Chapter 7

Conduct Problem Severity in mid Adolescence related to Decreased Fractional Anisotropy


In revision
Abstract

Previous studies of white matter integrity (i.e., fractional anisotropy \[ FA \]) have yielded conflicting results adolescents with Conduct Disorder (CD), with some studies showing reduced FA (Breeden, Cardinale, Lozier, VanMeter, & Marsh, 2015; Haney-Caron, Caprihan, & Stevens, 2014) and others increased FA (Passamonti et al., 2012; Sarkar et al., 2012; Zhang et al., 2014). Results have also been inconsistent in relation to associations between symptom severity and FA (Breeden et al., 2015; Haney-Caron et al., 2014; Sarkar et al., 2012; Zhang et al., 2014). The aim of the current study was to investigate FA, and its development, in relation to conduct problem (CP) severity in a large community-based sample of adolescents. Participants completed Magnetic Resonance Imaging scans at mid (baseline) and late adolescence and CP were assessed via parent questionnaires. In total, 115 adolescents (56 males) participated at baseline (mean age 16.63, SD 0.50) and 68 adolescents (32 males) during late adolescence (mean age 19.02, SD 0.46). The relationship between both baseline and change in CP and FA in the uncinate fasciculus (UF) was investigated. To investigate specificity, the inferior longitudinal fasciculus (ILF), the inferior fronto-occipital fasciculus (IFOF) and the superior longitudinal fasciculus (SLF) were also investigated. Group-comparison for sub-/clinical versus low CP using a general linear model was performed and whole brain comparison (TBSS) was included. Results showed that higher CP were related to decreased FA at baseline in the UF, as well as the ILF when comparing CP groups. Whole brain comparison indicated decreased FA in the IFOF for sub-/clinical CP group. Furthermore, results indicated developmental changes in FA were not related to changes in CP from mid to late adolescence. The current study showed that decreases in FA are related to variation in CP severity during mid adolescence in a large community-based sample.

Keywords. Conduct problems, Diffusion Tensor imaging, White matter, Uncinate fasciculus, Adolescence
Unravelling the neurobiological correlates of adolescent antisocial behaviours can significantly contribute to our understanding of the development of these behaviours and possibly contribute to more tailored intervention and prevention strategies in paediatric health. Investigation of brain structure might be fruitful in this regard. Neuroimaging studies have reported structural abnormalities related to antisocial behaviour (e.g., aggression, psychopathy and conduct disorder (CD)) in the frontal and temporal lobes, and in the limbic system (De Brito et al., 2009; Fairchild et al., 2011, 2013; Wahlund & Kristiansson, 2009; Weber, Habel, Amunts, & Schneider, 2008; Yang & Raine, 2009). Paediatric brain maturation is thought to be critical for understanding risk pathways for psychopathology in general (Di Martino et al., 2014). Further, alterations in the trajectory of anatomical brain development have been proposed as an intermediate phenotype (i.e., a bridge between genetic and phenotypic factors) for neurodevelopmental disorders (Giedd, 2008).

In addition to cortical grey matter development, brain maturation involves refinement of connectivity through white matter tracts. It has been shown that normative development of white matter involves an increase of white matter integrity (i.e., fractional anisotropy (FA)) during adolescence (Lebel et al., 2012). Abnormalities in white matter integrity have been shown in neurodevelopmental disorders such as schizophrenia, depression and autism (Di Martino et al., 2014). Few studies have investigated white matter abnormalities in CD adolescents (Haney-Caron et al., 2014; Passamonti et al., 2012; Sarkar et al., 2012; Zhang et al., 2014). These studies have typically focused the uncinate fasciculus (UF), a major fibre tract connecting the frontal and the temporal lobes. For example, Passamonti and colleagues (2012) showed increased FA in the UF of CD adolescents compared to healthy controls. Sarkar and colleagues (2012) also found increased FA in the UF for CD adolescent males (with increased FA related to increased CD severity). Recently, Sarkar and colleagues (2016) reported more widespread increases within a similar sample. However, Haney-Caron and colleagues (2014) found widespread decreases in FA, but not in the UF, for adolescents diagnosed with CD. Specifically, major fibre tracts connecting the frontal lobe to other areas showed reductions in FA, including fibres within the anterior and superior corona radiata, fronto-occipital fasciculi (frontal and temporal lobes) and the left inferior longitudinal fasciculus. Further, these authors found widespread decreases in FA to be related to CD severity (in addition to two areas in the thalamus showing increased FA).
Finally, Breeden and colleagues (2015) found FA decreases in the stria terminalis/ fornix and the UF related to externalising symptoms and callous-unemotional traits in CD adolescents. Discrepancies between these studies may be due to methodological differences (e.g., tractography versus whole brain analysis), small sample sizes, mixed sex samples and/or different adolescent developmental stages of the included samples. Studies including adult antisocial populations have shown more consistent results, such as reduced FA compared to controls (Craig et al., 2009; Hoppenbrouwers et al., 2013; Motzkin, Newman, Kiehl, & Koenigs, 2011; Sundram et al., 2012) and reduced FA related to severity of psychopathy (Craig et al., 2009; Sobhani, Baker, Martins, Tuvblad, & Aziz-Zadeh, 2015; Wolf et al., 2015).

It remains unclear whether CD and/or adolescent conduct problem severity is related to increased or decreased white matter integrity and whether these changes are specific to particular white matter tracts. Interestingly, while Hummer and colleagues (2014) found no FA differences between CD and healthy adolescents, they did report an age-related increase of FA within the superior longitudinal fasciculus (SLF) in the healthy controls while this was absent for CD adolescents. While this study provides some evidence that development of white matter may be important in the development of adolescent conduct problems, further longitudinal research is required to more thoroughly test this speculation. Furthermore, it has been shown that FA abnormalities might be different for CD males versus females (Zhang et al., 2014). Zhang and colleagues reported that CD males showed increased FA in the UF compared to healthy males, while CD females showed (non significant) decreases FA in the UF compared to healthy females. As such, it is important to consider gender differences and developmental stages and/or age differences when investigating white matter integrity and its relation to adolescent conduct problems.

The current study aimed to investigate severity of conduct problems in relation to white matter integrity (i.e., FA) in mid adolescence in a large community-based sample. Furthermore, the development of white matter integrity from mid to late adolescence in relation to conduct problems was explored. It was hypothesised that white matter abnormalities (i.e., FA) would be related to CP symptom severity in mid adolescence, particularly in the UF. Furthermore, it was hypothesised that changes in white matter integrity will be related to changes in CP severity. While gender differences were examined, due
to the paucity of previous literature, no specific hypotheses were made. Supplementary analysis investigated both AD and RD in relation to CP symptom severity.

Methods

Participants

Participants in this study were a subsample of the Orygen Adolescent Development Study cohort, recruited from Melbourne, Australia. Based on the Early Adolescent Temperament Questionnaire-Revised (EATQ-R; Capaldi & Rothbart, 1992) students in their final year of primary school were selected, previously described by Yap, Allen and Ladouceur (2008). Children at extreme ends of the temperamental distribution were oversampled. Children who had no chronic illness, language or learning disabilities and did not use medication known to affect nervous system functioning were asked to take part in longitudinal research. Intelligence and Socioeconomic Status (SES) were assessed as part of a baseline assessment (~12 years old) of the larger study. Intelligence was assessed by the short form of the Wechler Intelligence Scale for Children (WISC). SES was estimated using the Australian National University Four (ANU4; Jones & McMillan, 2001) ranging from 0 – 100. The current study utilised data from Diffusion Tension Imaging (DTI) and questionnaire based assessments in mid (~16 years old) and late adolescence (~19 years old). Informed consent was obtained from the child and at least one parent/guardian at each assessment, consistent with guidelines of the Human Research Ethics Committee at The University of Melbourne, Australia.

Imaging processing

DTI images were acquired using a 3 Tesla system (MAGNETOM Trio, A Tim System, Siemens Medical Solutions) located at the Royal Children’s Hospital, Melbourne. DTI was obtained using a high angular resolution diffusion imaging (HARDI) acquisition. Gradient-weighted volumes were acquired using a multidirection, twice-refocused spin-echo echoplanar imaging sequence with the following parameters: 70 directions; diffusion-sensitising gradient (b-value) 2000
s/mm²; slice thickness 2.3 mm; repetition time (TR) 7300 ms; echo time (TE) 104 ms; field of view (FOV) 240 mm²; image matrix 104 x 104; and voxel size 2.3 mm³ (isotropic). Twice-refocused spin-echo has been shown to reduce eddy current-induced distortion (Reese, Heid, Weisskoff, & Wedeen, 2003). In addition, seven T2-weighted (i.e., b-value 0; no gradient weighting) volumes were acquired, interspersed throughout the gradient-weighted volumes. For the high-resolution T1-weighted acquisition, a three-dimensional magnetization-prepared rapid acquisition gradient echo sequence was used to obtain 176 T1-weighted contiguous 0.9-mm-thick slices. Imaging parameters were as follows: TR 1900 ms; TE 2.24 ms; flip angle 9°; FOV 230 mm²; image matrix 256 x 256; voxel size 0.9 mm³ (isotropic).

An initial data quality check ensured that excessive motion artefacts or noise were identified and excluded from the sample. For each participant, correction for the effects of head movements and eddy currents was performed at each time point. A brain mask was created by using one of the b=0 images and images were aligned into a common space using the nonlinear registration tool FNIRT (Andersson, Jenkinson, & Smith, 2007; Andersson, Jenkinson, & Smith, 2007) and FLIRT (Jenkinson, Bannister, Brady, & Smith, 2002). Finally, a mean FA skeleton was created based on the mean of the normalised FA maps and the aligned FA data for each subject was projected on this skeleton.

**Regions of interest**

Earlier connectivity studies of antisocial behaviour typically implicate fractional anisotropy (FA) in the uncinate fasciculus (UF) a white matter pathway directly connecting the frontal with the temporal lobes (Finger et al., 2012; Haney-Caron et al., 2014; Passamonti et al., 2012; Sarkar et al., 2013). As such the UF was investigated as the main region of interest (ROI). To investigate specificity of UF white matter abnormalities, the inferior longitudinal fasciculus (ILF), inferior fronto-occipital fasciculus (IFOF) and the superior longitudinal fasciculus (SLF) were included in ROI analyses. The JHU white matter tractography atlas was used to create a ROI map for each of these tracts and individual’s FA was extracted from each ROI separately. To assess the development of white matter integrity the percentile FA change from mid to late adolescence was calculated for each ROI. Additionally, whole brain voxelwise statistical analysis of FA data
was carried out using TBSS (Tract-Based Spatial Statistics; Smith, Jenkinson, & Johansen-Berg, 2006) part of FSL (Smith et al., 2004).

**Conduct Problems**

Conduct problems were measured during mid and late adolescence using the Child Behavioural CheckList (CBCL; Achenbach et al., 2008) filled in by one of the parents of the adolescents involved in the study. Each item is answered with a Likert scale consisting of ‘not true (1)’, ‘sometimes/somewhat true (2)’, or ‘often/totally true (3)’. The scale ‘Conduct Problems’ (CP) was used to assess conduct problem severity. Converted T-scores between 65 and 69 indicate subclinical problems, and T-scores above 69 indicate clinically relevant problems. The CBCL is a widely used questionnaire for assessing behavioural problems in children and adolescents and has shown good reliability (Achenbach et al., 2008).

**Callous Unemotional traits**

The Antisocial Personality Screening Device (APSD; Frick & Hare, 2001) was used to assess callous unemotional (CU) traits during mid-adolescence. The APSD consists of 20 self-report items each answered with a Likert scale consisting of ‘not at all true (0)’, ‘sometimes true (1)’, or ‘definitely true (2)’. Validity and reliability has been demonstrated (Muñoz & Frick, 2007). The CU subscale, consisting of 6 items, was calculated to assess CU traits specifically. Timing of the APSD assessment differed for CBCL questionnaire/ Imaging assessment. On average, this assessment was 19.7 months (S.D. 5.7) earlier then the CBCL questionnaire/ Imaging assessment in mid adolescence.

**Statistical analysis**

**Cross-sectional analyses**

The association between CP severity and white matter integrity during mid adolescence was investigated in two ways. First, to replicate group-comparison
results from earlier studies, the sample was divided into sub-/clinical CP group and a low CP group. Adolescents were allocated to either group based their converted CBCL T-score. Scores between 65 and 69 (indicating subclinical problems), and scores above 69 (indicating clinically relevant problems) formed the sub-/clinical groups, and scores below 65 formed the low CP group. Significant differences were investigated using a General Linear Model (GLM) with CP group as the fixed factor with age and gender as a covariate. Gender differences were not tested due to low power. CU traits were included as a covariate in follow-up analyses. Additionally, whole brain analysis of FA data was carried out using TBSS (Smith et al., 2006) including age and gender as covariates.

Second, correlations analyses were carried out to investigate whether severity of CP was related to white matter integrity (i.e., FA) in each of the ROIs in mid adolescence. Age and gender were included as covariates. In additional analyses, CU traits were entered as a covariate to assess whether white matter integrity in relation to CP was driven by CU traits (Breeden et al., 2015). To investigate whether males and females showed different relationships between FA and CP (Zhang et al., 2014), separate correlation analyses were performed for males and females. The correlation coefficients were tested for significant differences. Additionally, whole brain analyses of FA data was carried out using TBSS (Smith et al., 2006) including age and gender as covariates.

Supplementary analysis investigated mean axial (AD) and radial diffusivity (RD) in relation to CP symptom severity. Significant differences were investigated using a General Linear Model (GLM) with CP group as the fixed factor with age and gender as a covariate. Second, correlations analyses were carried out to investigate whether severity of CP was related to in each AD and RD of the ROIs in mid adolescence. Age and gender were included as covariates.

**Longitudinal analyses**

Correlation analyses were performed to assess associations between changes in CP and the percentile change score for FA for each ROI from mid to late adolescence. The time from mid to late adolescence and gender were included as covariates.
Results

Group-analyses

The two CP groups showed similar age and SES, the sub-/clinical CP group showed significantly lower IQ1 (see Table 1). Significant group differences were observed in the right UF and the left and right ILF (Table 2), and for the left IFOF a trend towards significance was observed. When additionally correcting for CU traits results were no longer significant, however trends towards significance were observed in the right UF (p=.074), the left ILF (p=.073). The TBSS analyses revealed a significant cluster with FA reductions for the sub-/clinical CP group relative to the low CP group within the IFOF tract of the left hemisphere (TFCE-clusterwise p<.05 corrected) located on the junction with the UF (see Figure 1).

Table 1
Descriptive statistics for the low and sub-/clinical CP group.

<table>
<thead>
<tr>
<th></th>
<th>sub-/clinical CP</th>
<th>low CP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=15</td>
<td>n=100</td>
</tr>
<tr>
<td></td>
<td>60% male</td>
<td>47% male</td>
</tr>
<tr>
<td>Age</td>
<td>16.70 (.34)</td>
<td>16.64 (.50)</td>
</tr>
<tr>
<td>IQ**</td>
<td>96.29 (10.28)</td>
<td>106.63 (11.31)</td>
</tr>
<tr>
<td>SES</td>
<td>50.60 (18.67)</td>
<td>59.32 (21.20)</td>
</tr>
<tr>
<td>CP**</td>
<td>70.60 (6.08)</td>
<td>52.68 (3.92)</td>
</tr>
<tr>
<td>CU traits</td>
<td>3.64 (1.91)</td>
<td>3.00 (1.89)</td>
</tr>
</tbody>
</table>

Note. **p<.005, CP= conduct problems T-scores, SES= social economic status.
Table 2
Group comparison for FA values in mid adolescence, while controlling for age and gender.

<table>
<thead>
<tr>
<th></th>
<th>sub-/clinical CP n=15</th>
<th>low CP n=100</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>UF left</td>
<td>.3641</td>
<td>.0186</td>
</tr>
<tr>
<td>UF right*</td>
<td>.3245</td>
<td>.0153</td>
</tr>
<tr>
<td>IFOF left^</td>
<td>.3976</td>
<td>.0164</td>
</tr>
<tr>
<td>IFOF right</td>
<td>.4001</td>
<td>.0161</td>
</tr>
<tr>
<td>ILF left*</td>
<td>.3689</td>
<td>.0147</td>
</tr>
<tr>
<td>ILF right*</td>
<td>.3852</td>
<td>.0154</td>
</tr>
<tr>
<td>SLF left</td>
<td>.3365</td>
<td>.0126</td>
</tr>
<tr>
<td>SLF right</td>
<td>.3225</td>
<td>.0106</td>
</tr>
</tbody>
</table>

Note. *=p<.05, ^=p<.07, CP= conduct problems, UF=uncinate fasciculus, IFOF= inferior fronto-occipital fasciculus, ILF= inferior longitudinal fasciculus, superior longitudinal fasciculus (SLF).

Figure 1
Significant FA decreases in mid adolescence for the sub-/clinical CP group relative to the low CP group corrected for age and gender (TFCE-clusterwise p<.05 corrected). Significance level of the finding is indicated by red-yellow colour scheme. Findings are overlaid on a green outline of the TBSS-generated tract skeleton.
FA and CP severity

Correlation analysis showed that CP severity in mid adolescence was related to FA measures in the right UF when correcting for age and gender (see Table 3 and Figure 2A). For the right ILF a trend towards significance could be observed (see Table 3 and Figure 1B). When correcting for CU traits, FA in the right UF remained significant \((r = -.208, df = 104, p < .05)\). When investigating males and females separately, only females showed significant correlations between FA and CP severity, however the gender difference was only statistically significant for the left IFOF (see Table 4). Finally, current results did not survive a Bonferonni correction for multiple comparisons \((p < .006)\). Additional TBSS regression analysis showed no significant clusters related to CP severity.

Table 3
Correlations between CP and FA measures in mid adolescence, while controlling for age and gender.

<table>
<thead>
<tr>
<th></th>
<th>FA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>df=111</td>
</tr>
<tr>
<td></td>
<td>r</td>
</tr>
<tr>
<td>CP x UF left</td>
<td>-.134</td>
</tr>
<tr>
<td>CP x UF right*</td>
<td>-.224</td>
</tr>
<tr>
<td>CP x IFOF left</td>
<td>-.137</td>
</tr>
<tr>
<td>CP x IFOF right</td>
<td>-.138</td>
</tr>
<tr>
<td>CP x ILF left</td>
<td>-.138</td>
</tr>
<tr>
<td>CP x ILF right</td>
<td>-.156</td>
</tr>
<tr>
<td>CP x SLF left</td>
<td>-.079</td>
</tr>
<tr>
<td>CP x SLF right</td>
<td>-.089</td>
</tr>
</tbody>
</table>

*Note.* *=p<.05. CP= conduct problems, UF=uncinate fasciculus, IFOF= inferior fronto-occipital fasciculus, ILF= inferior longitudinal fasciculus, superior longitudinal fasciculus (SLF).
Table 4
Correlations between CP and FA in mid adolescence, while controlling for age for males and females separately.

<table>
<thead>
<tr>
<th></th>
<th>FA males df=53</th>
<th></th>
<th>FA females df=56</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p</td>
<td>r</td>
<td>p</td>
</tr>
<tr>
<td>CP x UF left</td>
<td>-.049</td>
<td>.724</td>
<td>-.281</td>
<td>.032*</td>
</tr>
<tr>
<td>CP x UF right</td>
<td>-.157</td>
<td>.253</td>
<td>-.348</td>
<td>.007**</td>
</tr>
<tr>
<td>CP x IFOF left</td>
<td>-.013</td>
<td>.923</td>
<td>-.361</td>
<td>.005**</td>
</tr>
<tr>
<td>CP x IFOF right</td>
<td>-.038</td>
<td>.784</td>
<td>-.300</td>
<td>.022*</td>
</tr>
<tr>
<td>CP x ILF left</td>
<td>-.030</td>
<td>.827</td>
<td>-.324</td>
<td>.013*</td>
</tr>
<tr>
<td>CP x ILF right</td>
<td>-.145</td>
<td>.290</td>
<td>-.215</td>
<td>.105</td>
</tr>
<tr>
<td>CP x SLF left</td>
<td>.007</td>
<td>.961</td>
<td>-.242</td>
<td>.067</td>
</tr>
<tr>
<td>CP x SLF right</td>
<td>-.018</td>
<td>.894</td>
<td>-.242</td>
<td>.067</td>
</tr>
</tbody>
</table>

Note. *=p<.05, **=p<.005, for females only. CP=conduct problems, UF=uncinate fasciculus, IFOF= inferior fronto-occipital fasciculus, ILF= inferior longitudinal fasciculus, superior longitudinal fasciculus (SLF). ^=Significant difference between correlation coefficients for males and female 1-tail (Preacher, 2002).
Figure 2
Relationship between fractional anisotropy (FA) and conduct problem (CP) severity.

A. 
B.
**Longitudinal results**

The percentile FA change scores ranged from -10.54% – 14.42%, showing a mean increase in FA from mid to late adolescents for all regions of interest. Change scores for CP ranged from -13.00 – 11.33, in total 33.3% of the current sample showed no changes in CP from mid to late adolescence. Correlational analyses showed that none of the percentile FA changes were correlated with changes in conduct problems from mid to late adolescence.

**Discussion**

Previous studies of white matter integrity in adolescents with Conduct Disorder (CD) have yielded conflicting results with some showing reduced FA (Breeden et al., 2015; Haney-Caron et al., 2014) and others increased FA (Passamonti et al., 2012; Sarkar et al., 2012; Zhang et al., 2014). As noted above, discrepancies between studies may be due to methodological differences, small sample sizes, mixed sex samples and/or different adolescent developmental stages. The aim of the current study was to address these issues and investigate white matter integrity (i.e., FA) and its development in relation to severity of conduct problems in a large community-based sample of male and female adolescents. Results from both group-comparison and correlational analysis showed that higher conduct problem severity was related to decreased white matter integrity. Group-comparison results showed more widespread reductions, while dimensional analysis showed specific reductions in the right uncinate fasciculus (UF). When investigating males and females separately, results indicated that the relationship between conduct problem severity and FA was more pronounced in females. TBSS analyses comparing sub-/clinical CP adolescents with low CP adolescents revealed a small cluster of reduced FA in the left IFOF for the sub-/clinical CP group. Furthermore, results indicated that developmental changes in FA were not related to changes in conduct problems from mid to late adolescence.

To replicate group-comparison results from earlier studies, sub-/clinical CP adolescents were compared with low CP adolescents in the current study. These results showed that adolescents with subclinical and clinical conduct
problems in mid adolescence had significantly lower FA in the right UF, bilaterally in the ILF, with a trend towards significance for the right IFOF compared to adolescents with low conduct problems. This suggests that decreases in FA are not specific to the UF and may be more widespread in adolescents with subclinical and clinical conduct problems. Additionally, whole-brain analysis comparing the two groups showed a small cluster with FA reductions for the sub-/clinical CP group within the IFOF tract of the left hemisphere, located on the junction with the UF (see Figure 2). Differences in TBSS and the region of interest analysis may be due to methodological differences; TBSS can be seen as more locally defined. However, region of interest analysis is able to detect more subtle differences along the specific tracts. As such, TBSS analyses implicated a smaller region of FA reductions as compared to the region of interest results. The results found in the UF and ILF may have been too subtle and are not picked up in the whole brain analysis.

When investigating conduct problem severity on a dimensional level in mid adolescence results indicated that decreased white matter integrity (i.e., FA), specifically in the UF, was related to higher conduct problem severity. This is partly in line with our results from the group comparison analysis, showing decreased FA related to more severe conduct problems. These results suggest that the relation between reduced white matter integrity in the UF and conduct problems is not unique for CD diagnosed adolescents, but rather exists on a continuum of conduct problems in non-disordered adolescents (Sarkar et al., 2012). These results could not be replicated with whole brain analysis (i.e., Tract-Based Spatial Statistics [TBSS] analysis). As mentioned earlier, region of interest analysis is able to detect more subtle differences along the specific tracts and TBSS can be seen as more locally defined. As such, dimensional results are likely to have been too subtle to be detected by TBSS analysis. The additional areas implicated in the group-comparison results (i.e., the left and right ILF) may be specifically implicated in more severe conduct problems, rather than general symptom severity. Overall, current results are in line with former studies focused on adult antisocial populations showing reduced FA compared to controls (Craig et al., 2009; Hoppenbrouwers et al., 2013; Motzkin et al., 2011; Sundram et al., 2012) and reduced FA related to severity of psychopathy (Craig et al., 2009; Sobhani et al., 2015; Wolf et al., 2015). Adolescent studies have been less consistent with some showing reduced FA (Breeden et al., 2015; Haney-Caron et al., 2014), others increased FA (Passamonti et al., 2012; Sarkar et al., 2012;
Zhang et al., 2014) and in relation to CD symptom severity (Breeden et al., 2015; Haney-Caron et al., 2014; Sarkar et al., 2012; Zhang et al., 2014). In line with current results Breeden and colleagues (2015) showed decreased FA related to more externalising problems, specifically the UF when correcting for CU traits. In addition, Haney and colleagues (2014) found decreased FA in CD adolescents to be related to CD symptom severity.

The UF is the major fronto-temporal limbic tract connecting the orbito-frontal cortex (OFC) to the anterior temporal lobes. Although its exact role is not clear, it has been proposed that the UF allows temporal lobe-based stimulus association (i.e., memories) to modify behaviour via the OFC, with the interaction being instrumental in assigning value (Von der Heide, Skipper, Klobusicky, & Olson, 2013). The current results suggest that the right UF contributes towards variation in adolescent conduct problems through decreased connectivity (i.e., FA) between frontal and limbic systems. The IFOF directly connects the occipital, posterior temporal and orbito-frontal areas and the ILF is considered an indirect pathway connecting similar areas (Ashtari, 2012). It has been shown that the IFOF and the ILF white matter tracts show significant overlap, as well as the IFOF and the UF (Wahl et al., 2010). This may indicate functional as well as spatial overlap between these major white matter tracts. Interestingly, the whole brain analysis showed a significant cluster with FA reductions for the sub-/clinical CP group within the IFOF tract, located on the junction with the UF. Possibly, the areas of the IFOF located on the junction with the UF are particularly important for variations in conduct problems during mid adolescence.

It has been suggested that the relationship between white matter integrity and conduct problems may be opposite for males versus females (Zhang et al., 2014). When investigating the relationship between decreased FA and conduct problem severity for males and females separately, only females showed significant correlations between conduct problem severity and FA. Males only did not show any relationship between conduct problem severity and FA. It should be noted that the correlation coefficients for males and females only significantly differed for left IFOF. Possibly, the relationship between conduct problem severity and white matter integrity is more pronounced for adolescent females. This is not in line with Zhang and colleagues (2014) who reported marginal negative correlations between FA within the left UF and psychopathic
traits/ CU traits for CD males, while females showed non-significant results. However, in this study the relationship between FA and symptom severity was only investigated within CD diagnosed adolescents, which may explain contradicting results. Possibly, white matter abnormalities are typical for non-clinical conduct problems in females, but not for males. Pronounced white matter abnormalities might only be present in males when more severe conduct problems (i.e., CD) are present. This is in line with the gender-paradox, suggesting that conduct problems and abnormalities involved may be more severe when present in females (Berkout, Young, & Gross, 2011; Tiet & Wasserman, 2001). Future research should further investigate the gender differences regarding conduct problems severity and its relation with white matter integrity in clinical and non-clinical adolescents.

Importantly, the current study investigated for the first time, whether white matter development was related to changes in conduct problems from mid to late adolescence. Healthy FA development has repeatedly been shown to involve increases with age during adolescence (Asato, Terwilliger, Woo, & Luna, 2010; Barnea-Goraly, 2005; Bava et al., 2010). De Brito and colleagues (2009) suggesting a delay in brain maturation for CD adolescents. Possibly, a delay in brain white matter maturation, i.e. decreased FA, is related to the development of more severe conduct problems. Current cross-sectional results suggest are in line with the notion that delayed maturation (i.e., decreased FA) related to more severe conduct problems in mid adolescence. However, longitudinal results indicated that the development of FA was not associated with changes in CP during mid to late adolescence. As such, these results indicated that the development of white matter integrity does not relate to development of CP. It should be noted that the current study investigated a community-based sample. As such, changes observed in conduct problems might have been to little to pick up any relationship with the development of white matter integrity. As such, it seems that the development of white matter integrity does not contribute to the (relatively small) variations of the development of conduct problems in community-based samples. The development of more severe conduct problems could not be investigated. In this regard, future research should focus on including adolescents with more severe conduct problems in mid and late adolescence. Possibly, the development of white matter integrity contributes to the development of more severe conduct problems in late adolescence. Future research should include multiple DTI assessments from early to late adolescence.
in a sample including more severe antisocial behaviours to investigate the white matter development in relation to the development of conduct problems.

Limitations should be noted. Current results from the correlation analysis did not survive a Bonferroni correction of multiple comparisons, however since the regions of interest are interrelated (between hemispheres and between regions), it could be argued that such a correction is too strict. Furthermore, the current study investigated a range of conduct problems in a community-based sample. The current sample was not able to include many adolescents with severe conduct problems; the number of adolescents within the sub-/clinical range was rather small (n=15). This can be explained by recruitment of community-based children, rather than a specific sample selected to maximise severe conduct problems. Ideally, future studies should aim for a higher number of participants with severe conduct problems. Furthermore, the current study could not investigate the entire trajectory of white matter integrity and conduct problems across adolescence. Ideally, longitudinal research should include several assessment waves of both white matter integrity and conduct problems from childhood to late adolescence. However, the current study adds to existing literature by showing that white matter integrity of the UF white matter tract is implicated in conduct problem severity during adolescence within a large community–based sample. It is shown that different methodological approaches may produce additional implicated areas, such as the ILF and the IFOF tract. Furthermore, it is shown that the relationship between decreased white matter integrity and conduct problems was more pronounced in females.

Footnote

¹When adding IQ as an additional covariate in the General Linear Model (GLM) with CP group as the fixed factor with age and gender as a covariate, results remain similar. FA in the right UF and the right ILF reduced to trends toward significance (both p=.06), IFOF remained a similar trend towards significance (p=.08) and the left ILF remained significant (p=.03).
References


