 4, available online), we believe that our interpretation of the association between AD values and commission errors is consistent with an impulsivity account, albeit when target stimuli are emotional faces. The ROI analysis approach of using atlas-derived probability maps to extract tract means from the voxelwise skeleton, although common (eg, see Menks *et al.*[11]), is not optimal because of the use of an atlas-inferred rather than individually calculated trajectory to define the tracts. Furthermore, the results of our ROI analysis should be interpreted cautiously, as the correction for multiple comparisons was applied to each DTI index separately, rather than across all four indices simultaneously. Indeed, when we tested for group differences/interactions within all ROIs ($n = 16$) across all four DTI indices (ie, $16 \times 4 = 64$ tests), the reported ROI results did not survive this highly conservative multiple comparison procedure. However, when the findings were corrected for multiple comparisons within each DTI index (ie, for FA, AD, RD, and MD only; 16 tests) then all reported ROI results were significant. Finally, diffusivity measures can be influenced by factors such as partial volume, fiber crossing effects, fiber alignment, myelination density of the tract, tract coherence, or a combination of any or all of these factors, which are unrelated to "WM integrity."[63] In this context, the interpretability of any observed group differences is challenging. Thus, we have been careful to describe our results as differences in specific DTI metrics and the nature of diffusivity without specific reference to WM "integrity."[63]

In summary, female and male youths with CD exhibit common increases in AD in the corpus callosum and common reductions in RD and MD in the anterior

thalamic radiation, relative to TD youths. However, sex-specific effects of CD on WM microstructure were observed within the left uncinate fasciculus and projection pathways in the left hemisphere. It is important to note that although the results were not influenced by symptoms of comorbid disorders, unique variance associated with CD symptoms and callous traits exhibited opposing influences on corpus callosum AD, with callous traits identified as the unique clinical feature predicting higher AD and lower RD within the corpus callosum and anterior thalamic radiation, respectively. Finally, AD in the corpus callosum partially mediated the association between callous traits and impulsive responses to emotional faces in youths with CD. These data suggest that there are sex differences in the neurobiological basis of CD, and provide further evidence that callous traits may delineate a distinct subtype of CD.

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The authors confirm that all individuals listed as authors meet authorship criteria. Drs. Rogers, Gonzalez-Madruga, Clanton, Baker, Chowdhury, Kirchner, Andersson, Smaragdi, Puzzo, Kohls, Raschle, Menks, Steppan, Fairchild, De Brito and Mss. Pauli, Birch, Baumann, and Fehlbaum all contributed to the conception, design, analysis and interpretation of the data, drafting the article and revising it for publication with important intellectual content and final approval of the manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Profs. Konrad, Stadler, and Freitag provided important interpretation of data, intellectual contribution on drafting the article, and final approval of the version to be published and oversaw all aspects of the work ensuring that the accuracy or integrity of any part of the work was appropriately investigated and resolved.

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