White Matter Abnormalities Associated with ODD and CD in ADHD

Under review as:

ABSTRACT

BACKGROUND Both Attention-Deficit Hyperactivity Disorder (ADHD) and Oppositional Defiant Disorder/Conduct Disorder (ODD/CD) are associated with white matter (WM) abnormalities. ODD/CD is highly prevalent in ADHD, yet it is unclear whether this may have confounded current ADHD literature. The current study aimed to investigate the role of comorbid ODD/CD and antisocial behaviour in ADHD on WM microstructure.

METHODS Diffusion Tensor Imaging measures, fractional anisotropy (FA) and mean diffusivity (MD), were compared between ADHD+ODD/CD (n=43) and ADHD-only (n=117), aged 8-25 years.

RESULTS Comorbid ODD/CD was associated with lower FA in left fronto-temporal WM, which appeared independent of ADHD symptoms and was dimensionally associated with antisocial behaviour in ADHD+ODD/CD, but not in ADHD-only.

CONCLUSION Comorbid ODD/CD was associated with differences in WM microstructure, which may play a role in inconsistencies in ADHD literature. Altered development of these tracts may contribute to social-emotional and cognitive problems in children with oppositional and antisocial behaviour.
INTRODUCTION

Neuroimaging studies have consistently implicated abnormalities in brain structure and function in Attention Deficit/Hyperactivity Disorder (ADHD; Cortese et al., 2012; Nakao, Radua, Rubia, & Mataix-Cols, 2011). Diffusion Tensor Imaging (DTI) studies, investigating the microstructural properties of white matter (WM) tracts in the brain, have emerged quickly over the past decade. Meta-analytic evidence shows that WM abnormalities in ADHD are most consistently described by reduced fractional anisotropy (FA) in the right anterior corona radiata, right forceps minor, bilateral internal capsule, and left cerebellum (Van Ewijk et al., 2012). More recent findings implicate widespread WM alterations in ADHD, including frontostriatal tracts as well as tracts that connect regions involved in sensorimotor and higher-level cognitive functioning (Cortese et al., 2013; De Zeeuw et al., 2012). However, DTI findings in ADHD are still highly inconsistent in terms of the location and direction of findings, impeding generalizability and interpretability of WM abnormalities in the disorder (Van Ewijk et al., 2012). One possible source of heterogeneity in findings are differences in the in- or exclusion of comorbid disorders. Individuals with ADHD often suffer from one or more comorbid disorders, with Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD) being among the most frequent comorbid conditions (Connor, Steeber, & McBurnett, 2010). Although ODD and CD are distinct psychiatric disorders, they overlap substantially in terms of aetiology, pathophysiology, associated features and treatment, and ODD is often viewed as a milder variant of, or risk factor for, CD (Burke, Loeber, & Birmaher, 2002). Consequently, ODD/CD may be considered one domain of externalizing behaviour problems. DTI studies of ODD/CD are scarce, but available studies point towards altered WM microstructure in adolescents with ODD/CD, independent of the presence of comorbid ADHD symptoms. Three studies found lower FA in ODD/CD compared to controls (Haney-Caron, Caprihan, & Stevens, 2014; Li et al., 2005; Wang et al., 2012), mainly in frontotemporal WM tracts including the anterior corona radiata, fronto-occipital fasciculus, internal capsule and corpus callosum. Moreover, one study found higher mean diffusivity (MD) in these regions for ODD/CD (Wang et al., 2012). In contrast, two other studies found higher FA in the external capsule (Passamonti et al., 2012) and uncinate fasciculus (Passamonti et al., 2012; Sarkar et al., 2013) of adolescents with CD compared to controls. One whole-brain study did not find differences in FA between individuals with ODD/CD and psychopathic traits compared to controls (Finger et al., 2012), but did not take comorbid ADHD into account, in contrast to the most of the other studies (Haney-Caron et al., 2014; Passamonti et al., 2012; Sarkar et al., 2013; Wang et al., 2012). In summary, the
scarce literature available suggests frontotemporal and striatal WM alterations in ODD/CD. Two studies additionally explored whether lower FA in CD was associated with dimensional measures of antisocial behaviour. One study reported an association between CD severity and FA in widespread WM tracts (Haney-Caron et al., 2014), another found antisocial behaviour to be correlated with FA in the left uncinate fasciculus (Sarkar et al., 2013). These associations suggest that decreased FA in CD is likely to be directly related to the antisocial symptoms of the disorder, rather than an epiphenomenon. However, both studies examined these correlations across both groups (CD and healthy controls) and found dimensional results in the same direction as in their categorical analysis. Consequently, it is possible that these dimensional associations were driven by the categorical group differences. To our knowledge, no studies have investigated whether a dimensional association between antisocial behaviour and WM microstructure was present in both groups separately, and whether this association would be different for both groups. Taken together, current literature suggests that both ADHD and ODD/CD are associated with altered WM microstructure, mainly characterised by reduced FA. WM tracts that appear affected in ODD/CD (i.e. frontotemporal and striatal WM) overlap with regions of lower FA in ADHD. Importantly, currently available DTI studies in ADHD have either not mentioned the in- or exclusion of ODD/CD at all, or included participants with ODD/CD but did not test or describe the possible confounding effect. Therefore, it is currently unknown whether - and to what extent - ODD/CD-related WM abnormalities may have influenced results of these ADHD studies. It is possible that comorbid ODD/CD in some of these samples may have driven results of abnormal WM microstructure that are currently being attributed to ADHD.

To shed light on the possible confounding effect of ODD/CD-related abnormalities in ADHD DTI research, we compared WM microstructure between ADHD patients with and without comorbid ODD/CD. To further elucidate the nature of WM microstructure abnormalities in ODD/CD, we investigated whether a dimensional measure of antisocial behaviour was associated with WM abnormalities in both groups.
METHODS

Participants

Participants were part of the NeuroIMAGE cohort (Von Rhein et al., 2014). Inclusion criteria for the current study were: age between 8-30 years, European Caucasian descent, IQ≥70, and no known neurological or genetic disorder. Comorbid psychiatric disorders reported by parents were excluded, except for ODD, CD and pervasive developmental disorder not otherwise specified (PDD-NOS). Complete data (i.e. information on ADHD, ODD, CD and antisocial behaviour, and a DTI scan) were available for 160 individuals with ADHD, of whom 43 had ODD/CD (35 ODD, 1 CD, 7 ODD+CD), resulting in a “comorbid group” (ADHD+ODD/CD; n=43) and an “ADHD-only” group (ADHD without ODD/CD; n=117). The current sample partially overlaps with the sample used in our study comparing WM microstructure in ADHD to healthy controls, in which we found lower FA and higher MD to be associated with ADHD in widespread regions (Van Ewijk et al., 2014).

Measures and materials

To determine ADHD, ODD and CD diagnoses, all participants were assessed with the Schedule for Affective Disorders and Schizophrenia for School-Age Children - Present and Lifetime Version (K-SADS-PL; Kaufman et al., 1997). Parents were interviewed about their children’s behaviour during the past six months, and additionally, all children above 12 years were interviewed themselves, separate from their parents. ODD and CD diagnoses were determined based on the K-SADS-PL using DSM-IV criteria. For ADHD, interview scores were supplemented with Conners’ questionnaires (Conners, Erhardt, & Sparrow, 1999; Conners, Sitarenios, Parker, & Epstein, 1998) using a comprehensive diagnostic algorithm, resulting in a diagnostic category as well as the total number of ADHD symptoms. For a full description of diagnostic procedures, see Von Rhein and colleagues (2014).

The presence of antisocial behaviour was assessed with the Observed Antisocial Behavior Questionnaire (Geluk et al., 2012). The OAB is based on the Self-Report of Antisocial Behavior (Loeber, Stouthamer-Loeber, Van Kammen, & Farrington, 1989), and covers 42 antisocial and delinquent behaviours such as stealing, cheating, fighting and threatening others. One item that assesses smoking was excluded, given the association between nicotine and WM microstructure (Lin, Wu, Zhu, & Lei, 2013; Paul et al., 2008). The OAB was filled in by
all participants in the absence of their parents, and a total score was calculated from all behaviours that had occurred during the past six months. Antisocial behaviour and diagnostic group were moderately positively correlated towards higher rates of antisocial behaviour for the comorbid group ($r=.33$, $p<.001$).

Full scale IQ was estimated by a two-subtest short form (Vocabulary and Block Design) of the Wechsler Intelligence Scale for Children-III (WISC-III) or Wechsler Adult Intelligence Scale III (WAIS-III; for participants ≥17 years), to be used for exclusion of participants with IQ<70.

Additional information was collected to assess autism spectrum symptoms (using the Children’s Social Behavior Questionnaire; CSBQ), comorbid internalizing disorders (using the K-SADS-PL sections for depression and anxiety disorders), history of ADHD medication use (yes or no), and socio-economic status (Buis, 2010).

**Procedure**

The current study was part of a comprehensive assessment protocol (Von Rhein et al., 2014), including a DTI scan. Data acquisition was carried out in The Netherlands, either at the VU University Amsterdam and VU University Medical Centre, or at the Radboud university medical center and Donders Centre for Cognitive Neuroimaging in Nijmegen. Before the DTI scan, all participants were familiarized with the scanning procedure using a mock-scanner. Participants were asked to withhold the use of psychoactive medication for 48 hours before measurement. Fourteen participants were not able to comply, resulting in nine participants with a 24-hour washout and five participants using medication during assessment (equally distributed between the two groups; $p=.45$). The study was approved by the Dutch local medical ethics committees, and all participants signed informed consent (parents signed for participants under 12 years of age). Afterwards, participants received a reward of €50 and a copy of their MRI scan.

**Imaging acquisition and (pre-)processing**

MRI scanning was carried out on either a 1.5 Tesla Sonata or a 1.5 Tesla Avanto MRI scanner (Siemens, Erlangen, Germany), using the same Siemens 8-channel head coil. Whole-brain, high-resolution T1-weighted anatomical images were acquired in the sagittal plane (MP-RAGE, 176 slices, acquisition matrix 256x256, voxel size 1x1x1mm; TE/TR=2.95/2730ms, TI=1000ms, FA=7°, GRAPPA-acceleration 2). Eddy-current compensated diffusion-weighted
SE-EPI images were collected during one acquisition consisting of five volumes without directional weighting (b value of zero), followed by 60 volumes with non-collinear gradient directions (60 interleaved slices, matrix 64x64, voxel size 2x2x2.2mm, TE/TR=97/8500ms, b-value 1000s/mm², GRAPPA-acceleration 2).

SPM8 (Wellcome Trust Centre for Neuroimaging) functionality was employed to correct for residual eddy currents and realign all diffusion-weighted images of each subject using affine transformations and mutual information as a cost function. Mutual information was also used to first rigidly co-register the realigned images with the T1 image and then non-linearly along the EPI phase-encode direction to unwarp the imaging distortions that result from magnetic susceptibility inhomogeneities (Visser, Qin, & Zwiers, 2010). The PATCH method (Zwiers, 2010) was applied to correct for motion-induced artefacts and robustly estimate the diffusion tensor images. From these tensor images, 3D FA and MD maps were derived for each subject, and further processed using the standard procedures within the Tract Based Spatial Statistics (TBSS; Smith et al., 2006) toolbox of FSL (FMRIB Analysis group, Oxford, UK). Each participant’s DTI scan and FA map were manually screened for the presence of scan artefacts, such as problems caused by unwarping the images, motion-induced artefacts, and insufficient coverage of the scanning field. If artefacts could not be removed, this participant was excluded from subsequent analyses. Subsequently, all FA and MD maps were brain-extracted using the BET tool, and non-linearly transformed to MNI152 standard space and averaged into a single 3D image, on which a mean WM skeleton was created. A threshold was set (FA>.30) in order to reduce cross-participant variability and misalignment and to restrict analyses to the main WM tracts. Finally, each participant’s FA and MD image was projected onto this skeleton, and resulting data were used for voxelwise statistics.

Data analysis

Group differences in sample characteristics were investigated using analysis of variance and chi square tests in SPSS (version 21, IBM, Chicago, IL, USA). Voxelwise TBSS analyses were performed in FSL with the randomise tool, which is based on permutation testing. A General Linear Model (GLM) was built with diagnostic group as predictor (comorbid versus ADHD-only), while correcting for number of ADHD symptoms, age and scan site. Results were obtained using Threshold-Free Cluster Enhancement (TFCE), providing results at \( p<.05 \) using FWE correction for multiple testing. Anatomical labels of voxels showing significant effects were identified using the built-in Harvard-Oxford and JHU atlases for WM tracts in FSLview.
Subsequent follow-up analyses were conducted to examine the role of antisocial behaviour, age and ADHD symptoms, and to evaluate the robustness of our main results. All follow-up analyses were conducted in SPSS on mean FA values from regions in which a significant group difference was found in the TBSS analysis (no differences were observed in MD). Linear Mixed Models (LMM) were used with a random intercept per family, to account for correlated data within families, and the same predictors and covariates were included as in the TBSS analysis (i.e. diagnostic group, ADHD symptoms, age and scan site).

First, to examine the robustness of our results, we tested whether SES or autism spectrum symptoms had confounded our main group effect, given the group differences on these measures (see Table 1). Confounders were added to the LMM one at a time, and changes in the main effect were evaluated. Second, to investigate whether observed group differences from the TBSS analysis were dependent on age or number of ADHD symptoms, the LMM was run with a group x age and a group x ADHD symptoms interaction. Furthermore, to test whether lower FA in the comorbid group could be explained by higher rates of antisocial behaviour, the LMM was run with a dimensional measure of antisocial behaviour (normalized with Van der Waerden’s transformation) and its interaction with diagnostic group as predictors.

**RESULTS**

Sample characteristics are summarized in Table 1.

The TBSS analysis revealed several clusters of decreased FA in the comorbid group compared to the ADHD-only group (Figure 1). Clusters of decreased FA were mainly located in WM tracts and subcortical structures of the left hemisphere. More specifically, decreased FA was found in the left corticospinal tract, uncinate fasciculus, inferior fronto-occipital fasciculus, corpus callosum (genu and splenium), and subcortical structures in and around the basal ganglia (thalamus, putamen, pallidum and internal capsule). Using the built-in Harvard-Oxford and JHU atlases in FSL, masks were created for findings in each of these affected regions (Fig 2, left panel), and mean FA values for each participant were extracted from each mask for follow-up analyses. No differences in MD and no elevated FA for the comorbid group were found.

Follow-up analyses were conducted in SPSS on FA values from each of the five affected regions. First, we tested whether group differences in SES or autism spectrum symptoms had confounded our main effect. Adding each of these variables to the model did not change
the significance of the main effect (i.e. lower FA for comorbid versus ADHD-only), indicating that group differences in FA were robust for differences in SES and autism spectrum symptoms in each of the five regions. Second, we tested whether the effect of diagnostic group was dependent on age or number of ADHD symptoms. Both the group x age and group x ADHD symptoms interactions were not significant in any of the five regions (all $p > .05$), indicating that lower FA for the comorbid group was present at all ages and all levels of ADHD symptoms. Furthermore, we examined the interaction between diagnostic group and antisocial behaviour as measured by the OAB (Figure 2, right panel). Results showed a significant interaction in the uncinate fasciculus ($F_{1,147} = 5.073, p = .026$) and subcortical structures ($F_{1,147} = 6.224, p = .014$), as well as a trend towards significance for the inferior fronto-occipital fasciculus ($F_{1,147} = 2.808, p = .096$). The interaction was not significant for the corpus callosum ($F_{1,147} = 1.701, p = .194$) and corticospinal tract ($F_{1,147} = 2.090, p = .150$), and no main effect of antisocial behaviour was found in these two tracts ($F_{1,146} = 0.217, p = .642$ and $F_{1,151} = 0.246, p = .621$, respectively). The significant interactions and trend were further examined by testing the association between antisocial behaviour and FA in each diagnostic group separately. Results revealed a significant negative association between antisocial behaviour and FA in the uncinate fasciculus and subcortical structures in the comorbid group ($F_{1,38} = 4.437, p = .042$ and $F_{1,38} = 4.547, p = .039$, respectively), but not in ADHD-only ($F_{1,112} = 0.320, p = .537$ and $F_{1,112} = 0.732, p = .394$, respectively). The inferior fronto-occipital fasciculus revealed a trend towards significance in the comorbid group ($F_{1,38} = 2.987, p = .096$), and a non-significant association in ADHD-only ($F_{1,94} = 0.364, p = .548$).

Additional follow-up analyses were conducted to examine whether the observed lateralization of TBSS findings was associated with language impairment in ODD/CD. To this end, the LMM was re-run on FA values from each of the five regions, with the Vocabulary standardized score of the WISC-III/WAIS-III and its interaction with diagnostic group as predictors. Results revealed no effect of Vocabulary on FA and no significant interaction with diagnostic group in any of the five regions (all $p > .05$).
Table 1. Sample characteristics.

<table>
<thead>
<tr>
<th></th>
<th>ADHD-only (n=117)</th>
<th>Comorbid (n=43)</th>
<th>Test statistics</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (M, SD)</strong></td>
<td>17.3 (3.4)</td>
<td>17.2 (3.2)</td>
<td>$F_{1,158} = 0.03$</td>
<td>.865</td>
</tr>
<tr>
<td><strong>Gender (% male)</strong></td>
<td>67.5%</td>
<td>67.4%</td>
<td>$\chi^2_{1,N=160} = 0.99$</td>
<td>.568</td>
</tr>
<tr>
<td><strong>Number of ADHD symptoms (M, SD)</strong></td>
<td>12.6 (2.8)</td>
<td>14.0 (2.9)</td>
<td>$F_{1,158} = 7.68$</td>
<td>.006</td>
</tr>
<tr>
<td><strong>Scan site (% Amsterdam)</strong></td>
<td>39.3%</td>
<td>48.8%</td>
<td>$\chi^2_{1,N=160} = 1.17$</td>
<td>.184</td>
</tr>
<tr>
<td><strong>Antisocial behaviour (M, SD)</strong></td>
<td>3.6 (3.7)</td>
<td>6.4 (4.4)</td>
<td>$F_{1,158} = 16.12$</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Vocabulary standardised score (M, SD)</strong></td>
<td>9.4 (2.7)</td>
<td>8.4 (2.5)</td>
<td>$F_{1,158} = 4.45$</td>
<td>.036</td>
</tr>
<tr>
<td><strong>IQ (M, SD)</strong></td>
<td>100.0 (15.1)</td>
<td>93.1 (11.8)</td>
<td>$F_{1,158} = 7.40$</td>
<td>.007</td>
</tr>
<tr>
<td><strong>Hand preference (% right-handed)</strong></td>
<td>87.9%</td>
<td>90.7%</td>
<td>$\chi^2_{1,N=159} = 0.50$</td>
<td>.777</td>
</tr>
<tr>
<td><strong>Socio-economic status (M, SD)</strong></td>
<td>11.7 (2.3)</td>
<td>11.2 (2.0)</td>
<td>$F_{1,158} = 1.15$</td>
<td>.285</td>
</tr>
<tr>
<td><strong>Internalizing disorder (%)</strong></td>
<td>2.6%</td>
<td>7.1%</td>
<td>$\chi^2_{1,N=158} = 1.75$</td>
<td>.192</td>
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<tr>
<td><strong>Autism spectrum symptom score (M, SD)</strong></td>
<td>9.9 (7.4)</td>
<td>16.0 (8.2)</td>
<td>$F_{1,153} = 19.61$</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>History of ADHD medication use (%)</strong></td>
<td>89.4%</td>
<td>90.5%</td>
<td>$\chi^2_{1,N=155} = 0.04$</td>
<td>.553</td>
</tr>
</tbody>
</table>

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a As measured by Observed Antisocial Behavior Questionnaire (OAB).
b The ADHD-only group included 1 ambidexter participant.
c Affect and anxiety disorders, as measured by the K-SADS-PL.
d As measured by the Children’s Social Behavior Questionnaire (CSBQ).
DISCUSSION

The current study aimed to shed light on the possible confounding effect of ODD/CD comorbidity on WM microstructure findings for ADHD. Several regions of reduced FA were found in individuals with ADHD+ODD/CD compared to those with ADHD alone (Figure 1), suggesting that ADHD+ODD/CD might be a specific subgroup of ADHD with (partly) different underlying neuropathology. Clusters of reduced FA were mainly located in frontotemporal WM tracts and subcortical regions of the basal ganglia. More specifically, reduced FA was located in the left corticospinal tract, uncinate fasciculus, inferior fronto-occipital fasciculus, corpus callosum (genu and splenium), and subcortical structures in and around the basal ganglia (thalamus, putamen, pallidum and internal capsule). No differences in MD were observed between the groups.

Our findings are helpful in resolving the inconsistencies in the prior DTI literature for ADHD by showing that ADHD patients with and without ODD/CD differ in WM microstructure in several tracts. Therefore, it is possible that results from ADHD samples including participants comorbid for ODD/CD were confounded, or possibly even better explained, by the presence of comorbid ODD/CD in these samples. It is important to keep this in mind when interpreting the current literature and take this into account in future studies.

Reduced FA in frontotemporal and striatal regions concurs with previous DTI findings in ODD/CD (Haney-Caron et al., 2014; Li et al., 2005; Wang et al., 2012), but also in ADHD (de Zeeuw et al., 2012; Van Ewijk et al., 2012; Van Ewijk et al., 2014). In our previous study we showed that individuals with ADHD, compared to healthy controls, had lower FA in widespread regions, including frontotemporal and striatal WM (Van Ewijk et al., 2014). Importantly, these findings were not confounded by comorbid ODD/CD. In the current study, including a largely overlapping sample, we found lower FA for ADHD+ODD/CD compared to ADHD-only in frontotemporal and striatal regions, which appeared to be independent of ADHD symptom severity. While it is important to note that these two studies cannot be directly compared, such overlap may indicate that ADHD and ODD/CD have additive effects on WM microstructure in these regions, with the comorbid group showing more profound WM abnormalities compared to ADHD-only. Such an effect could implicate stronger WM abnormalities for children with both disorders combined, creating a higher vulnerability to cognitive and behavioural problems for these children. This could, in turn, partly underlie the poorer adverse outcomes reported for
Figure 1. TBSS results of the categorical analysis. Red and yellow regions represent regions of lower fractional anisotropy (FA) for the comorbid group (ADHD+ODD/CD) compared to the ADHD-only group. Results are overlaid on a standard MNI152 template, and were “thickened” towards the full width of the tract for visualisation purposes.
Figure 2. Left panel: five regions in which follow-up analyses were conducted, created by masking significant results from the TBSS analysis (Figure 1) with tracts and regions from the built-in Harvard-Oxford and JHU atlases in FSL. Right panel: mean fractional anisotropy (FA) values from each of these regions for each diagnostic group, plotted against a quantitative measure of antisocial behaviour. Diagnostic group interacted with antisocial behaviour in subcortical structures ($p = .014$) and the uncinate fasciculus ($p = .026$), and a trend towards significance was found in the inferior longitudinal fasciculus ($p = .096$). The interaction was not significant in the corticospinal tract ($p = .150$) and corpus callosum ($p = .194$).
children with ADHD+ODD/CD, compared to those with ADHD or ODD/CD alone (Connor et al., 2010; Loeber et al., 2000).

Current findings fit well with theories of frontotemporal and frontostriatal brain dysfunction in ODD/CD (Rubia, 2011; Vloet et al., 2008). The basal ganglia are well-known for their central role in the reward circuitry and emotional functioning, and the orbitofrontal cortex plays a crucial role in controlling representational memory, incentive motivation, and reward processes. Reduced brain activation in these regions has consistently been linked to aggression and psychopathy (Blair, 2004). The uncinate fasciculus, connecting the orbitofrontal cortex with temporal lobe regions, plays an essential role in combining reward and punishment history, memory representations, value assignment and updating, and decision-making (Von Der Heide, Skipper, Klobusicky, & Olson, 2013).

At the neurobiological level, reduced FA could implicate abnormalities in a wide range of tissue properties such as reduced myelin or lower axonal density (Jones, Knosche, & Turner, 2013), and could signify disrupted signal transfer in these tracts. As a consequence, perturbation of the uncinate fasciculus and other WM tracts connecting the (orbito)frontal and temporal lobes could cause problems in social-emotional functioning, due to the lack of emotional and motivational value in the decision-making process (Von Der Heide et al., 2013). Importantly, WM microstructure in frontotemporal and striatal regions has been shown to continue to develop into adulthood in healthy subjects, with increasing FA and decreasing MD over age. Given that our sample largely consisted of adolescents, it is unclear whether reduced FA in ODD/CD in our sample represents a developmental delay, which could catch up in adulthood, or whether it signifies a more persistent deficit. Longitudinal studies could provide more insight. Taken together, our finding of lower FA in comorbid ADHD+ODD/CD could represent suboptimal development of frontotemporal WM tracts, which could play a role in the social-emotional and cognitive problems associated with ODD/CD.

Antisocial behaviour interacted with group status in the uncinate fasciculus and WM surrounding the basal ganglia, and a trend was found in the inferior fronto-occipital fasciculus. This interaction revealed that lower FA was mainly present in individuals with comorbid ODD/CD in combination with high rates of antisocial behaviour. Comorbid ODD/CD with low rates of antisocial behaviour, and antisocial behaviour without an ODD/CD diagnosis, did not appear to be associated with lower FA (Figure 2, right panel). No association was found between antisocial behaviour and FA in the corticospinal tract and corpus callosum. It is
important to note that our ODD/CD group mainly consisted of individuals with ODD (98%), and only a minority of participants had CD (18%), while our measure of antisocial behaviour mostly represented CD-like behaviours. Therefore, it is possible that our finding in fact signifies an interaction between ODD (represented by our diagnostic group) and CD (represented by antisocial behaviour), and that WM pathology is strongest in individuals with both disorders combined. Although ODD and CD are highly correlated constructs, this result suggests that both disorders may interact on a neurobiological level, suggesting that ODD and CD may better be treated as separate constructs in future studies investigating WM microstructure.

Tracts of lower FA in comorbid ODD/CD were lateralized to the left hemisphere, suggesting that findings may be related to a lateralized brain function, such as handedness or language functioning. While handedness is unlikely to explain the lateralization of our results, given that our groups did not differ on handedness (Table 1), our groups did differ on vocabulary skills, and language deficits have frequently been reported in children with ODD/CD (Hogan, 1999). DTI studies have shown that WM microstructure in the genu (Kim et al., 2006) and the splenium (Fryer et al., 2008) of the corpus callosum and the left inferior fronto-occipital fasciculus (Duffau et al., 2005) is associated with language abilities and impairment. Functional magnetic resonance imaging (fMRI) evidence also suggests a role of the uncinate fasciculus in language processing (Vigneau et al., 2006), although evidence for this tract is less consistent. It is possible that suboptimal development of frontotemporal and callosal tracts may signify a shared pathophysiology underlying both the language difficulties and behavioural symptoms of ODD/CD. This theory was not directly supported by our data, in which FA was not associated with vocabulary scores, or a previous study, in which verbal ability were not associated with FA abnormalities in CD (Haney-Caron et al., 2014). However, ODD/CD is associated with a wide range of language difficulties, including receptive listening and reading and expressive speech and writing, which were not explicitly sampled in the current study. Therefore, it stays possible that other indices of language and reading ability than vocabulary are associated with WM microstructure in these regions.

Current findings should be viewed in the light of some strengths and limitations. Strengths include our large sample size and possibility to check for a wide variety of confounding factors. The lack of a pure ODD/CD group restricts the generalizability of findings to comorbid ODD/CD in ADHD, but not to pure ODD/CD (without ADHD). Nevertheless, we did not find an interaction between ODD/CD and ADHD symptom severity, suggesting that our findings for
comorbid ODD/CD are largely independent of ADHD and may generalize to pure ODD/CD. A study combining four groups (controls, pure ODD/CD, pure ADHD, and a comorbid group) could shed more light on the specificity of these effects. Moreover, longitudinal studies could provide more insight into the development of WM microstructure and associated functions throughout the development in individuals with and without ODD/CD.

Despite these limitations, our study adds significantly to the scarce literature on comorbid ODD/CD in ADHD, and on WM microstructure in ODD/CD. Our results show that comorbid ODD/CD in ADHD is associated with differences in WM microstructure, compared to individuals with ADHD alone. WM pathology was strongest in individuals with comorbid ODD/CD in combination with high rates of antisocial behaviour, and was mainly located in frontotemporal and striatal regions. Altered development of these tracts may well underlie problems with social-emotional decision-making, reward processing and motivational control, and predispose to the development of oppositional and antisocial behaviour. Given the high prevalence of ODD/CD in ADHD, and of both ODD and CD in general, more research focusing on this important and specific (sub)group is warranted.
REFERENCES


