Frontotemporal white-matter microstructural abnormalities in adolescents with conduct disorder: a diffusion tensor imaging study

S. Sarkar1,4†, M. C. Craig1,3†, M. Catani1,2,3, F. Dell’Acqua1,2,3, T. Fahy1,2, Q. Deeley1,2‡ and D. G. M. Murphy1,2‡

1 Department of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, King’s College London, London, UK
2 NIHR Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust and Institute of Psychiatry, King’s College London, UK
3 Natbrainlab, Department of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, King’s College London, London, UK

Background. Children with conduct disorder (CD) are at increased risk of developing antisocial personality disorder (ASPD) and psychopathy in adulthood. The biological basis for this is poorly understood. A preliminary diffusion tensor magnetic resonance imaging (DT-MRI) study of psychopathic antisocial adults reported significant differences from controls in the fractional anisotropy (FA) of the uncinate fasciculus (UF), a white-matter tract that connects the amygdala to the frontal lobe. However, it is unknown whether developmental abnormalities are present in the UF of younger individuals with CD.

Method. We used DT-MRI tractography to investigate, for the first time, the microstructural integrity of the UF in adolescents with CD, and age-related differences in this tract. We compared FA and perpendicular diffusivity of the UF in 27 adolescents with CD and 16 healthy controls (12 to 19 years old) who did not differ significantly in age, IQ or substance use history. To confirm that these findings were specific to the UF, the same measurements were extracted from two non-limbic control tracts. Participants in the CD group had a history of serious aggressive and violent behaviour, including robbery, burglary, grievous bodily harm and sexual assault.

Results. Individuals with CD had a significantly increased FA (p = 0.006), and reduced perpendicular diffusivity (p = 0.002), in the left UF. Furthermore, there were significant age-related between-group differences in perpendicular diffusivity of the same tract (Zobs = 2.40, p = 0.01). Controls, but not those with CD, showed significant age-related maturation. There were no significant between-group differences in any measure within the control tracts.

Conclusions. Adolescents with CD have significant differences in the ‘connectivity’ and maturation of UF.

Introduction

Conduct disorder (CD) has been reported to occur in up to 16% of school-aged children (Olsson, 2009). It is defined by a persistent display of antisocial behaviour such as deception, theft, vandalism and violence within a 6–12-month period prior to age 18 years (APA, 2000). Importantly, children with severe CD cost society 10 times more to support into adulthood than those without (Scott et al. 2001). Furthermore, there is a strong association between CD and other psychiatric disorders, for example substance use (Kessler et al. 1996) and mood disorders (Vloet et al. 2008), and persistent antisocial behaviour in adulthood. For instance, up to 75% of children with CD grow up to have adult antisocial personality disorder (ASPD) (Gelhorn et al. 2007). Current treatment interventions are not effective in the majority of children with CD (Kazdin, 1995). Despite the significant impact on individuals and society as a whole, the biological determinants of CD are poorly understood.

It is unlikely that CD can be explained by differences in the development of a single brain region. Nevertheless, increasing evidence suggests that childhood CD and adulthood antisocial behaviour are
associated with abnormalities in the anatomy and function of brain regions associated with the limbic system, and particularly the orbitofrontal cortex (OFC) and amygdala (Sterzer & Stadler, 2009; Fairchild et al., 2011; Sarkar et al., 2011). Studies of cognitive processing in children and adults with antisocial behaviour have reported impairments in neuropsychological tasks sensitive to differences in function of the OFC and amygdala, for example in reversal learning (Budhani et al., 2005; Budhani et al., 2006) and emotion processing, respectively (Levenston et al., 2000; Blair et al., 2001, 2006). Damage to these brain regions is associated with CD (Ishikawa & Raine, 2003) and adult antisocial behaviour (see Brower & Price, 2001), and with impaired perception of fear and anger (Scott et al., 1997; Adolphs et al., 1998). In vivo functional brain imaging studies, from our group and others, also report significant differences in activation of these regions, and/or regions modulated by them, in children with CD (Finger et al., 2008; Marsh et al., 2008) and adult criminal psychopaths (Raine et al., 1997; Kiehl et al., 2001; Deeley et al., 2006). There is also initial evidence that adolescents with CD have reduced functional ‘connectivity’ between the amygdala and OFC (Marsh et al., 2008, 2011). However, little is known about the anatomy of limbic brain regions, or the connections between them, in children with CD.

Some structural magnetic resonance imaging (MRI) studies have reported that adults with antisocial behaviour have significantly reduced volumes of the amygdala (Yang et al., 2009) and OFC/prefrontal cortex (PFC) grey matter (Raine et al., 2000; de Oliveira-Souza et al., 2008). Only nine structural MRI studies have been published to date on children/adolescents with CD (Bussing et al., 2002; Krueger et al., 2004; Sterzer et al., 2007; Huebner et al., 2008; De Brito et al., 2009, 2011; Fahim et al., 2011; Fairchild et al., 2011; Hyatt et al., 2011). These reported that young people with CD have significantly reduced grey-matter volume in the temporal lobes (Krueger et al., 2004; Huebner et al., 2008; Hyatt et al., 2011) and anterior insula (Sterzer et al., 2007) bilaterally, and left (Sterzer et al., 2007; Huebner et al., 2008) or bilateral (Fairchild et al., 2011) amygdala. However, evidence for differences within other regions, such as the PFC, is less consistent. For example, grey-matter volume and/or concentration of the PFC has been reported as no different (Sterzer et al., 2007), reduced (Huebner et al., 2008; Fahim et al., 2011) and increased (De Brito et al., 2009). This variability probably arises because most studies were of relatively small heterogeneous samples that differed in several key respects, such as the age ranges of people studied (e.g. older adolescents frequently engage in higher levels of substance misuse than younger children). In addition, some did not control for potential confounding factors such as overall cognitive ability (Bussing et al., 2002) and co-morbid attention-deficit/hyperactivity disorder (ADHD) (Bussing et al., 2002; Huebner et al., 2008). Importantly, studies have not considered the presence of callous–unemotional (CU) traits, often referred to as psychopathic tendencies. These are a constellation of interpersonal and emotional characteristics that accompany disruptive or antisocial behaviour in approximately 25% of children with childhood-onset CD (Frick, 1998). Traits include low fearfulness, impulsivity, shallow affect, poor empathy and an absence of guilt (Hare, 1991; Christian et al., 1997). Children with CU traits show a pattern of neuropsychological deficits that implicate limbic/prefrontal dysfunction (Blair et al., 2006; Dadds et al., 2006; Finger et al., 2008; Marsh et al., 2008). Thus, CU traits delineate a distinct subset within CD that require consideration in research.

Brain regions do not function in isolation; they form part of brain ‘systems’. Hence it is crucial to investigate the white-matter connections linking brain regions putatively implicated in CD. We previously reported that adults with ASPD and psychopathy had a significant reduction in fractional anisotropy (FA) of the uncinate fasciculus (UF), a white-matter tract connecting the amygdala and OFC (Craig et al., 2009). A recent study also reported reduced FA of the UF alongside several other tracts (Sundram et al., 2012). FA value is derived from diffusion tensor MRI scanning (DT-MRI), and is an indicator of white-matter microstructural integrity through the quantification of directional differences in the diffusion of water molecules inside tissues. FA is derived from the difference between two absolute values, parallel/axial diffusivity ($D_{\text{para}}$) and perpendicular/radial diffusivity ($D_{\text{perp}}$), the rates of diffusion observed along versus across fibre tracts, respectively. FA values range from 0 (perfectly isotropic diffusion) to 1 (perfectly anisotropic diffusion), providing a proxy measure of tissue integrity (Horsfield & Jones, 2002). The microstructural basis for FA value is thought to lie with properties such as the organization within and between fibres, axonal diameter, and myelination (Beaulieu, 2009; Paus, 2010). By contrast, $D_{\text{perp}}$ is considered a marker for reduced membrane integrity, which has its basis in reduced myelin content, and intraaxonal factors (see Beaulieu, 2009), based on the observation that increased $D_{\text{perp}}$ occurs with demyelination. Reduced $D_{\text{perp}}$ is also seen in typical brain maturation and is associated with increasing FA (Lebel et al., 2008).

In summary, there is preliminary evidence that microstructural integrity of the UF (as measured using DT-MRI) is reduced in antisocial adults. However, it is
unknown whether children with CD have similarly abnormal anatomy, or maturation, of this same tract as compared to their non-CD peers.

Therefore, we extended our prior work and investigated white-matter tract anatomical ‘connectivity’ within the limbic system of children with CD and healthy controls who did not differ significantly in age or IQ. As brain anatomy is modulated by chronic exposure to factors such as alcohol and substance misuse, which are frequently found in these populations (Versace et al. 2008), we additionally assessed self-reported substance use history. We tested the main hypothesis that children with CD have significant differences in the microstructural integrity of the UF, as indexed by reduced FA, and increased $D_{\text{perp}}$. To confirm that any differences we found were specific to the limbic amygdala–OFC network, the same measurements were extracted from two non-limbic control tracts: the inferior fronto-occipital fasciculus (IFOF) and the inferior longitudinal fasciculus (ILF). We also tested the subsidiary hypotheses that: (1) individuals with CD and controls have significant age-related differences in the FA and $D_{\text{perp}}$ of the UF; and (2) the degree of white-matter abnormality is related to severity of antisocial behaviour and CU traits.

### Table 1. Description of the cohort

<table>
<thead>
<tr>
<th></th>
<th>Conduct disorder ($n = 27$)</th>
<th>Healthy controls ($n = 16$)</th>
<th>$p$ value</th>
<th>$\chi^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>16 (2)</td>
<td>16 (2)</td>
<td>0.858</td>
<td></td>
</tr>
<tr>
<td>Mean FSIQ</td>
<td>99 (8)</td>
<td>103 (10)</td>
<td>0.098</td>
<td></td>
</tr>
<tr>
<td>Conduct problems (SDQ)</td>
<td>6 (2)</td>
<td>3 (1)</td>
<td>0.009**</td>
<td></td>
</tr>
<tr>
<td>Hyperactivity (SDQ)</td>
<td>7 (2)</td>
<td>6 (2)</td>
<td>0.375</td>
<td></td>
</tr>
<tr>
<td>Total problems (SDQ)</td>
<td>18 (5)</td>
<td>12 (5)</td>
<td>0.000**</td>
<td></td>
</tr>
<tr>
<td>Callous–unemotional traits (APSD)</td>
<td>7 (2)</td>
<td>5 (2)</td>
<td>0.012*</td>
<td></td>
</tr>
<tr>
<td>Total score (APSD)</td>
<td>25 (7)</td>
<td>19 (6)</td>
<td>0.005**</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>52</td>
<td>63</td>
<td>0.717</td>
<td></td>
</tr>
<tr>
<td>Black/African-Caribbean</td>
<td>33</td>
<td>25</td>
<td>0.735b</td>
<td></td>
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<tr>
<td>Other</td>
<td>15</td>
<td>13</td>
<td>1.000b</td>
<td></td>
</tr>
<tr>
<td>Substance use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cannabis – ever used</td>
<td>60</td>
<td>40</td>
<td>0.407</td>
<td></td>
</tr>
<tr>
<td>Cannabis – used in past month</td>
<td>50</td>
<td>67</td>
<td>0.638b</td>
<td></td>
</tr>
<tr>
<td>Alcohol – ever used</td>
<td>75</td>
<td>100</td>
<td>0.057b</td>
<td></td>
</tr>
<tr>
<td>Alcohol – used in past month</td>
<td>73</td>
<td>67</td>
<td>1.000b</td>
<td></td>
</tr>
<tr>
<td>Cocaine – ever used</td>
<td>10</td>
<td>0</td>
<td>0.496b</td>
<td></td>
</tr>
<tr>
<td>Amphetamine – ever used</td>
<td>10</td>
<td>0</td>
<td>0.496b</td>
<td></td>
</tr>
<tr>
<td>Any other drug a – ever used</td>
<td>15</td>
<td>7</td>
<td>0.619b</td>
<td></td>
</tr>
</tbody>
</table>

FSIQ, Full-Scale Intelligence Quotient; SDQ, Strengths and Difficulties Questionnaire; APSD, Antisocial Process Screening Device.

Values given as percentage or mean (standard deviation).

* Excluding alcohol and cannabis.

b Fisher’s exact probability test.

* Significant $p$ value $\leq 0.05$. ** Significant $p$ value $\leq 0.005$.

### Method

This study was approved by the Joint South London and Maudsley Research Ethics Committee (243/00).

### Participants

Twenty-seven CD participants aged between 12 and 19 years were recruited from: (i) an Institute of Psychiatry database of adolescents with conduct problems (CPs); (ii) three Youth Offending Teams; (iii) five Pupil Referral Units (PRUs; facilities providing education to children who cannot attend mainstream schools, e.g. following school exclusion); (iv) four youth projects; and (v) two mainstream educational institutions. A further 16 right-handed males were recruited as controls from the general public, through schools and youth services (i.e. youth clubs, ‘Connexions’ and several youth charities) within the same geographical areas (deprived and inner city) as the CD group. Groups did not differ significantly in age, full-scale IQ (FSIQ), ethnicity and self-reported history of alcohol or cannabis use (Table 1). Although more CD individuals ($n = 27$) than controls ($n = 0$) had previously used amphetamines and cocaine, this difference was not statistically significant. Furthermore,
measures of current hyperactivity and the number of boys who had ever received a diagnosis of ADHD (Table 1) did not differ significantly between groups.

All study participants satisfied MRI safety requirements and were medication free, did not have a psychiatric history (other than CD, ADHD or referrals for anger management), spoke English as their first language and were right-handed as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). FSIQ was measured using the vocabulary and matrix reasoning subtests of the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999). We excluded individuals with an FSIQ < 80.

### Measures

#### Questionnaires

Parent and self-report versions of the Strengths and Difficulties Questionnaire (SDQ; Goodman, 1999) and Antisocial Process Screening Device (APSD; Frick & Hare, 2001) were administered. The SDQ was used to obtain CP and hyperactivity measures whereas the APSD assessed CU traits. Following methods of other groups, accepted subscales for both measures comprised the higher rater’s score for each item (Jones et al. 2009).

#### Interviews

CD and oppositional defiant disorder (ODD) subsections of the Kiddie Schedule for Affective Disorders and Schizophrenia – Present and Lifetime Version (K-SADS-PL; Kaufman et al. 1997) were used to obtain a research diagnosis of CD. Screening interviews for these disorders were administered to all participants, with those meeting criteria for CD or ODD given complete interviews for both disorders. No participants met criteria for ODD in the absence of CD. Finally, participants meeting CD criteria who additionally scored ≥20 on the APSD parent or self-report questionnaire were then interviewed using the Psychopathy Checklist Youth Version (PCL-YV; Forth et al. 2003). Scores ≥20 were used to indicate the presence of psychopathic traits (Finger et al. 2008). Interviews were conducted by a research psychologist (S.S.) trained and supervised by a psychiatrist (Q.D.). Additional information about antisocial behaviour was gathered from teachers, youth club workers, social workers and parents.

Participants in the CD group had a history of serious aggressive and violent behaviour, including robbery, burglary, grievous bodily harm and sexual assault.

### Procedure

Full written informed consent was taken from participants, and additionally from a parent/guardian where boys were aged <16 years. Postal versions of parent questionnaires were obtained where older participants attended their test session unaccompanied.

#### DT-MRI acquisition

Each DT-MRI image was acquired using a GE Signa HDx 3.0-T MR scanner (General Electric, USA), with actively shielded magnetic field gradients (maximum amplitude 40 mT/m). The body coil was used for RF transmission, and an eight-channel head coil for signal reception, allowing a parallel imaging (Array Spatial Sensitivity Encoding Technique; ASSET) speed-up factor of two. Head movement was minimized by fitting extra padding beside the participant’s head. Each volume was acquired using a multi-slice peripherally gated doubly refocused spin–echo planar imaging (EPI) sequence, optimized for precise measurement of the diffusion tensor in parenchyma, from 60 contiguous near-axial slice locations with a voxel size of 1.85 x 1.85 x 2.4 mm. The echo time was 104.5 ms and the effective repetition time varied between subjects in the range 12 and 20 RR intervals. Based on the recommendations of Jones et al. (2002), the maximum diffusion weighting was 1300 s mm$^{-2}$ and, at each slice location, four images were acquired with no diffusion gradients applied, together with 32 diffusion-weighted images in which gradient directions were distributed uniformly in space. The sequence ran for approximately 15 min.

#### DT-MRI data preprocessing

All data were first converted to NIfTI format and then each raw diffusion dataset underwent a full quality control check where all $b_0$ values and diffusion-weighted volumes were inspected visually for image corruption, motion artefacts and signal drop-out effects using the light-box function available inside fslview (part of FSL software; www.fmrib.ox.ac.uk/fsl). Datasets showing more than two motion artefacts in different volumes on the same slice were removed from the study. Datasets showing significant head movements (> 1 cm) were removed. No participant data acquired in this study required removal due to motion artefacts. Data were eddy current and motion corrected using ExploreDTI (Leemans et al. 2009). The diffusion tensor was estimated following removal of outlier data (RESTORE function; Chang et al. 2005) and whole-brain tractography was performed on the data. Whole-brain tractography parameters selected as seed voxels all those with FA ≥0.2. Streamlines were propagated using Euler integration applying a b-spline...
interpolation of the diffusion tensor field (Basser et al. 2000), and the tractography algorithm step size of 0.5 mm. Where FA < 0.2 or when the angle between two consecutive tractography steps was larger than 30°, tractography stopped. Finally, diffusion tensor maps (FA, mean diffusivity, FA-colour, $D_{\text{par}}$, $D_{\text{perp}}$, mean diffusion weighted image) were estimated and exported to TrackVis (Wang & Wedeen, 2007). Full details are given elsewhere (Jones et al. 2002).

**DT imaging (DTI) tractography**

TrackVis software was used to hand dissect in native space. The tract of interest (UF) plus the two control tracts IFOF and ILF were dissected in the same order for all data by a trained and reliable operator (S.S.) blind to clinical groupings. Dissection of the three tracts was performed one hemisphere at a time using the region of interest (ROI) approach described elsewhere (Catani et al. 2002; Catani & Thiebaut de Schotten, 2008) in the order (i) IFOF, (ii) UF and (iii) ILF (see top of Fig. 1). The UF was defined with the first ROI placed on the axial slice at the level of the medial temporal lobe and the second ROI placed coronally slightly posterior to the external capsule. Short fibres that did not enter either termination of the tract were excluded, as were long fibres extending to regions outside the frontal and temporal lobes. These fibres were omitted through placement of exclusion ROIs.

**Statistical analysis**

All statistical analyses were carried out using SPSS software (SPSS Inc., USA). Repeated-measures analysis was used with the within-subjects variables of tract (UF, IFOF, ILF) and hemisphere (left, right), and CD as the between-subjects variable. This tested for significant differences in FA and $D_{\text{perp}}$ between CD and control participants in the UF and the two control tracts. *Post-hoc* analyses were carried out to identify significantly differing tract values between boys with CD and healthy controls using one-way analysis of variance (ANOVA). Analyses were Bonferroni corrected for multiple comparisons.

Where a significant FA/$D_{\text{perp}}$ difference was detected, *post-hoc* analyses were carried out to examine the relationship between these measures and age in each group using Pearson’s correlations; we then determined if there were significant between group differences in these relationships using Z-observation analysis (Pallant, 2007). Finally, we examined whether significant differences in DT-MRI parameters were associated with greater severity of CPs or CU traits within, first, the whole sample and, second, the CD group only. Correlations were carried out between DT-MRI measures and (i) total SDQ score, (ii) SDQ CP score, (iii) total APSD score and (iv) APSD CU traits score, controlling for age.

**Results**

**Tractography**

The CD group had significant differences from controls in the left UF, with a greater FA (CD 0.471; control 0.451; $p=0.006$) and reduced $D_{\text{perp}}$ (CD $0.583 \times 10^{-3} \text{mm}^2/\text{s}$; control $0.611 \times 10^{-3} \text{mm}^2/\text{s}$;
They also had significantly greater FA in the right UF (CD 0.468; control 0.455; \( p = 0.040 \)) but this did not withstand Bonferroni correction. No significant differences were observed between groups in either FA or \( D_{\text{perp}} \) within the two control tracts (IFOF, ILF; Table 2; Fig. 1).

**UF and age**

Within the CD group there was no significant association between left UF FA and \( D_{\text{perp}} \) and age. By contrast, there was a significant negative correlation between age and \( D_{\text{perp}} \) of the left UF (\( r = -0.625, t = 0.01 \)) within the control group, and this differed significantly from the non-significant correlation seen in CD (\( Z_{\text{obs}} = 2.40, p = 0.01 \); Table 3, Fig. 2). DT-MRI indices between high and low CU groups did not differ significantly from one another (\( Z_{\text{obs}} = 0.55 \)).

**UF and antisocial behaviour measures**

Significant correlations were found between left UF FA/\( D_{\text{perp}} \) abnormality and severity of all SDQ/APSD behavioural scores within the whole sample (Table 4). There was also a strong trend, but this did not reach statistical significance, between APSD scores in the CD group alone (\( p = 0.09 \); Fig. 3).

**Discussion**

We report, for the first time, that adolescents with CD have significantly increased microstructural integrity of the UF as compared to healthy controls. This increase was tract specific, that is no between-group differences were found in the ‘control’ tracts. DT-MRI analysis found that the expected decline of \( D_{\text{perp}} \) with age was not seen in the CD group as it was in controls. We also found a significantly different relationship between age and this measure in the two groups. Moreover, *post-hoc* analysis found a significant relationship between microstructural abnormality and severity of antisocial behaviour in the whole sample, although not in the CD group alone. The significant findings reported here were found in the left UF; however, there was a trend towards significance in the right hemisphere.

These results support our *a priori* hypothesis that antisocial behaviour is associated with specific abnormalities in limbic connections (i.e. as opposed to global white-matter changes). However, the difference we

Table 2. Results of the one-way ANOVA showing differences in DTI measures of the UF and control tracts between CD and healthy controls

<table>
<thead>
<tr>
<th>Tract</th>
<th>Parameter</th>
<th>Hemisphere</th>
<th>CD Mean (s.d.)</th>
<th>Controls Mean (s.d.)</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>UF</td>
<td>FA</td>
<td>Left</td>
<td>0.47 (0.02)</td>
<td>0.45 (0.02)</td>
<td>0.006*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Right</td>
<td>0.47 (0.02)</td>
<td>0.46 (0.02)</td>
<td>0.040</td>
</tr>
<tr>
<td></td>
<td>( D_{\text{perp}} )</td>
<td>Left</td>
<td>0.56 (0.03)</td>
<td>0.61 (0.03)</td>
<td>0.002*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Right</td>
<td>0.59 (0.03)</td>
<td>0.60 (0.03)</td>
<td>0.306</td>
</tr>
<tr>
<td>IFOF</td>
<td>FA</td>
<td>Left</td>
<td>0.51 (0.02)</td>
<td>0.50 (0.02)</td>
<td>0.321</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Right</td>
<td>0.52 (0.02)</td>
<td>0.51 (0.02)</td>
<td>0.281</td>
</tr>
<tr>
<td></td>
<td>( D_{\text{perp}} )</td>
<td>Left</td>
<td>0.55 (0.03)</td>
<td>0.57 (0.03)</td>
<td>0.115</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Right</td>
<td>0.54 (0.04)</td>
<td>0.56 (0.03)</td>
<td>0.159</td>
</tr>
<tr>
<td>ILF</td>
<td>FA</td>
<td>Left</td>
<td>0.48 (0.03)</td>
<td>0.47 (0.02)</td>
<td>0.101</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Right</td>
<td>0.48 (0.02)</td>
<td>0.48 (0.02)</td>
<td>0.454</td>
</tr>
<tr>
<td></td>
<td>( D_{\text{perp}} )</td>
<td>Left</td>
<td>0.57 (0.04)</td>
<td>0.59 (0.03)</td>
<td>0.062</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Right</td>
<td>0.57 (0.03)</td>
<td>0.58 (0.04)</td>
<td>0.093</td>
</tr>
</tbody>
</table>

DTI, Diffusion tensor imaging; CD, conduct disorder; s.d., standard deviation; UF, uncinate fasciculus; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; FA, fractional anisotropy; \( D_{\text{perp}} \), perpendicular diffusivity value and s.d. \( \times 10^{-3} \) mm\(^2\)/s.

* Significant after Bonferroni correction.

Table 3. Pearson’s correlations between left UF FA and \( D_{\text{perp}} \) with age in CD group compared to healthy controls

<table>
<thead>
<tr>
<th></th>
<th>Age–CD group</th>
<th>Age–controls</th>
<th>( Z_{\text{obs}} ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FA left</td>
<td>-0.06/0.75</td>
<td>0.45/0.08</td>
<td>1.60</td>
</tr>
<tr>
<td>( D_{\text{perp}} ) left</td>
<td>0.09/0.64</td>
<td>-0.63/0.01*</td>
<td>2.40*</td>
</tr>
</tbody>
</table>

UF, Uncinate fasciculus; FA, fractional anisotropy; \( D_{\text{perp}} \), perpendicular diffusivity; \( r \), correlation coefficient; \( p \), significance level; CD, conduct disorder; \( Z_{\text{obs}} \), observation.

* Two-tailed significance level: \( p < 0.05 \).
found was in the opposite direction to what was hypothesized (i.e. increased FA). The UF tract is the major frontotemporal limbic tract and it connects the amygdala and OFC. Damage to this tract leads to impairments of conditional associative learning in animals (Gaffan & Eacott, 1995; Gutnikov et al., 1997). Reversal learning, a form of conditional associative learning, involves learning to ‘reverse’ responses that were previously rewarded but are later punished. Difficulties with reversal learning have been demonstrated in adults with antisocial behaviour and psychopathy (Budhani et al., 2005, 2006). Furthermore, children with CD and CU traits show abnormal blood oxygen level-dependent (BOLD) activation in the ventromedial PFC on reversal tasks during functional MRI (Finger et al. 2008). It has been suggested that reversal learning deficits contribute to the perseveration of antisocial behaviour in both young people and adults, in which individuals fail to learn to avoid behaviour that has negative consequences for themselves and others (Sundram et al. 2012). Our findings may help to explain the biological basis of this issue, which will be a focus of our future studies.

In addition, altered ‘connectivity’ of the OFC and amygdala secondary to abnormal development of the UF may contribute to impaired regulation of amygdala activity by the OFC, which in turn may contribute to the abnormal emotional processing and behavioural disinhibition observed in young people with CD and adults with ASPD/psychopathy (Blair, 2008). For example, a prior study reported reduced functional ‘connectivity’ between the amygdala and ventromedial PFC in children with CD and CU traits during an emotional processing task (Marsh et al. 2008). Furthermore, a DTI-MRI study of healthy children reported that a measure of engagement in dangerous and risky activities correlated positively with FA, and negatively with $D_{\text{perp}}$ in frontal white-matter tracts (Berns et al. 2009). It was also proposed that this may be attributable to earlier maturation of these tracts in high-scoring youngsters. Finally, the converse could be posited: that abnormal development of limbic and prefrontal grey matter may underlie the development of abnormal limbic–prefrontal circuitry.

Our findings raise the question of how age, behaviour and disorder-related differences in FA relate to the underlying biology and its developmental determinants. Our results show that, whereas in typical children $D_{\text{perp}}$ of the left UF decreases with age, in CD it does not. Moreover, the relationship between this DT-MRI measure and increasing age differed significantly between groups. As discussed previously, myelination is one process thought to underlie the decreasing $D_{\text{perp}}$ values and increasing FA seen in typical maturation (Song et al. 2003; Lebel et al. 2008), alongside greater axonal calibre (Paus, 2010) and reduced neuronal branching (Silk et al. 2009). It is not clear which of these factors makes the greater contribution to our findings. However, we also found significantly reduced $D_{\text{perp}}$ in the left UF accompanied by increased FA in CD, suggesting that these individuals may differ from controls with respect to the myelination of this tract. It is known that myelination differs by age and brain region (Lebel et al. 2008), and is modulated by learning and environmental experience. For example, increased myelination has been found to accompany intensive practice of motor tasks, such as piano playing (Bengetsson et al. 2005) and juggling (Scholz et al. 2009). In addition, children with ADHD showed increased FA in frontal tracts, which the authors speculated may arise from early myelin damage that later triggers hypermyelination (Li et al. 2010). Finally, FA changes are associated with social and emotional experience. For example, children who
experience severe deprivation in early childhood have significant decreases in FA of the left UF as compared to control children (Eluvathingal et al. 2006). Similarly, it was reported that young adults exposed to high levels of verbal abuse from their parents during childhood have significant reduction in FA of two left hemisphere limbic tracts (cingulum and fornix) and the arcuate fasciculus (Choi et al. 2009). Therefore, changes in tract integrity seen in developmental psychopathologies, such as those observed in this study, may have arisen from a complex mixture of social and biological factors. This highlights both the need for future studies of white-matter maturation to consider (for example) environmental and social variables, and the potential relevance of early interventions to prevent or moderate the course of developmental disorders.

Table 4. Correlations between UF DT-MRI measures and antisocial behaviour scores in the whole sample

<table>
<thead>
<tr>
<th></th>
<th>Left UF FA</th>
<th>Right UF FA</th>
<th>Left UF D_{perp}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r/p</td>
<td>r/p</td>
<td>r/p</td>
</tr>
<tr>
<td>(i) SDQ total</td>
<td>0.32/0.019*</td>
<td>0.33/0.018*</td>
<td>−0.38/0.007**</td>
</tr>
<tr>
<td>(ii) SDQ CP</td>
<td>0.32/0.021*</td>
<td>0.27/0.042*</td>
<td>−0.37/0.008**</td>
</tr>
<tr>
<td>(iii) APSD total</td>
<td>0.40/0.005**</td>
<td>0.32/0.019**</td>
<td>−0.39/0.005**</td>
</tr>
<tr>
<td>(iv) APSD CU traits</td>
<td>0.40/0.004**</td>
<td>0.36/0.009***</td>
<td>−0.37/0.008**</td>
</tr>
</tbody>
</table>

UF, Uncinate fasciculus; DT-MRI, diffusion tensor magnetic resonance imaging; SDQ, Strengths and Difficulties Questionnaire; APSD, Antisocial Process Screening Device; CP, Conduct problems; CU, callous-unemotional traits; FA, fractional anisotropy; D_{perp}, perpendicular diffusivity; r, correlation coefficient; p, significance level.

* p < 0.05, ** p < 0.01.

Our post-hoc investigation revealed a significant association between CD/CU traits and UF FA/D_{perp} in the sample as a whole but only a trend to significance in the CD group alone. This preliminary finding suggests that this tract may contribute towards the generation of behavioural variation in adolescents, perhaps through an increased ‘connectivity’ between frontal and limbic systems, but further (larger) studies are required.

Finally, the increased FA reported in CD adolescents was in the opposite direction to our a priori hypothesis, which had been based on findings in adults with antisocial behaviour (Craig et al. 2009). One possible explanation for this may be that white-matter maturation of the UF in children with CD follows a different developmental trajectory to that of healthy individuals, consistent with abnormal patterns of white-matter maturation in non-CD children who indulge in extreme risk-taking behaviours (Berns et al. 2009); that is, an initially increased rate of white-matter microstructural development in CD adolescents, with subsequent failure of typical development across adolescence. Such a mechanism may contribute towards a neurobiological explanation for the high rates of recidivism and treatment resistance found within persistently antisocial populations. For example, abnormal/precocious white-matter maturation in children with CD may interfere with neural mechanisms underpinning pro-social behaviour. However, it is only possible to investigate such a hypothesis through future longitudinal studies and the current study, like all previous published studies, was limited by its cross-sectional design.

Our study has several limitations. First, we did not find significant correlations between abnormalities in UF and measures of antisocial behaviour in the CD group alone (albeit we did find trends); this may have
resulted from lack of power due to our sample size. Second, we recruited antisocial children with CD from predominantly non-forensic community samples. These children had carried out extremely serious offences (e.g. robbery, grievous bodily harm and sexual assault). Nevertheless, if we had recruited from juvenile detention centres and other forensic settings, we would probably have identified children with more severe antisocial behaviour. This in turn may have highlighted greater differences in white-matter measures between groups that may have associated with behavioural measures. However, given the difficulty of recruiting from such settings, the current study selected participants with the highest levels of antisocial behaviour observable in community samples. Furthermore, our findings are more generalizable to the wider population of children with CD, whose antisocial behaviour does not cross the threshold for incarceration within the criminal justice system. Conversely, one of the strengths of the current study lies in its recruitment of a healthy control group who closely resemble the CD group in many respects, such as FSIQ and ethnicity. One final caveat is that these were used only as screening measures prior to grouping participants using the K-SADS-PL and PCL-YV, this was not thought likely to affect our results.

In summary, adolescents with CD have significant differences from controls in the microstructural anatomy, and maturation, of the UF. However, it is not clear how these abnormalities arise, or if they predict outcome. Studies of antisocial behaviour within larger cohorts and across the lifespan are required.

Declaration of Interest

None.

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