Microstructural White Matter Alterations in the Corpus Callosum of Girls With Conduct Disorder

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Objective: Diffusion tensor imaging (DTI) studies in adolescent conduct disorder (CD) have demonstrated white matter alterations of tracts connecting functionally distinct fronto-limbic regions, but only in boys or mixed-gender samples. So far, no study has investigated white matter integrity in girls with CD on a whole-brain level. Therefore, our aim was to investigate white matter alterations in adolescent girls with CD.

Method: We collected high-resolution DTI data from 24 girls with CD and 20 typically developing control girls using a 3T magnetic resonance imaging system. Fractional anisotropy (FA) and mean diffusivity (MD) were analyzed for whole-brain as well as a priori–defined regions of interest, while controlling for age and intelligence, using a voxel-based analysis and an age-appropriate customized template.

Results: Whole-brain findings revealed white matter alterations (i.e., increased FA) in girls with CD bilaterally within the body of the corpus callosum, expanding toward the right cingulum and left corona radiata. The FA and MD results in a priori–defined regions of interest were more widespread and included changes in the cingulum, corona radiata, fornix, and uncinate fasciculus. These results were not driven by age, intelligence, or attention-deficit/hyperactivity disorder comorbidity.

Conclusion: This report provides the first evidence of white matter alterations in female adolescents with CD as indicated through white matter reductions in callosal tracts. This finding enhances current knowledge about the neuropathological basis of female CD. An increased understanding of gender-specific neuronal characteristics in CD may influence diagnosis, early detection, and successful intervention strategies.

Key words: conduct disorder, aggression, diffusion tensor imaging, pediatric neuroimaging, gender

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Conduct disorder (CD) is a mental disorder of childhood and adolescence, and is characterized by repeated patterns of rule-breaking and aggressive or defiant behavior that is outside the appropriate age norm (*DSM-5* 312.8).[1] A clinical diagnosis of CD affects familial, academic, and/or occupational functioning and can thus result in substantial societal costs. Clinically, CD and oppositional defiant disorder are subsumed under the diagnosis disruptive behavior disorder.[1] The estimated lifetime prevalence of CD corresponds to about 7% in girls and 12% in boys.[2] Consequently, the majority of research studies investigating CD has almost exclusively included male participants. However, considering the known gender differences in the prevalence and progression of CD, the importance of including gender as a critical factor within CD studies remains indispensable.[2] From 16% to 30% of adolescents with CD display comorbid attention-deficit/hyperactivity disorder (ADHD), resulting in a possible influence.[3] However, research has indicated that CD-specific deficits persist beyond the presence of comorbid ADHD symptoms.[4,5]

Behaviorally, reduced empathy, emotion processing, and regulation skills are key deficits in the behavioral symptomatology of CD. Likewise, impulsivity, decision making, and reinforcement learning are commonly affected.[6] In line with the known behavioral phenotype, functional neuroimaging studies in CD have revealed neuronal characteristics affecting the emotion processing, regulation, and threat circuitries of the brain, as indicated by neuronal alterations in amygdala, insula, prefrontal, superior temporal, and cingulate cortex.[7-10] In line with functional evidence, changes in gray and white matter structure in brain areas of the frontal, limbic, and temporal lobe have been identified when comparing CD to typically developing youths.[11-13] For example, by using voxel-, surface-, or cortical thickness–based morphometry analysis, structural alterations in CD have been linked to the amygdala, insula, precuneus, prefrontal cortex, cingulate cortex, and corpus callosum.[12,14-16] Structural and functional brain alterations are further dependent on age of onset, CD symptom severity, or the level of callous-unemotional traits displayed. Heightened scores are thereby predictive of a negative disease progression and the development of antisocial behavior later in life.[8-10,16] Regionally specific structural changes have been linked to alterations within the white matter tracts, or neural circuitries, connecting these regions, for example, the prefrontal-limbic circuit.

Neural circuits such as the prefrontal-limbic system may be investigated using diffusion tensor imaging (DTI), a technique that measures structural connectivity. DTI can

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inform about the fiber consistency and microstructural integrity of white matter tracts (e.g., fractional anisotropy [FA] or mean diffusivity [MD]). Previous DTI studies in male or mixed-gender groups of adolescents with disruptive behavior disorders have reported white matter increases and decreases in tracts comprising the corpus callosum, corona radiata, superior longitudinal fasciculus, fronto-occipital fasciculus, uncinate fasciculus, stria terminalis, and cerebellar peduncle.[4,17-19]

To date it is unclear whether previously identified white matter alterations in boys with CD are also present in girls with CD. Two studies, one using a region of interest approach[20] and the other based on post hoc examinations of female adults with a prior CD diagnosis, provide the first evidence about potentially unique white matter characteristics in female CD.[21] However, no study to date has investigated whole-brain white matter alterations in female adolescents with a clinical diagnosis of CD using DTI. Therefore, the present study aims to bridge this gap in knowledge by comparing white matter tracts in girls with CD compared to typically developing controls through voxel-based DTI-TK using both a whole-brain and a region-of-interest approach. By using a more conservative whole brain approach as well as investigations within an a priori–defined regions of interest method, we aim to gain novel insights into white matter alteration in girls with CD that also allow comparability to past studies. Based on previous evidence implicating white matter alterations within the neurobiology of CD, we hypothesize that in a group of only girls with CD, alterations in white matter structures are likewise observed (i.e., in the uncinate fasciculus, corpus callosum, corona radiata, fornix, cingulum, and fronto-occipital fasciculus).[4,5,17-19] Comorbid ADHD symptoms will be accounted for by the repetition of analysis in girls with CD without ADHD comorbidity. Finally, using correlational analyses, we will investigate whether callous-unemotional traits, which are known to increase the symptom severity and disease progression of CD,[22] may be linked to the observed microstructural alterations.

METHOD

Participants

A total of 44 female adolescents of average intelligence, 24 with CD (age range, 12–18 years) and 20 typically developing controls (age range, 12–19 years), were recruited through healthcare institutions and schools within this Swiss National Foundation study investigating adolescent CD. Some participants were also part of FemNAT-CD, a project across Europe (http://www.femnat-cd.eu/). All patients fulfilled the *DSM-5* criteria for CD using the semi-structured diagnostic interview Kiddie Schedule for Affective Disorders–Present and Lifetime versions (K-SADS-PL)[23]; healthy controls were free of any psychiatric or neurological disorder. In line with the known overlap between CD and ADHD,[3] we here identified nine patients with CD and comorbid ADHD symptoms. Furthermore, two patients were diagnosed with present alcohol abuse and five patients with present substance abuse. Handedness was assessed using the Edinburgh Handedness Inventory.[24] All participants completed two testing sessions, including clinical interview/psychometric testing and one magnetic resonance imaging (MRI) appointment. The MRI session occurred on average 2.6 months (±2.3 for CD; ±2.9 for controls) after the clinical interview. All participants and caretakers provided verbal and written informed consent to take part in the study as approved by the local ethics committee in Basel, Switzerland (Ethikkommission Nordwest- und Zentralschweiz).

Psychometric Testing

Participants completed a battery of standardized psychometric tests measuring psychopathic traits (Youth Psychopathic Traits Inventory [YPI] self-report, based on 10 dimensions/50 items rated on a four-point Likert scale),[25] callous-unemotional traits (Inventory of Callous-Unemotional [ICU] traits parent-report, based on 24 items rated on a 4-point Likert scale),[26] aggressive behavior (Reactive–Proactive Aggression Questionnaire, a 26-item self-report),[27] and pubertal status.[28] In addition, behavioral problems were recorded through parental reports (Child Behavior Checklist).[29] Furthermore, parental socioeconomic status was estimated using a 6-point educational scale based on the International Standard Classification of Education.[30] Clinical and psychometric data analyses were based on the homogeneity of variance (Levene) test and parametric (two-sample *t* test) or nonparametric testing (Mann–Whitney *U* test) as implemented in SPSS v23 software (IBM Corp., Armonk, NY). Group characteristics are presented in Table 1. There were no significant differences in respect to age, handedness, puberty status, socioeconomic status, or performance IQ. The present group of girls with CD is comparable in scores to previously described CD samples, including heightened aggression, callousness, and psychopathy scores.[4,20] Compared to controls, total and verbal but not performance IQ was significantly lower in girls with CD.

DTI Acquisition

Whole-brain neuroimaging data was acquired using a 3T MRI system (Siemens Prisma, Erlangen, Germany) and a 20-channel phased-array radio frequency head coil. A single-shot echo planar imaging (EPI) sequence was used with the following acquisition parameters: A>>P phase encoding direction; echo spacing of 0.65 milliseconds, GRAPPA parallel imaging with an acceleration factor of 2, phase partial Fourier 6/8 acquisition, matrix 128 × 128, field of view 256 mm, 2 × 2 mm^2 in-plane resolution, slice thickness 2.0 mm, no slice gap, 62 contiguous axial slices, TR = 7,500 milliseconds, TE = 71 milliseconds, and bandwidth of 1776 Hz/pixel. Diffusion-sensitive gradients were applied along 64 directions (b = 800 s/mm^2), and two additional images were collected without a diffusion gradient (b0 = 0 s/mm^2) with A>>P and P>>A phase encoding directions, necessary for distortion corrections of the EPI imaging data during analysis.

DTI Data Processing

Before preprocessing, all images underwent quality control using DTIPrep in addition to visual checks through two independent reviewers (W.M.M., R.F.) to exclude artifact-influenced gradient directions. EPI distortions were corrected using eddy and TopUp in FSL 5.0 and the brain functional MRI (fMRI) software library.[31,32] With FSL-BET, individual brain masks were created. Subsequently, FA and MD values were obtained by using the FSL-DTIfit algorithm. Again, visual checks were applied to ensure good coherence between individual FA and MD maps and corresponding diffusion tensor eigenvectors.

To increase specificity, particularly for smaller tracts,[33,34] a voxel-based analysis as opposed to tract-based statistics was used. Most importantly, by using DTI-TK and an existing tensor template (the IXI aging template v3.0 in standard space), a study-specific customized adolescent brain template was created based on our

TABLE 1 Group Characteristics of Girls With Conduct Disorder (CD) and Typically Developing Controls (TD)

Variable	CD Mean (±SD)	TD Mean (±SD)	*p* Value	n (CD/TD)
Age, y	15.8 (±1.4)	16.3 (±1.8)	.262	(24/20)
Age of CD onset			–	
Child-onset (<10 y)	5	–		
Adolescent-onset (≥10 y)	19	–		
Handedness			.319	(22/20)
Left-handed	2	4		
Right-handed	20	16		
IQ (WISC-IV)*	99.5 (±10.5)	108.1 (±10.9)	.011	(24/20)
Verbal IQ*	96.9 (±13.3)	111.3 (±13.5)	.001	(24/20)
Performance IQ	102.1 (±11.1)	105.0 (±11.5)	.398	(24/20)
Aggression (RPQ)	13.1 (±9.3)	8.6 (±4.3)	.127[a]	(20/20)
Psychopathic traits (YPI)*	107.5 (±22.1)	92.2 (±18.6)	.019	(23/20)
Callous-unemotional traits (ICU)*	28.6 (±10.8)	17.0 (±6.1)	.001	(16/17)
Puberty status	3.9 (±0.4)	4.2 (±0.7)	.233[a]	(18/19)
Socioeconomic status	5.0 (±1.8)	5.5 (±1.4)	.502	(13/12)

Note: For all tests, mean scores and standard deviations (SD) are reported. ICU = Inventory of Callous-Unemotional Traits; RPQ = Reactive–Proactive Questionnaire; WISC-IV = Wechsler Intelligence Scale for Children–Fourth Edition; YPI = Youth Psychopathic Traits Inventory.

[a]*Mann–Whitney U test.*

**Significant group difference (p < .05), 2-tailed t test.*

study population.[35] Subsequently, all participants' DTI volumes were aligned to our customized template, using the affine and diffeomorphic alignment of DTI-TK. DTI-TK uses a deformable registration algorithm optimizing the white matter alignment of DTI images between participants based on the tensors themselves.[35] Therefore, an advantage of using DTI-TK is the more precise spatial normalization of the DTI data. Consequently, a higher sensitivity for white matter alterations is achieved.[33,34] After normalization, the FA and MD data were smoothed using a Gaussian kernel with full width at half maximum of 6 mm.

Statistical Whole Brain and Region of Interest Analysis

Statistical analyses were performed using both a whole-brain and a region-of-interest approach. All analyses were based on a permutation inference (n = 5,000), with demeaned age and total IQ scores as covariates. Results are based on between-group two-sample *t*-tests (two-tailed) and presented using a threshold-free cluster enhancement, $p \leq .05$ familywise error (FEW) corrected. The ICBM-DTI-81 atlas was implemented for determining tracts that lie within the clusters resulting from the analysis. In addition, the mean eigenvalues (λ1, λ2, λ3) were estimated. To evaluate specific white matter tracts previously identified in males with disruptive behavior disorder,[4,5,18,19] we further chose to investigate six tracts using an a priori–defined region of interest approach. More specifically, these regions were generated from the ICBM-DTI-81 atlas for white matter tracts that were altered in previous studies investigating CD: the uncinate fasciculus, corpus callosum, corona radiata, fornix, cingulum, and fronto-occipital fasciculus.[4,5,17-19,36]

Post Hoc Region of Interest Analysis

Evidence indicates that adolescents with CD can be further dissociated depending on the level (high versus low) of callous-unemotional traits displayed.[10,16,37-39] There were not enough girls with high/low callous-unemotional traits to allow further subgroup analysis. However, post hoc correlation analysis comparing the mean FA and MD values in anatomically defined areas of interest to callous-unemotional traits (corrected for IQ and age) were conducted to assess the influence of callousness on white matter alterations in girls with CD. Correlational analyses were conducted using the ICU questionnaire, as well as the callous-unemotional subscale of the YPI. Both questionnaires are commonly used to distinguish relevant subgroups of individuals with CD based on callous-unemotional traits.[16,38,39] In addition, we planned to investigate the effect of comorbid ADHD symptoms, present in nine girls with CD, on our findings by re-estimation of DTI analysis excluding the nine girls with CD/ADHD, and by multiple linear regression analyses using CD and ADHD symptoms as independent variables (with age and intelligence as covariates) and clusters of significant whole-brain FA changes in girls with CD as dependent variables.

RESULTS

Whole Brain DTI Findings in Female CD

On a whole-brain level, DTI analysis identified one significant cluster of FA increases centered in the body of the corpus callosum expanding toward the right cingulum and the left corona radiata when comparing girls with CD to healthy controls (Table 2, Figure 1; for eigenvalues [λ1, λ2, λ3], see Table S1, available online).

Region-of-Interest–Based DTI Findings in Female CD

Further analyses within six a priori–based regions of interest derived from the literature on male CD (i.e., the uncinate fasciculus, corpus callosum, corona radiata, fornix, cingulum, and fronto-occipital fasciculus) likewise confirmed several significant clusters of FA and MD alterations in girls with CD (Table 2). When compared to their typically developing peers, girls with CD displayed increased FA within the body of the corpus callosum, the right cingulate, and the left anterior part

TABLE 2 Montreal Neurological Institute (MNI) Peak Coordinates of Microstructural White Matter Alterations in Girls With Conduct Disorder (CD) Compared to Typically Developing Controls (TD)

No. Brain Region	L/R	Coordinates of Peak Location[a] X	Y	Z	Cluster Size (No. of Voxels)	*p* Value[b]
Fractional Anisotropy						
CD>TD						
1 Bilateral corpus callosum (body)	L	−1	−26	24	2,291	.038
2 Corpus callosum (body)[c]	R	1	−26	24	5,926	.005
3 Cingulum (cingulate)[c]	R	12	−23	34	544	.011
4 Corona radiata (anterior)[c]	L	−15	31	−3	91	.047
TD>CD						
5 Cingulum (hippocampal)[c]	L	−20	−18	−27	196	.040
6 Fornix[c]	R	2	−2	8	69	.046
Mean Diffusivity						
CD>TD						
1 Fornix[c]	R	3	−3	8	109	.040
TD>CD						
2 Corpus callosum (body)[c]	R	4	−24	26	5,490	.010
3 Cingulum (cingulate)[c]	R	7	−14	33	1,197	.004
4 Uncinate fasciculus[c]	R	38	−1	−18	156	.040

Note: L = left; R = right.
[a] *MNI space.*
[b] *Threshold-free cluster enhancement, p ≤ .05, familywise error corrected.*
[c] *Region of interest.*

of the corona radiata, but lower MD in the callosal body and right cingulate. The opposite pattern was observed for the left hippocampal part of the cingulum and the right hemispherical fornix, where FA was found to be significantly decreased in girls with CD, but MD was increased in the fornix. Finally, within the right uncinate fasciculus, girls with CD had lower MD, but no differences in FA, compared to typically developing girls.

Post Hoc Region of Interest Analysis

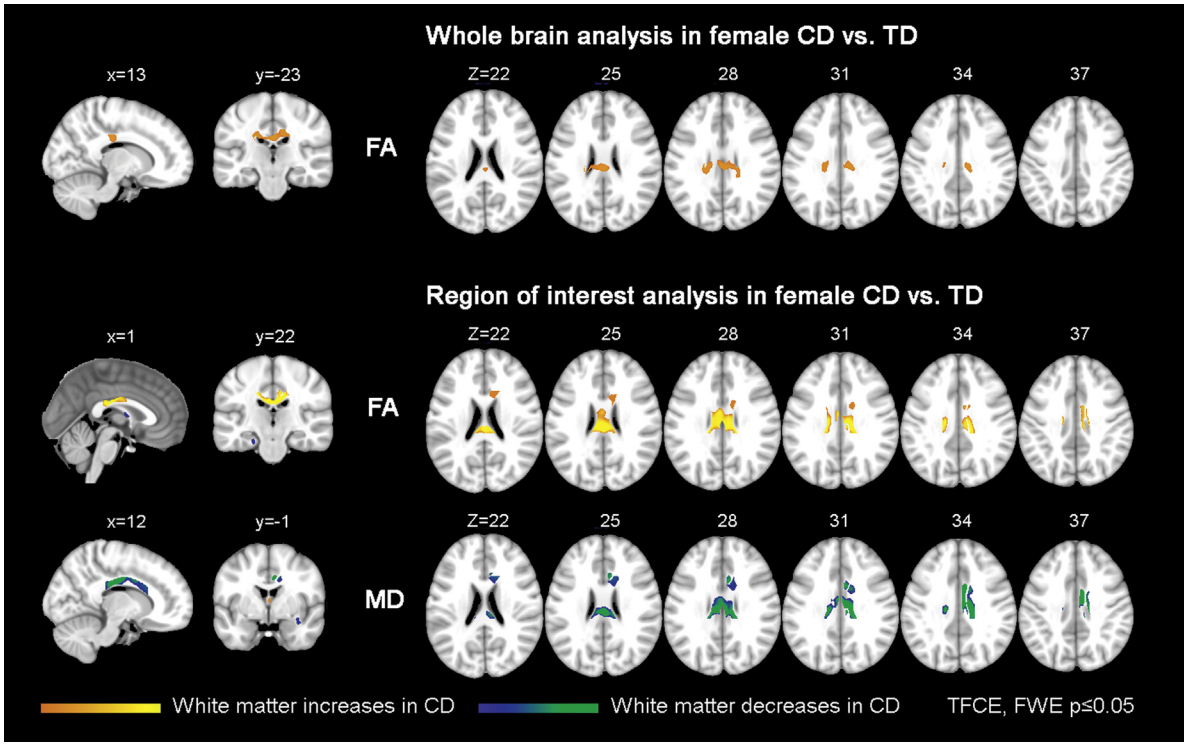
Correlation analyses indicated no significant relationship between callous-unemotional traits (either ICU or YPI) and the MD or FA values within anatomically defined regions of interest in the group of girls with CD. Furthermore, results of an additional DTI analysis excluding the nine girls with CD/ADHD remained significant (see Table S2, available online). In addition, a multiple linear regression analysis indicated that ADHD symptoms do not explain any additional variance observed within the results (R^2 change = 0.019; $F_{1,39}$ = 1.09; p = .303).

DISCUSSION

For the first time, we here describe white matter alterations in female adolescents with CD using a whole-brain DTI analysis. More specifically, female CD is characterized by increased FA scores within the body of the corpus callosum, expanding toward the right cingulum and the left corona radiata. Further investigations within a priori–defined regions of interest reveal additional clusters of significantly altered white matter integrity in brain areas including the bilateral cingulum, left anterior corona radiata, right uncinate fasciculus, and right fornix. Overall, these findings align with findings in male CD or adolescents with aggressive behavior.[4,12,17-20,40,41] These findings were corrected for age and IQ and were proved independent of ADHD symptoms, which is in line with previous studies indicating that characteristic CD alterations remain after removal/control for ADHD comorbidity.[4,5]

The herein-observed white matter alterations within the body of the corpus callosum are in line with previous research in CD. For example, Zhang *et al.*[17] used tract-based spatial statistics to demonstrate FA increases within the body and genu of the corpus callosum of male adolescents with CD. The corpus callosum is the largest white matter tract of the brain and is crucial for interhemispheric communication. It has abundant projections (so-called callosal radiations) to and from the cortices of both hemispheres, and is generally subdivided into three distinct areas: the genu, the body, and the splenium. Each part thereby connects functionally distinct brain regions. Whereas the genu connects parts of the frontal lobes (executive and higher-order cognitive processing) and the splenium temporal/occipital regions (visual processing), the body of the corpus callosum as identified here is specifically thought to connect motor, parietal, and temporal areas important for motoric and emotion processing tasks.[42] Interhemispheric processing is known to become progressively relevant with increasing cognitive demand. An intact connectivity through the body of the corpus callosum may

FIGURE 1 (Top) Increased fractional anisotropy (FA) values in the body of the corpus callosum in girls with conduct disorder (CD) compared to controls (TD). Note: In a priori–defined regions of interest, increased FA (middle) and mean diffusivity (MD) (bottom) alterations in CD were detected in areas including right corpus callosum, cingulum, left anterior corona radiata, right fornix, and uncinate fasciculus. FWE = familywise error.



thus be critical for enabling higher-order skills such as emotion regulation.[15] Furthermore, fibers of the callosal body connect to the insula,[43] a structure associated with emotion processing and commonly altered in CD.[14] We therefore conclude that changes in the body of the corpus callosum of girls with CD may result in reduced interhemispheric processing and consequent lower emotion regulation abilities. In line with our findings, callosal alterations are linked to several childhood-onset neuropsychiatric disorders (e.g., ADHD or developmental dyslexia).[44,45]

It is important to note that corpus callosum alterations are commonly identified; however, reports differ in regard to the precise underlying neuroanatomical variations. For example, two studies including mixed-gender groups of adolescents with and without CD reported no FA differences[46] but reduced radial diffusivity, which is the DTI measure for the transverse component of diffusion direction. Such inconsistencies may result from differences in the DTI methods or analysis approaches applied, small sample sizes, or missing group heterogeneity (e.g., clinical criteria) variation in accompanying traits (e.g., high/low callous-unemotional traits), unbalanced gender, or differences in the age of participants tested. For instance, previous studies have either used voxel-based analysis or tract-based spatial statistics (but rarely a combination), which may explain differences in results observed. Since DTI-TK has been shown to enhance the specificity of the normalization of DTI data,[33] we overall recommend using this tool (also prior to tract-based approaches) to increase sensitivity in future studies.

Developmentally, the corpus callosum matures throughout childhood and adolescence,[47] with a peak typically expected around 20 to 35 years of age.[47] Based on this knowledge, three possible explanations for FA increases in CD may be used: accelerated maturation, causing the FA peak to shift to an earlier age; an earlier degeneration following the initial overproliferation[4,17]; or compensatory processes following an initial undermyelination.[48] These explanations would be in line with the finding that adults with an antisocial personality disorder or a previous diagnosis of CD display FA reductions within the corpus callosum,[21,49] whereas increases are more commonly detected in younger individuals (e.g., the herein-presented findings of Zhang *et al.*[17]). Therefore, we agree with previous suggestions and hypothesize that an initial overacceleration of white matter maturation, either due to excessive stimulation following early life stress or as a consequence of a compensatory mechanism, cause the characteristic changes in the corpus callosum in adolescents with CD and may potentially be followed by the onset of an earlier degeneration. However, future studies implementing longitudinal designs are needed to test whether differences in white matter trajectories within the corpus callosum are original or are results of the behavioral challenges observed.

Investigating a priori–defined regions of interest-based data in males,[5,17-19] additional FA increases (i.e., in the right cingulum, left anterior, corona radiata) but also decreases (i.e., in the left hippocampal part of the cingulum and right fornix) were detected. One area identified is the cingulum, a large c-shaped white matter tract positioned directly above the corpus callosum and connecting frontal, temporal, and limbic brain regions. Its anterior part in particular is linked to cognitive and emotion processing.[50,51] In line with our results, structural (i.e., voxel-based morphometry, DTI, surface-based morphometry) and functional (e.g., emotion, empathy, and pain processing) cingulum alterations have been identified in CD.[7,13,18,21] In line with previous findings,[15,17,18,49] we identified the corona radiata to distinguish girls with CD from healthy controls.[18,24,25,52] Containing a fan-shaped array of ascending and descending projection fibers and fanning out widely,[50] the position of white matter alterations within this structure varies and remains debated. However, alterations within the left anterior corona radiata were linked to increased impulsivity.[17] Finally, we herein identified the fornix, a white matter tract connecting the hippocampus with the mammillary body, medial temporal lobe, and the anterior thalamic nuclei.[50,53] Being part of the limbic system, the fornix and hippocampus are crucial for learning and memory processes.[54] Reduced FA in the fornix and the uncinate fasciculus has been associated with early life stress,[21,55] which is common in the etiology of CD. It is worth mentioning that we did not observe FA alterations in the uncinated fasciculus in girls with CD, but only reduced MD values. A reduction in MD may indicate increased myelination or more compact white matter tracts; however, various factors (e.g., fiber crossings) may play a role.[56] Although reduced FA are consistently reported in male individuals with psychopathy,[41,49,57,58] findings in adolescent CD show decreases,[18,19] increases, or no changes in FA at all.[4,20,40,46] Differences may be due to variations in study designs, small sample sizes, unbalanced or single-sex studies, age/developmental differences, or no control for comorbidities.

A potential limitation of the present work is that the overall intelligence score was significantly lower in girls with CD. Although we used the overall intelligence score as a covariate of no interest within the analysis conducted, it is still possible that intelligence may have influenced the data. Interestingly, only verbal IQ differentiated girls with CD from controls, whereas performance IQ was comparable between the groups. Furthermore, past DTI studies focusing on intelligence have indicated that FA values are unrelated to variations in IQ.[59] According to past research age of CD onset may distinguish meaningful neurobiological subgroups.[4] This study included both child-onset (n = 5) and adolescent-onset (n = 19) CD in girls, which may have affected the final results. Although no study has yet demonstrated differences in white matter integrity between child- and adolescent-onset CD groups, it is recommended to investigate this topic further. Finally, some of the girls with CD had a diagnosis of alcohol and/or substance abuse, which was shown to strongly correlate with CD severity,[60,61] and consequent brain activation.[52] Therefore, we cannot exclude potential effects on the presented results.

Research has suggested that boys have an increased propensity to develop disruptive behavior disorders as opposed to girls, who require a higher loading of biological risk factors to develop CD.[62] An increased understanding of the neurobiological basis of CD across both genders is crucial to improve individualized diagnostics and to facilitate early detection of children at risk, in particular because a timely start of intervention program precedes success.[63] Here we have identified structural white matter changes specific for the corpus callosum in girls with a diagnosis of CD. Our findings align with results in male adolescents with CD who display corpus callosum deficits but who are on average about 2 years younger.[17] Thus it could be hypothesized that these alterations may indeed be a characteristic of both males and females with CD, however, linked to different sensitive periods. Continuous developmental research of the uniqueness and shared features of both female and male individuals with CD is needed to draw conclusions adaptable for both genders. &

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TABLE S1 Means and Standard Deviations (SD) for the λ1, λ2, λ3 Eigenvalues (10-3 mm^2/s) in the Corpus Callosum (Body) of Female Adolescents With Conduct Disorder (CD) and Typically Developing Controls (TD)

	λ1 (SD)	λ2 (SD)	λ3 (SD)
CD	1.34 (0.03)	0.63 (0.03)	0.53 (0.03)
TD	1.35 (0.05)	0.65 (0.04)	0.55 (0.04)

TABLE S2 Microstructural White Matter Alterations in 15 Girls With Conduct Disorder (CD) and Without Attention-Deficit/Hyperactivity Disorder (ADHD) Comorbidity Compared to 20 Typically Developing Controls (TD) Using Fractional Anisotropy (FA) and Mean Diffusivity (MD)

		Coordinates of Peak Location[a]				
No. Brain Region	L/R	X	Y	Z	Cluster Size (No. of Voxels)	*p* Value[b]
Fractional Anisotropy						
CD>TD						
1 Bilateral corpus callosum (body)	L	−1	−24	24	560	.046
2 Bilateral corpus callosum (body)	L	−13	−22	32	197	.050
3 Corpus callosum (body)[c]	R	1	−25	23	6,725	.003
4 Cingulum (cingulate)[c]	R	12	−23	34	159	.022
TD>CD						
5 Cingulum (hippocampal)[c]	L	−22	−20	−27	628	.005
Mean Diffusivity						
CD>TD						
—						
TD>CD						
1 Corpus callosum (body)[c]	R	4	−25	25	7,644	.003
2 Cingulum (cingulate)[c]	R	7	−13	33	903	.008
3 Uncinate fasciculus[c]	R	37	3	−20	58	.047

Note: L = left; R = right.

[a] *Neurological view (Montreal Neurological Institute space).*

[b] *Threshold-free cluster enhancement, p ≤ .05, familywise error corrected.*

[c] *Region of interest.*