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Gonzalez-Madruga, Karen; Rogers, Jack; Toschi, Nicola; Riccelli, Roberta; Smaragdi, Areti; Puzzo, Ignazio; Clanton, Roberta; Anderson, Jesper; Baumann, Sarah; Kohls, Gregor; Raschle, Nora Maria; Fehlbaum, Lynn Valérie; Menks, Willeke Martine; Stadler, Christina; Konrad, Kerstin; Freitag, Christine M.; De Brito, Stephane; Sonuga-Barke, Edmund; Fairchild, Graeme

DOI:

[10.1017/S0033291718003951](https://doi.org/10.1017/S0033291718003951)

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*Document Version*

Peer reviewed version

*Citation for published version (Harvard):*

Gonzalez-Madruga, K, Rogers, J, Toschi, N, Riccelli, R, Smaragdi, A, Puzzo, I, Clanton, R, Anderson, J, Baumann, S, Kohls, G, Raschle, NM, Fehlbaum, LV, Menks, WM, Stadler, C, Konrad, K, Freitag, CM, De Brito, S, Sonuga-Barke, E & Fairchild, G 2020, 'White matter microstructure of the extended limbic system in male and female youth with conduct disorder', *Psychological Medicine*, vol. 50, no. 1, pp. 58-67.  
<https://doi.org/10.1017/S0033291718003951>

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Checked for eligibility: 20/12/2018

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## **White matter microstructure of the extended limbic system in male and female youth with conduct disorder**

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Word count: 4540

Keywords: Conduct disorder, callous-unemotional traits, spherical deconvolution, tractography, ADHD, white matter, diffusion tensor imaging (DTI), sex differences.

## **Abstract**

**Background:** Previous studies of conduct disorder (CD) have reported structural and functional alterations in the limbic system. However, the white matter tracts that connect limbic regions have not been comprehensively studied. The uncinate fasciculus (UF), a tract connecting limbic to prefrontal regions, has been implicated in CD. However, CD-related alterations in other limbic tracts, such as the cingulum and the fornix, have not been investigated. Furthermore, few studies have examined the influence of sex and none have been adequately powered to test whether the relationship between CD and structural connectivity differs by sex. We examined whether adolescent males and females with CD exhibit differences in structural connectivity compared to typically-developing controls.

**Methods:** We acquired diffusion-weighted MRI data from 101 adolescents with CD (52 females) and 99 controls (50 females). Data were processed for deterministic spherical deconvolution tractography. Virtual dissections of the UF, the three subdivisions of the cingulum (retrosplenial, parahippocampal and subgenual cingulum), and the fornix were performed and measures of fractional anisotropy (FA) and hindrance-modulated orientational anisotropy (HMOA) were analysed.

**Results:** The CD group had lower FA and HMOA in the right retrosplenial cingulum tract relative to controls. Importantly, these effects were moderated by sex - males with CD significantly lower FA compared to male controls, whereas CD and control females did not differ.

**Conclusions:** Our results highlight the importance of considering sex when studying the neurobiological basis of CD. Sex differences in retrosplenial cingulum connectivity may contribute to sex differences in the clinical presentation of CD.

Word count abstract: 248

## 1 **Introduction**

2 Conduct Disorder (CD) is diagnosed in children and adolescents who display a pattern of behaviour in  
3 which societal rules and the rights of others are violated (American Psychiatric Association, 2013).  
4 Although the lifetime prevalence of CD is higher amongst males than females (by a ratio of  
5 approximately 2.4:1), it is increasingly prevalent in adolescent females. Individuals with CD have  
6 poor prognoses with negative adult outcomes that include criminality, alcohol abuse, unemployment,  
7 and poor mental and physical health. CD is one of the main reasons for referral to child and  
8 adolescent mental health services, and places a high burden on the affected individuals, families and  
9 society in general. Therefore, CD can be considered a major mental and public health priority and  
10 gaining a better understanding of its neurodevelopmental underpinnings is critical.

11  
12 It has been proposed that limbic system dysfunction may underlie antisocial behaviour. Brain regions  
13 that make up the limbic system include the anterior cingulate cortex (ACC) and posterior cingulate  
14 cortex (PCC), orbitofrontal cortex (OFC), ventromedial prefrontal cortex (vmPFC), hippocampus,  
15 hypothalamus, amygdala, and medial temporal lobe (Rolls, 2004, 2013). The limbic system is  
16 involved in emotion processing and regulation, reward-related decision-making and a range of other  
17 cognitive functions (Blair, 2008). Evidence implicating limbic brain structures in antisocial behaviour  
18 comes from a number of sources. Two structural magnetic resonance imaging (sMRI) meta-analyses  
19 concluded that the most robust abnormalities in grey matter volumes observed in this population are  
20 in limbic brain structures, such as the amygdala, ACC and vmPFC (Aoki et al., 2014; Raschle et al.,  
21 2015; Rogers and De Brito, 2016). In line with this, a recent meta-analysis of fMRI studies reported  
22 that CD individuals consistently displayed underactivation in the ACC and vmPFC during tasks  
23 involving emotion processing, and ‘hot’ (motivationally-relevant) executive functions, and in  
24 dorsolateral prefrontal cortex (dlPFC), dorsal ACC, and hippocampus during ‘cool’ (non-affective)  
25 executive function tasks (Alegria et al., 2016).

26  
27 Given this evidence for structural alterations and abnormal neural activity in limbic regions in  
28 individuals with CD, it is possible that the structural connections linking these regions are also  
29 compromised. The major limbic system white matter (WM) pathways include the fornix, the  
30 cingulum, and the uncinate fasciculus (UF; Catani et al., 2013). Structural connectivity and the micro-  
31 structural properties of brain tissue are frequently assessed using diffusion tensor imaging (DTI)  
32 techniques (Catani and Thiebaut de Schotten, 2012). However, previous DTI studies in youths with  
33 CD and related disorders have had several limitations. First, the majority of DTI studies in CD have  
34 focused on males (although see Menks et al., 2017). Therefore, possible sex differences in the  
35 microstructural integrity of limbic system-related tracts have not been investigated. This is important  
36 as the neurobiological basis of CD has been shown to differ in several respects between males and

37 females (Fairchild et al., 2013; Decety et al., 2015; Smaragdi et al., 2017). Only one small study  
38 directly compared males and females with CD (n=14 and 13, respectively) in terms of WM  
39 microstructure (Zhang et al., 2014). It investigated fractional anisotropy (FA) values of the UF using  
40 deterministic tractography (which investigates specific anatomical pathways). Interestingly, the  
41 authors found higher FA values in the UF in males, but not females, with CD. These preliminary  
42 findings suggest that WM microstructural alterations in temporo-frontal regions might be specific to  
43 males with CD.

44

45 Additionally, aside from one very recent study (Sethi et al., 2018), previous studies using DTI-based  
46 tractography methods in individuals with CD have largely focused on the UF tract (Passamonti et al.,  
47 2012; Sarkar et al., 2013; Zhang, Gao, et al., 2014). The fact that these studies focused on this tract  
48 may have been due to earlier studies in adults with antisocial personality disorder (ASPD; an adult  
49 condition of which CD is an antecedent) and psychopathy, finding lower FA in the UF in these  
50 individuals compared to healthy controls (Craig et al., 2009). However, opposite findings have been  
51 reported in youths with CD, who show higher FA values in the UF relative to healthy controls  
52 (Passamonti et al., 2012; Sarkar et al., 2013; Zhang, Gao, et al., 2014). Similarly, a study  
53 investigating the dorsal and ventral components of the cingulum tract, reported lower radial  
54 diffusivity (RD) in the dorsal cingulum bundle in individuals with CD compared to controls (Sethi et  
55 al., 2018). This was opposite to the pattern observed in adults with ASPD (Sethi et al., 2014). Several  
56 authors have suggested that the opposite patterns observed in WM microstructural measures in youths  
57 and adults might be due to abnormally accelerated maturation of WM tracts in individuals with CD  
58 (Passamonti et al., 2012; Sarkar et al., 2013b; Zhang, Gao, et al., 2014). Although these previous  
59 studies were important first steps in understanding CD-related alterations in structural connectivity,  
60 the focus of research needs to be expanded to consider additional limbic system tracts. It is also  
61 important to test whether alterations in WM microstructure are common or distinct across males and  
62 females with CD.

63

64 An additional limitation of prior studies is that they used either tractography methods or a  
65 characterization of WM diffusivity exclusively based on the diffusion tensor model. Although the  
66 diffusion tensor model is most frequently used to reconstruct WM tracts and characterise diffusivity in  
67 WM (Basser et al., 2000), this approach has several limitations. First, it is not well-suited for studying  
68 complex fibre configurations such as crossing fibres, branching regions or intra-voxel combinations  
69 of different tissue types (e.g., WM fibres and grey matter). Second, while FA is the most commonly  
70 used index to quantify water diffusivity in studies using tensor-based models, it is calculated at a  
71 voxel level and is determined by several microstructural and macrostructural features, such as  
72 myelination of WM fibres, size and packing density of cells and number of crossing fibres  
73 (Vanderauwera et al., 2015). Thus, partial volume effects (i.e., not fibre- or tissue -specific) can affect

74 DTI indices (e.g., FA, RD), and voxel-average diffusion MRI parameters such as FA, lack within-  
75 voxel single fibre population specificity (Dell'Acqua et al., 2013; Raffelt et al., 2015). Novel non-  
76 tensor models such as constrained spherical deconvolution (SD) have the potential to overcome these  
77 limitations and more accurately characterise the underlying architecture of specific WM tracts  
78 (Dell'Acqua et al., 2010). In addition, the hindrance-modulated orientational anisotropy (HMOA)  
79 index that can be derived using SD algorithms provides greater sensitivity in terms of detecting  
80 microstructural changes in specific WM tracts than FA (Dell'Acqua et al., 2013). Finally, most  
81 previous DTI studies included relatively small samples - typically groups of 15 participants or fewer  
82 (Sethi et al., 2018; Finger et al., 2012; Haney-Caron et al., 2014; Passamonti et al., 2012; Zhang, Gao,  
83 et al., 2014).

84

85 The present study addresses a number of these limitations, and extends previous findings by, first,  
86 examining sex differences in the relationship between CD and WM microstructure. Second, by  
87 examining two key limbic WM tracts overlooked in prior studies: the fornix and the cingulum  
88 bundles - the retrosplenial (RSC), parahippocampal (PHC) and subgenual cingulum (SGC; Jones et  
89 al., 2013) - as tracts plausibly involved in the pathophysiology of CD. Third, by enhancing statistical  
90 power and the robustness of our results by substantially increasing the sample size compared to  
91 previous studies. Finally, by employing a novel method – constrained SD. Recent studies have  
92 compared tensor versus non-tensor models in clinical samples and suggested that the latter approach  
93 provides more accurate and robust results (Auriat et al., 2015). However, to increase comparability  
94 with previous studies, we also estimated indices of FA - the most widely-used parameter in previous  
95 structural connectivity research.

96

97 We hypothesised that differences between CD and control groups would be most evident in limbic  
98 tracts involved in socio-emotional processes (i.e., subgenual cingulum, retrosplenial cingulum, and  
99 UF) in comparison with posterior and lateral limbic WM tracts (e.g., parahippocampal cingulum). We  
100 also hypothesised that CD-related alterations in WM microstructure would be most evident in males  
101 (Zhang et al., 2014). In addition, recent DTI studies have shown that individuals with CD and  
102 elevated callous-unemotional (CU) traits may differ from those with low levels of CU traits in terms  
103 of WM microstructural abnormalities (Sethi et al., 2018; Puzzo et al., 2017). Thus, we also  
104 investigated whether CU traits contributed to the WM microstructural alterations observed in CD. We  
105 also tested for correlations between WM measures and the grandiose-manipulative and impulsive-  
106 irresponsible subdimensions of psychopathy and CD symptoms.

## 107 **Methods**

## 108 **Participants**

109

110 Participants for this study were recruited at four different sites involved in the Neurobiology and  
111 Treatment of Female Conduct Disorder (FemNAT-CD; [www.femnat-cd.eu](http://www.femnat-cd.eu)) study - University of  
112 Southampton, University of Birmingham, University Hospital Aachen, and University of Basel. All  
113 participants and the majority of their parents underwent a diagnostic interview that was based on  
114 DSM-IV criteria (the Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and  
115 Lifetime; Kaufman et al., 1997). At the UK sites, IQ was assessed using the two subtest form of the  
116 Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999) whereas the German version of the  
117 Wechsler Intelligence Scale for Children (Wechsler, 2003) was used at the other sites. The *t* and  
118 standard scores from all sites were transformed into *z*-scores and then combined to yield estimates of  
119 full-scale IQ.

120 The Match program (Van Casteren and Davis, 2007) was used to select an IQ-, age- and gender-  
121 matched sample from the subset of participants for whom diffusion MRI data were available (*n*=325).  
122 There are dramatic changes in WM development across childhood and adolescence (Casey et al.,  
123 2008), thus we excluded children aged 9-12 years (*n*=57; see Supplementary Material for more  
124 information). A total sample of 200 adolescents (101 with conduct disorder (52 females) and 99  
125 healthy controls (50 females) was included in the present analyses – all aged 13-18 years. The Youth  
126 Psychopathic traits Inventory (YPI; Andershed et al., 2002); a self-report questionnaire assessing  
127 overall psychopathic traits and sub-dimensions of psychopathy, and the parent-report Inventory of  
128 Callous Unemotional traits (ICU; Essau, Sasagawa and Frick, 2006); a standardized measure  
129 including callous, uncaring and unemotional subscales, were used to assess psychopathic and callous-  
130 unemotional (CU) traits, respectively.

## 131 **Diffusion-weighted MRI data acquisition**

132

133 Diffusion-weighted MRI data were acquired with the following parameters: Repetition time (TR) =  
134 8000ms (Achieva), 8800ms (Tim-Trio), 7500ms (Prisma); echo-time (TE) = 87ms (Achieva), 92ms  
135 (Tim-Trio), 71ms (Prisma) and a bandwidth of 1633.3 Hz/Px (Achieva) or 1776 Hz/Px (Tim-Trio &  
136 Prisma); echo-spacing = 0.75ms (Achieva), 0.73ms (Tim-Trio), 0.65ms (Prisma); slice thickness =  
137 2.0mm; field of view (FOV) = 256 x 256 x 124mm; acquisition matrix = 128 x 128; voxel-size =  
138 2×2×2mm; 62 contiguous axial slices (no slice gap). Images were acquired with diffusion gradients  
139 (b-value=1500 s/mm<sup>2</sup>) applied in 64 non coplanar and non collinear directions and two b-value=0  
140 (s/mm<sup>2</sup>) volumes with reversed phase encoding (blip-up/blip-down), yielding pairs of images with  
141 distortions in opposite phase-encode directions to enable accurate estimation and correction for  
142 susceptibility-induced distortions.

143

144 **Pre-processing**

145

146 Datasets were corrected for head motion and eddy current distortions using FSL (Andersson and  
147 Sotiropoulos, 2016). Distortions in the magnetic field were estimated. The estimated field was  
148 subsequently used, together with all the diffusion data, to estimate eddy current-induced distortions  
149 and subject movement (Andersson and Sotiropoulos, 2016). Movement-induced signal dropout was  
150 identified and the lost signal was replaced by a non-parametric Q-space interpolation (Andersson et  
151 al., 2016).

152

153 Spherical deconvolution was calculated using the damped Richardson-Lucy algorithm (Dell'Acqua et  
154 al., 2010) with a fibre response parameter of  $\alpha = 1.5$ , 400 algorithm iterations, threshold parameters of  
155 0.06, and a harmonic order of 8 ( $l_{max}=8$ ). An absolute (0.1%) and relative (5%) threshold on the  
156 Fibre Orientation Distribution (FOD) amplitude were applied to exclude spurious local connections  
157 (Dell'Acqua et al., 2013).

158

159 Whole brain deterministic tractography was performed using a step size of 0.5mm with a limit set to  
160 display streamlines between 20 and 400 mm. The Euler algorithm was used to follow the orientation  
161 vector of least curvature (angle threshold of 45°). Spherical deconvolution and tractography analysis  
162 was performed using StarTrack software (<https://www.mr-startrack.com/>). Explore DTI was used for  
163 the tensor fit. Tensor-derived FA and HMOA values of WM microstructural organisation were  
164 exported to TrackVis. We report FA values in the present study for the purpose of increasing  
165 comparability with previous studies.

166

167 **Delineation of Regions of Interest**

168 TrackVis was used to reconstruct the fornix, cingulum bundle subdivisions and UF. Reconstruction of  
169 these tracts has previously been described (fornix and UF: (Stieltjes et al., 2013), and CB  
170 subdivisions: (Jones et al., 2013)). The Boolean logic (AND, and NOT gates) was employed to  
171 delineate the CB's subdivisions, the fornix and the UF (Figure 1 shows the reconstruction for all of  
172 the limbic WM tracts).

173

174 **Statistical analysis**

175 Matlab\_R2016 was used to carry out statistical analysis. Shapiro-Wilk tests were used to verify  
176 normality of HMOA and FA values across subjects.. Tract measures of HMOA and FA were analysed  
177 using a general linear model (GLM) to test for effects of diagnosis and sex-by-diagnosis interactions.



178 The GLM included the following covariates which have been shown to be associated with WM  
179 microstructural integrity in adolescent studies: age (Asato et al., 2010), IQ (Dunst et al., 2014), and  
180 site (coded as binary fixed effect). Where significant sex-by-diagnosis interactions were found, we  
181 followed these up by comparing FA and HMOA values between CD and healthy control males, and  
182 between CD and healthy control females.

183

184 ADHD is a neurodevelopmental disorder that frequently co-occurs with CD, and previous DTI studies  
185 have shown that comorbid ADHD strongly modulates WM effects (Wang et al., 2012). Thus, we  
186 repeated the GLM analysis while adding current ADHD symptoms (i.e., those displayed in the last  
187 year) as an additional covariate.

188

189 In addition, there is some evidence for structural differences between the childhood-onset (CO) and  
190 adolescent-onset (AO) variants of CD (Fairchild et al., 2015). Accordingly, we used the same model  
191 to compare these subgroups, to assess the validity of combining these subgroups in our main analysis.

192

193 The significance threshold was adjusted using the Benjamin-Hochberg false discovery rate (FDR:  
194  $q < 0.05$ ) correction for multiple comparisons across each parameter independently. Effect sizes for  
195 diagnosis effects were calculated using Cohen's  $d$  and effect sizes for sex-by-diagnosis interactions  
196 were expressed as partial eta-squared ( $\eta^2$ ).

197 In cases where significant main effects of diagnosis were observed, we followed these up by running  
198 a GLM analysis (only in the CD group), to test for associations between CD symptoms, psychopathy  
199 (YPI total), dimensions of psychopathic traits (grandiose-manipulative, and impulsive-irresponsible  
200 traits), CU traits (YPI subscale and ICU total), ICU subscales (callousness, uncaring, unemotional),  
201 and measures of HMOA and FA. Lastly, given that the CD sample included many individuals with  
202 comorbid ADHD, we also explored the relationship between ADHD symptoms and measures of  
203 HMOA and FA. These correlational analyses were run in a mixed-sex CD group (males and females  
204 with CD) as well as in each sex separately.

205

## 206 **Results**

### 207 **Demographic Variables**

208 Individuals in the CD group had significantly more CD, ODD, and ADHD symptoms than healthy  
209 controls. They also scored higher in overall psychopathic traits, as well as callous-unemotional,  
210 grandiose and manipulative, and impulsive and irresponsible subdimensions of psychopathy (Table

211 1). There were no significant differences between males and females in the age-of-onset of CD (i.e.,  
212 childhood-onset vs. adolescent-onset).

213

214 In terms of psychiatric comorbidity in individuals with CD, males and females differed only in rates  
215 of substance abuse (M>F); there were no other significant differences between males and females.  
216 Finally, there was an unequal sample distribution across the sites (see Supplementary Table 1). To  
217 address this issue, we included site as a covariate of no interest.

218

### 219 **Tractography results**

220 There were no significant differences between the CO-CD and AO-CD subtypes in HMOA or FA in  
221 any WM tract.

222

### 223 **Main effects of diagnosis**

224 Relative to controls, individuals with CD had lower HMOA in bilateral retrosplenial cingulum (RSC;  
225 right:  $t(190)=-2.22$ ,  $p=0.03$ ,  $d=0.10$ ; left:  $t(190)=-2.27$ ,  $p=0.02$ ,  $d=0.16$ ), and lower FA in the right  
226 RSC ( $t(190)=-2.91$ ,  $p=0.004$ ,  $d=0.28$ ). However, after correcting for multiple comparisons, only the  
227 effect on right RSC FA remained significant ( $pFDR=.03$ ; Figure 2). There were no significant group  
228 differences in HMOA or FA in any of the other limbic WM tracts.

229

### 230 **Sex-by-diagnosis interactions**

231 We observed sex-by-diagnosis interactions for HMOA in bilateral RSC (right:  $t(190)=2.08$ ,  $p=0.04$ ,  
232  $\eta^2=0.02$ ; left:  $t(190)=1.99$ ,  $p=0.05$ ,  $\eta^2=0.02$ ), and FA in right RSC ( $t(190)=2.75$ ,  $p=0.006$ ,  
233  $\eta^2=0.04$ ). All interactions followed the same pattern: males with CD showed lower values than male  
234 controls, whereas females with CD showed higher values than female controls (Figure 3). However,  
235 only the sex-by-diagnosis interaction for right RSC FA survived correction for multiple comparisons  
236 ( $pFDR=.05$ ). No other significant interaction effects were found in the other limbic tracts (see  
237 Supplementary Table 2). Post-hoc analysis showed that relative to male controls, CD males had lower  
238 HMOA in bilateral retrosplenial cingulum (RSC; right:  $t(190)=-2.52$ ,  $p=0.04$ ,  $d=0.39$ ; left:  $t(190)=-$   
239  $1.99$ ,  $p=0.04$ ,  $d=0.37$ ) and lower FA in the right RSC ( $t(190)=-2.91$ ,  $p=0.01$ ,  $d=0.47$ ). However, after  
240 correcting for multiple comparisons, only the effect in right RSC FA remained significant  
241 ( $pFDR=.03$ ). There were no significant differences between female CD and control groups.

242

### 243 **ADHD comorbidity as a potential confound**

244 The main effects of diagnosis observed for FA in the right RSC ( $p=0.03$ ) and for HMOA in bilateral  
245 RSC (left:  $p=0.05$ ; right:  $p=0.05$ ) in CD versus healthy control males remained significant after

246 factoring out current ADHD symptoms. However, only the group difference in right RSC FA  
247 remained significant (pFDR=0.03) after correcting for multiple comparisons. Moreover, significant  
248 main effects of diagnosis emerged in the right UF when factoring out ADHD symptoms: participants  
249 with CD showed lower FA ( $t(189)=2.00$ ,  $p=0.05$ , pFDR=0.05), and HMOA ( $t(189)=2.07$ ,  $p=0.04$ ,  
250 pFDR=0.05; Figure S1) relative to healthy controls. Unlike the findings for the RSC, this main effect  
251 of diagnosis in the UF was not qualified by a significant sex-by-diagnosis interaction.

252

### 253 **Correlations between structural connectivity measures and CD symptoms, ADHD symptoms,** 254 **and psychopathic or callous-unemotional traits**

255

256 Within the CD sample, there was a positive correlation between current CD symptoms and right RSC  
257 HMOA ( $r=.36$ , pFDR=0.02; Figure 4). There were no other significant correlations between CD,  
258 ADHD symptoms, overall psychopathic traits, the subdimensions of psychopathy, CU traits or the  
259 ICU subscales (Callousness, Uncaring, Unemotional) and measures of WM in other tracts.

260

261 As effects of diagnosis were found in males, but not in females with CD, we conducted correlational  
262 analyses in males and female groups separately. A strong positive correlation between current CD  
263 symptoms ( $r=.45$ , pFDR=0.002; Figure S2), and a negative correlation between current ADHD  
264 symptoms ( $r= -.31$ , pFDR=0.03; Figure S3) and right RSC HMOA was found in the male CD group.  
265 No effects of CU or psychopathic traits were observed in CD males. No significant correlations were  
266 found between clinical symptoms or CU/psychopathic traits or subscales and measures of structural  
267 connectivity in females with CD. Moreover, there were no significant sex-by-CD symptoms or sex-  
268 by-CU/psychopathic traits interactions for either HMOA or FA.

269

270

### 271 **Discussion**

272 Abnormalities in the limbic system have been consistently implicated in the pathophysiology of CD  
273 (Alegria et al., 2016; Raschle et al., 2015; Rogers and De Brito, 2016). We extended the DTI  
274 literature by including female participants and a much larger sample than has been studied to date  
275 (N=200). This allowed us to test whether females and males with CD show common or distinct  
276 alterations in limbic WM microstructure. We also investigated limbic WM tracts beyond the UF and  
277 capitalised on recent methodological advances in diffusion-weighted image processing by employing  
278 spherical deconvolution (SD) models. This approach provides a more reliable estimation of multiple  
279 fibres passing through a voxel with distinct orientations.

280

281 Our findings extend knowledge regarding alterations in limbic WM tracts in CD and support the  
282 hypothesis that abnormalities in fronto-limbic tracts are involved in the pathophysiology of this  
283 disorder. However, such abnormalities appear to be limited to males with CD – no such effects were  
284 found in females. More specifically, only males with CD showed lower FA in the right RSC relative  
285 to male controls. In fact, there was a suggestion that the opposite pattern was observed in females  
286 (females with CD appeared to show higher FA and HMOA values relative to control females) –  
287 although this was not statistically significant.

288

289 Previous DTI studies have found structural abnormalities in regions that overlap with the RSC. A  
290 recent study using a similar approach to the present study (i.e., region of interest-based tractography)  
291 investigated dorsal and ventral cingulum WM microstructure in male youths with CD (Sethi et al.,  
292 2018). Lower RD values were observed in bilateral dorsal cingulum in the CD group relative to  
293 controls (Sethi et al., 2018). FA values normally increase when RD decreases, and the opposite  
294 pattern seems associated with myelin loss and axonal abnormalities (Harsan et al., 2006). Although  
295 the anatomical delineation of the cingulum bundle differed between the two studies (i.e., dorsal and  
296 ventral in Sethi et al. versus retrosplenial, parahippocampal and subgenual cingulum in the present  
297 study), the dorsal part of the cingulum overlaps most closely with the RSC tract compared to the other  
298 cingulum bundles – thus the findings are congruent in terms of location, but not in the direction of the  
299 effects. In addition, the Sethi et al. (2018) study differs from the present study in the use of tensor-  
300 based models versus non-tensor models.

301

302 The RSC is composed of fibres that connect the medial prefrontal cortex, dlPFC, ACC, PCC, medial  
303 temporal lobe, and angular gyrus together (Jones et al., 2013). These regions have been associated  
304 with social-emotional processing, self-reflection, executive functions and moral decision-making.  
305 They are key nodes of the default mode network (DMN) that is responsible for self-referential  
306 processing (Leech et al., 2012). Previous studies investigating DMN connectivity in youths with CD  
307 have reported reduced connectivity between core DMN regions including the medial PFC, PCC,  
308 precuneus and superior temporal gyrus, relative to controls (Broulidakis et al., 2016; Zhou et al.,  
309 2016). It has been proposed that DMN dysfunction in CD may reflect delays in the development of  
310 brain circuits linked to self-awareness, regulating emotions, moral judgments and future planning  
311 (Zhou et al., 2015). Impairments in these processes have been reported in CD (e.g. White et al., 2014).  
312 The RSC connects core regions that make up the DMN. Thus, the abnormal functional connectivity of  
313 the DMN observed in previous studies may have a structural basis in altered RSC connectivity.

314

315 Although group differences in FA in the UF only became significant after controlling for comorbid  
316 ADHD symptoms, our results are in contrast to findings reported by Zhang et al. (2014). We did not  
317 observe any sex-by-diagnosis interactions in this WM tract. Both males and females with CD

318 appeared to be equally affected in terms of showing lower UF FA. However, in line with Zhang et al.  
319 (2014), we also observed sex differences in the RSC tract in youths with CD. Males with CD showed  
320 lower FA (and HMOA at an uncorrected level) relative to sex-matched healthy controls, whereas  
321 there were no significant differences between CD and control females.

322 Previous DTI studies of CD have observed higher FA values in male-only samples, suggesting  
323 accelerated maturation in individuals with CD. Here, we observed lower FA in males with CD  
324 compared to male controls. Although the results observed here were in a previously unstudied tract, it  
325 suggests that WM maturation is delayed in males with CD. Delayed maturation of WM is associated  
326 with poor inhibitory control (Simmonds et al., 2014) - a key feature of CD.

327

328 Furthermore, our correlational analyses showed that CD symptoms were significantly (positively)  
329 correlated with HMOA of the right RSC tract in males, but not females. Therefore, the present study  
330 provides new evidence for sex differences in the neurobiological basis of CD – RSC WM  
331 abnormalities were observed in males but not females. We also observed a significant negative  
332 correlation between ADHD symptoms and HMOA in the right RSC tract in males but not females,  
333 indicating that ADHD comorbidity may have influenced the differences between CD and control  
334 males in the RSC. This is of significance due to the substantial overlap of ADHD and CD, and  
335 symptom dimensions related to ADHD such as impulsivity and hyperactivity have been associated  
336 with the development of antisocial behaviour in childhood (Barkley et al., 2004).

337 Several neuropsychological studies investigating aspects of executive functioning (i.e., assessing  
338 inhibition/attention and decision-making), are consistent with our findings by showing divergent  
339 results in males and females with CD. Males with CD exhibit deficits in reversal learning (Herpertz et  
340 al., 2008) and differ in terms of decision-making (e.g., making more risky choices) relative to control  
341 males, whereas CD females do not differ from control females (Sidlauskaite et al., 2017). In addition,  
342 our finding of a sex-by-diagnosis interaction in the RSC highlights the importance of taking sex into  
343 account when studying the neurobiology of CD, and the problems that might arise when combining  
344 males and females with CD in the same group (Smaragdi et al., 2017). Future studies should  
345 investigate the functional consequences of altered RSC structural connectivity in males and females  
346 with CD by employing resting state functional connectivity methods, and by using  
347 neuropsychological tasks tapping decision-making and empathic processes in the same sample.

348

### 349 **Strengths and limitations**

350

351 The strengths of this study include the investigation of additional limbic WM tracts by using a more  
352 comprehensive approach – SD tractography. The main benefit of this approach is to resolve fibre-

353 crossing issues. In addition, SD techniques improve the accuracy of fibre tracking compared to  
354 models based on the diffusion tensor alone (Dell'Acqua et al., 2010). Secondly, the comparatively  
355 large sample size in the present study (N=200), which included males and females with and without  
356 CD, allowed us, for the first time, to comprehensively investigate sex differences in the relationship  
357 between CD and structural connectivity. Another strength is the fact that the CD group was assessed  
358 using standardised, semi-structured interviews based on DSM-IV criteria as well as obtaining detailed  
359 information about comorbid disorders and accounting for ADHD comorbidity in our statistical  
360 analyses.

361

362 However, our study also had several limitations. First, the sample ranged in age from 13-18 years.  
363 The CD and control groups did not differ in age; however, age is known to have an important effect  
364 on white matter development. Thus, we included age as a covariate of no interest in all analyses.  
365 Second, the sex distribution across the sites was uneven (more girls were tested at some sites than  
366 others), and although quality control procedures were performed prior to starting data acquisition  
367 (e.g., matching acquisition parameters and going through a site qualification process), combining data  
368 from different sites and scanner manufacturers (Phillips and Siemens) may introduce unintended  
369 variability. However, to reduce the impact of this variability, all analyses included site as a covariate  
370 of no interest. Finally, although we used SD methods to reconstruct the WM tracts, indices of FA  
371 were derived from tensor-based models fitted to b=1500 diffusion-weighted data and projected onto  
372 the SD-derived tracts. Hence there is a potential source of variability in terms of comparing the  
373 present FA measures with those reported in previous studies, although several earlier studies adopted  
374 a similar approach (e.g., Christiansen et al., 2016, Rojkova et al., 2016).

375

376 In conclusion, we found that male adolescents with CD differed from healthy controls in retrosplenial  
377 cingulum white matter microstructure – showing lower FA and HMOA values in this tract. This effect  
378 was not seen in females with CD. These differences in structural connectivity may help explain sex  
379 differences in CD and its clinical presentation. Given the overlap of the RSC tract with brain regions  
380 that constitute the DMN, and its role in connecting these regions together, future studies should  
381 investigate whether there are sex differences in DMN functional connectivity in CD. This would  
382 improve our understanding of the pathophysiology of CD and could lead to improved diagnosis and  
383 treatments for both sexes.

384

### 385 **Acknowledgments**

386 We sincerely thank our participants and their families for taking part in this study. We also thank Dr.  
387 Flavio Dell'Acqua for his guidance and advice in this study, and Dr. Etta Howells for providing  
388 training in white matter tract dissection. Karen Gonzalez-Madruga was partly funded by a PhD  
389 studentship from the National Council of Science and Technology (CONACYT), Mexico.

390

391 **Financial Support**

392 This study was funded by the European Commission's Seventh Framework Programme for research,  
393 technological development and demonstration (FP7/ 2007 – 2013) under Grant Agreement no.  
394 602407 (FemNAT-CD; coordinator: Professor Christine Freitag, Goethe University).

395

396 **Conflicts of interest**

397 Prof. Freitag receives royalties for books on Attention-Deficit/Hyperactivity Disorder and Autism  
398 Spectrum Disorder. She has served as consultant to Desitin and Roche. Prof. Sonuga-Barke has  
399 received speaker fees, consultancy, research funding and conference support from Shire Pharma.  
400 Speaker fees from Janssen Cilag, consultancy from Neurotech solutions, Aarhus University,  
401 Copenhagen University and Berhandlerling, Skolerne, Copenhagen, KU Leuven. Book royalties from  
402 OUP and Jessica Kingsle. Edmund Sonuga-Barke has been awarded grants from the MRC, ESRC,  
403 Wellcome Trust, Solent NHS Trust, European Commission, Child Health Research Foundation New  
404 Zealand, NIHR, Nuffield Foundation, Fonds Wetenschappelijk Onderzoek-Vlan-deren (FWO), and  
405 MQ—Transforming Mental Health. Dr. Fairchild has received funding from the European  
406 Commission, the UK Medical Research Council, the National Council for Science and Technology  
407 (CONACYT), the UK Economic and Social Research Council and Kids' Company. Prof. Konrad has  
408 received speaker fees from Shire Pharmaceuticals and Medice. Prof. Stadler receives royalties for a  
409 book on aggression. Dr. De Brito has received speaker fees from the Child Mental Health Centre and  
410 the Centre for Integrated Molecular Brain Imaging. All other co-authors declare no potential conflicts  
411 of interest.

412

413

414 **Ethical standards**

415 The authors assert that all procedures contributing to this work comply with the ethical standards of  
416 the relevant national and institutional committees on human experimentation and with the Helsinki  
417 Declaration of 1975, as revised in 2008.

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