

# Neuroimaging findings in disruptive behavior disorders

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Decades of research have shown that youths with disruptive behavior disorders (DBD) are a heterogeneous population. Over the past 20 years, researchers have distinguished youths with DBD as those displaying high (DBD/HCU) versus low (DBD/LCU) callous-unemotional (CU) traits. These traits include flat affect and reduced empathy and remorse, and are associated with more severe, varied, and persistent patterns of antisocial behavior and aggression. Conduct problems in youths with HCU and LCU are thought to reflect distinct causal vulnerabilities, with antisocial behavior in youths with DBD/HCU reflecting a predominantly genetic etiology, while antisocial behavior in youths with DBD/LCU is associated primarily with environmental influences. Here we selectively review recent functional (fMRI) and structural (sMRI) magnetic resonance imaging research on DBD, focusing particularly on the role of CU traits. First, fMRI studies examining the neural correlates of affective stimuli, emotional face processing, empathy, theory of mind, morality, and decision-making in DBD are discussed. This is followed by a review of the studies investigating brain structure and structural connectivity in DBD. Next, we highlight the need to further investigate females and the role of sex differences in this population. We conclude the review by identifying potential clinical implications of this research.

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## Introduction

Disruptive behavior disorders (DBD), which include conduct disorder/conduct problems and oppositional defiant disorder, are characterized by aggressive and antisocial behavior during childhood and adolescence.<sup>1</sup> These behaviors are among the most common reasons for a childhood referral to mental health and educational services.<sup>2</sup> DBD are associated with problems socially within the school or workplace, which can often lead to

legal problems, criminality, and arrest.<sup>3</sup> As a result, bringing up a child with DBD costs society 10 times more than a child who displays no conduct problems.<sup>2</sup> Crucially, DBD in youths are not only predictive of antisocial and aggressive behaviors in adulthood, but also substance misuse, other mental health problems, and poor physical health.<sup>4</sup>

Decades of research have highlighted that youths with DBD are a heterogeneous population that incorporates different subtypes.<sup>5</sup> Several useful approaches have accounted for this heterogeneity,<sup>6</sup> but the approach that distinguishes youths with DBD as those displaying high (DBD/HCU) versus low (DBD/LCU) callous-unemotional (CU) traits has attracted considerable interest over the past 20 years.<sup>5</sup> CU traits reflect a lack of empathy and guilt, combined with a shallow affect and the callous use of others for one's own gain. Among antisocial adults, high levels of CU traits characterize adult psychopaths—a particularly severe group of antisocial individuals.<sup>7</sup> While youths cannot be labeled as psychopaths, those with DBD/HCU are thought to be at risk of developing psychopathy in adulthood,<sup>8,9</sup> and as result have been the focus of intense research. Genetic,

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behavioral, experimental, and neuroimaging studies have shown that youths with DBD/HCU and those with DBD/LCU are characterized by different vulnerabilities.<sup>5</sup> This resulted in the recent inclusion of CU traits as the “with Limited Prosocial Emotions” specifier for the diagnosis of conduct disorder in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5<sup>1</sup>). Twin studies indicate that conduct problems in youths with DBD/HCU are highly heritable, while conduct problems in youths with DBD/LCU are moderately heritable, but largely influenced by environmental factors.<sup>10</sup> Unlike youths with DBD/LCU, youths with DBD/HCU display behaviors akin to adults with psychopathy, notably committing violent crimes at a younger age and displaying a more severe and varied pattern of conduct problems, including instrumental aggression and sadistic acts of violence.<sup>6,11</sup> Youths with DBD/HCU have a preference for novel and dangerous activities, present with a lack of emotional responsiveness to negative emotional stimuli, are impaired at processing others’ fearful and sad facial expressions and vocal tones, and are relatively insensitive to punishment,<sup>8</sup> all of which are consistent with a low fearfulness temperamental style.<sup>6</sup> By contrast, youths with DBD/LCU are typically less aggressive, mostly displaying threat-based reactive aggression,<sup>9</sup> This most likely reflects a hostile attributional bias in response to real or perceived social threat, such as angry faces or ambiguous neutral faces.<sup>12</sup> Finally, youths with DBD/LCU have problems regulating their emotions, and display a low frustration tolerance and high levels of anger, impulsivity, and emotional distress.<sup>6,11</sup> They are also more responsive and empathic to the distress of others<sup>13</sup> and to negative stimuli.<sup>9,11</sup>

In addition to distinguishing among subtypes of youths with DBD, there is a growing need to explore the influence of sex, particularly in the context of neuroimaging research.<sup>14</sup> Male and female adolescents with DBD may express antisocial behavior in different ways, and show structural differences in the brain and different abnormalities in brain function. However, very little neuroimaging research has investigated females with DBD or directly compared males and females with DBD. While 13.8% of male adolescents present with conduct disorder, only 6.7% of female adolescents show the same presentation.<sup>15</sup> Further, males aged 10–17 years are more likely to have been contacted by the police and convicted for a criminal offence than females.<sup>16</sup> Similarly, the age of onset of antisocial behavior is different between the sexes; while more males are diagnosed with conduct disorder aged 10, with a downward trend after this age, the rate of conduct disorder in females peaks at 16 years.<sup>15</sup> One possible reason behind these skewed diagnosis rates could be that the DSM-5 criteria for conduct disorder show a bias

towards behaviors more often exhibited by males.<sup>14</sup> While males are more likely to show overt behaviors, such as vandalism and aggressive stealing, females are more likely to show covert behaviors, such as lying and sabotaging relationships.<sup>17</sup> With the aim of extending research on females with DBD, the FemNAT-CD consortium (<http://www.femnat-cd.eu>) – a large multisite European study, of which our group is a part – will assess the environmental and neurobiological factors that might underpin sex differences in conduct disorder. For the purposes of this review, the few published neuroimaging studies that have examined females with DBD and considered the influence of sex differences in DBD will be discussed.

In this article, we selectively review recent functional (fMRI) and structural (sMRI) magnetic resonance imaging research on DBD, focusing particularly on the role of CU traits. First, fMRI studies examining the neural correlates of affective stimuli, emotional face processing, empathy, theory of mind, morality, and decision-making in DBD will be discussed (see Table 1). This is followed by a review of the studies investigating brain structure and structural connectivity in DBD (see Table 2). Next, recent studies investigating female samples and the role of sex differences are discussed. We conclude the review by identifying potential clinical implications of this research.

## Functional Magnetic Resonance Imaging Evidence

### *Affective stimuli and emotional face processing*

Several fMRI studies have examined the neural correlates of negative affective stimuli (e.g., IAPS stimuli<sup>18</sup>) and face processing in DBD, and have identified an atypical response in this population within a set of cortical and subcortical regions including, among others, the orbitofrontal cortex (OFC), ventromedial prefrontal cortex (VMPFC), anterior cingulate cortex (ACC), insula, temporal lobe, and the amygdala.<sup>19,20</sup> However, studies that do not take into account individual differences in CU traits have produced a mixed account of the reported amygdala response, with evidence of both amygdala hypo- and hyper-reactivity to negative affective stimuli.<sup>21,22</sup> Given evidence indicating that youths with DBD/HCU and DBD/LCU are characterized by distinct emotional, cognitive, and behavioral responses to affective stimuli and faces,<sup>8,11</sup> these inconsistent findings may partly result from variations in CU traits across samples.<sup>23</sup> Compared to typically developing (TD) youths, youths with DBD/LCU have consistently been found to exhibit hyperactivity in the amygdala when processing both fearful faces<sup>23</sup> and fearful eyes.<sup>24</sup> These results might partly explain why youths with DBD/LCU have a propensity toward emotion regulation difficulties

and reactive aggression when they feel threatened.<sup>5</sup> By contrast, fMRI studies that have assessed CU traits have consistently shown that youths with DBD/HCU exhibit amygdala hypoactivity during the processing of conscious<sup>25,26</sup> (but see Refs. <sup>27,28</sup>) and unconscious fearful faces.<sup>23</sup> These findings have been recently extended by White *et al.*,<sup>29</sup> who showed that an atypical amygdala response to consciously processed fearful faces in youths with DBD/HCU is not secondary to an attentional deficit (ie, increased top-down control) but is specifically related to the CU component of psychopathic traits. These findings and others<sup>30</sup> are inconsistent with the response modulation hypothesis, which posits that emotional deficits seen in psychopathy stem from a core deficit in selective attention that limits the processing of peripheral information.<sup>31</sup> In sum, amygdala hypoactivity could partly explain the high propensity for proactive aggression seen in youths with DBD/HCU.<sup>8</sup> In support of this view, a recent study showed that amygdala response to fearful faces in youths with DBD mediated the association between CU traits and proactive aggression.<sup>32</sup>

### *Empathy, theory of mind, and morality*

Empathy deficits in relation to DBD have been extensively documented,<sup>5</sup> with recent fMRI studies examining differences in neural response to perceived pain in others. The experience and observation of perceiving others in pain elicits activation in a network of regions, including the ACC, anterior insula, amygdala, and striatum, which mediate the affective perception of pain, as well as the somatosensory cortex, supplementary motor cortex, and periaqueductal gray, which mediate the perceived somatosensory sensation of pain.<sup>33</sup> Surprisingly, Decety *et al.*<sup>34</sup> found that when viewing others in pain, youths with DBD had an increased neural response in regions including the anterior insula, anterior mid-cingulate, dorsal striatum, and amygdala compared to TD youths. This pattern of results was interpreted as reflecting enjoyment in the DBD youths when seeing someone else in pain. However, because CU traits were not measured by Decety *et al.*, it is also possible that the youths with DBD were characterized by low levels of CU traits and associated high emotional reactivity, which could have led to the observed increase in neural response. This hypothesis is supported by two recent studies that include a measure of CU traits.<sup>35,36</sup> Youths with DBD, as compared to TD youths, showed reduced activation to the perceived pain in others in the ACC, anterior insula, and inferior frontal gyrus.<sup>36</sup> Crucially, within the DBD group, unique variance associated with callous traits was negatively correlated with the response in the ACC and anterior insula. Consistent with these results, Marsh *et al.*<sup>35</sup> found that

those with DBD/HCU, compared to TD youths, showed reduced response in the ACC and ventral striatum to perceived pain in others. These youths also showed reduced activity in the amygdala and insula in response to others' pain, but not when imagining that the pain was their own. Importantly, the affective and interpersonal features of measured psychopathy were negatively related to the induced brain response to perceiving pain in others in the amygdala and ACC. Finally, using a more complex affective-processing task including cartoon vignettes, Sebastian *et al.*<sup>37</sup> found that cartoons requiring understanding of distress in others within the context of social situations produced reduced amygdala and anterior insula activity in youths with DBD relative to TD youths. This reduced activation was negatively correlated with the unique variance associated with CU traits. Using the same task, O'Nions *et al.*<sup>38</sup> found that cartoon scenarios that require the interpretation of others' intentions did not induce a significantly different brain response in youths with DBD/HCU compared to TD youths. These results dovetail with behavioral and experimental data,<sup>13</sup> and highlight the fact that youths with DBD/HCU do not have a deficit in understanding the mental states of others, as has been shown for children with autism spectrum disorder.<sup>13,38</sup> Rather, they show reduced empathic responses to others' distress cues.<sup>13</sup>

The immoral judgment seen in youths with DBD/HCU may result from impairments in emotional empathy and decision-making (see decision-making section below)—deficits thought to reflect dysfunctions within the amygdala-VMPFC circuitry and striatum.<sup>8</sup> Consistent with this view, a recent study found that compared to TD youths, those with DBD/HCU exhibited reduced amygdala response and reduced amygdala-OFC connectivity during moral judgments about legal actions.<sup>39</sup>

Taken together, these results provide emerging evidence of neural vulnerabilities that might hamper successful socialization of youths with DBD/HCU, putting them at increased risk of displaying severe antisocial behavior and proactive aggression without feeling guilt or empathy for their victims.

### *Decision-making*

Poor and rash decision-making is another central feature of DBD.<sup>40</sup> A large body of experimental data has identified an association between DBD, CU traits, and impairments in decision-making.<sup>8,19</sup> Neural correlates of these associations have recently been explored within the context of functional neuroimaging studies. For example, compared to TD youths and youths with ADHD, youths with DBD showed a reduced neural response in the OFC during rewarded responses.<sup>41</sup> In another study, when deciding between a low-risk/low-reward or high-

risk/high-reward option, youths with DBD and substance use disorders displayed a reduced neural response in a number of regions, including the OFC, ACC, basal ganglia, insula, and amygdala, compared to TD youths.<sup>42</sup> In response to wins, DBD youths also had a lower response in the ACC, among other regions, compared to TD youths, but a higher response to losses in the OFC, among other regions.<sup>42</sup> However, as these studies did not take the influence of CU traits into account, it is unclear how these atypical responses relate to DBD and/or CU traits. Studies using standard learning (ie, passive avoidance learning) and reversal learning paradigms have also shown that, compared to TD youths<sup>43,44</sup> and youths with ADHD,<sup>43</sup> youths with DBD/HCU exhibit atypical responses to reward and punishment within the OFC/VMPFC and caudate. According to a recent study by White *et al.*,<sup>45</sup> these functional differences reflect compromised representations of reinforcement expectancies (ie, the expected value associated with a stimulus/action) within the VMPFC and aberrant prediction error signaling within the caudate (ie, the signal representing the difference between the level of reward/punishment received and the level expected, enabling reinforcement expectancies to be updated). These results are supported by a follow-up study that revealed that during a decision-making task with environmental (eg, threatening images) rather than monetary reinforcers, DBD youths showed reduced modulation of expected value information used to guide decision-making within bilateral caudate regions compared to TD youths<sup>46</sup> (but see also Ref.<sup>42</sup>). Given the lack of association between CU traits and expected value signals in the caudate in these two studies by White *et al.*,<sup>45,46</sup> one interpretation is that caudate dysfunction may represent a shared impairment in DBD that is not influenced by levels of CU traits. These results fit with behavioral studies that have shown that youths with DBD, irrespective of level of CU traits, display altered decision-making under risk<sup>47</sup> and altered temporal discounting of future rewards.<sup>48</sup> Taken together, these results provide a potentially important account of why youths with DBD, including those with HCU, persistently engage in antisocial, aggressive, and risk-taking behaviors despite the resulting adverse consequences, such as exclusion from schools and imprisonment.

### Structural Magnetic Resonance Imaging Evidence

Atypical neural responses in youths with DBD might be partly underpinned by differences in brain structure and/or connectivity. In this section, we first review sMRI studies on youths with DBD who were not subdivided using measures of CU traits. This is followed by a review of the small number of studies that have used sMRI data

to examine the correlates of CU traits using group comparisons and/or parametric analyses.

sMRI studies on youths with DBD commonly report atypical brain structure in regions central to emotion processing and regulation, empathy, morality, and decision-making.<sup>19,20</sup> The majority of these studies used whole-brain and automated imaging analysis methods, such as voxel-based morphometry (VBM) to examine gray matter volume (GMV) and surface-based morphometry (SBM) to measure cortical thickness and folding. VBM studies consistently observed reduced GMV in fronto-temporal regions, such as the OFC, insula, and amygdala,<sup>49–55</sup> with two studies reporting an overall reduction in GMV in youths with DBD (13%<sup>53</sup>; 6%<sup>51</sup>). Negative correlations were also reported between the volume of the anterior insula and lifetime CD symptoms<sup>54</sup> and aggressive behavior.<sup>55</sup> Studies using SBM have also shown that youths with DBD have thinner cortex or folding irregularities in areas of reduced GM, namely the OFC, insula, and ACC.<sup>52,56</sup> Cortical thinning in more posterior regions, such as the superior temporal cortex and precuneus, was also detected,<sup>56,57</sup> as well as reduced volume of the striatum and the amygdala.<sup>57</sup> By contrast, studies using diffusion tensor imaging (DTI) to examine the integrity of white matter tracts have thus far yielded inconsistent results, notably for the uncinate fasciculus, which connects the OFC to the amygdala. While no microstructural differences in this fiber tract have been reported between youths with DBD and TD youths,<sup>58</sup> others do report increased fractional anisotropy (FA).<sup>59–61</sup> Interestingly, reduced FA in the arcuate fasciculus<sup>62</sup> and increased FA in the corpus callosum<sup>63</sup> in youths with DBD compared to TD youths has also been found. These mixed findings may partly reflect variation in methods of analysis (tract-based spatial statistics [TBSS] vs tractography), different age ranges, and, for some studies, a failure to account for levels of CU traits in the sample (eg,<sup>58</sup>).

To date, only three sMRI studies (two using VBM) have compared youths with DBD/HCU traits to TD youths. One study showed that a subclinical sample of boys with DBD/HCU traits compared to TD youths presented with increased GM concentration in the medial orbitofrontal and rostral/dorsal anterior cingulate cortices and bilateral temporal lobes—regions that are implicated in decision-making, morality, and empathy.<sup>64</sup> Given evidence of reduction in GM with increasing age in typical development,<sup>65</sup> these results were interpreted as reflecting delayed cortical maturation in the DBD/HCU sample. A follow-up study by De Brito *et al.*<sup>66</sup> using the same sample supports this claim, with decreased white matter concentration observed in boys with DBD/HCU compared to TD youths in frontal, ACC, and temporal regions, consistent with the previous study by De Brito *et al.*<sup>64</sup> Follow-up analyses on twins revealed

**TABLE 1. Functional MRI studies of disruptive behaviour disorders in youths**

Study	Nature of sample	Participants	fMRI paradigm	Measure of CU traits	Main Results <sup>a</sup>
Sterzer <i>et al.</i> (2005) <sup>22</sup>	Clinical	27 males: 13 CD (8 comorbid for ADHD); 14 TD controls, aged 9–15 years (M: 12.7)	Passive viewing of emotional stimuli	None	CD > Controls: Deactivation within right anterior cingulate cortex and left amygdala in response to negative pictures (after controlling for anxiety and depression symptoms).
Stadler <i>et al.</i> (2007) <sup>77</sup>	Community	27 males: 13 CD; 14 TD controls aged 9–14 years (M age: 12.8)	Passive viewing of emotional stimuli	None	CD < Controls: reduced activation in the right ACC in response to negative affective pictures.
Herpertz <i>et al.</i> (2008) <sup>21</sup>	Clinical	44 males: 22 CD/childhood-onset (16 comorbid for ADHD); 22 TD controls, aged 12–17 years (M: 14.7)	Passive viewing of emotional stimuli	None	CD (childhood-onset) > Controls: Increased left amygdala activation to negative relative to neutral pictures.
Marsh <i>et al.</i> (2008) <sup>25</sup>	Community	36 children/adolescents: 12 CD/ODD/HCU (7 male); 12 ADHD (8 male); 12 TD controls (6 male), aged 10–17 years (M: 14.2)	Implicit processing of emotional facial expressions	YPI, APSD & PCL-YV	CD/ODD/HCU < ADHD/Controls: Reduced amygdala activation while processing fearful faces. CU trait severity negatively correlated with connectivity between the amygdala and VMPFC.
Finger <i>et al.</i> (2008) <sup>43</sup>	Community	42 adolescents: 14 CD/ODD (HCU) (9 male); 14 ADHD (10 male); 14 TD controls (9 male), aged 10–17 years (M: 13.6)	Probabilistic response reversal learning task	YPI, APSD & PCL-YV	CD/ODD/HCU > ADHD/Controls: Increased activity in bilateral medial frontal gyri during punished reversal error learning. Increased caudate activity (decreased for controls) during punished reversal errors. Multiple regression analyses indicate that CU traits predicted variability in VMPFC response.
Rubia <i>et al.</i> (2009) <sup>41</sup>	Community	48 males: 14 CD; 18 ADHD; 16 TD controls, aged 9–16 years (M: 13.10)	Rewarded Continuous Performance Test	None	CD < ADHD & Controls: Decreased activation in the right OFC ADHD < CD & Controls: Decreased activation in posterior cingulate gyrus
Decety <i>et al.</i> (2009) <sup>34</sup>	Community	16 male/female adolescents: 8 CD/childhood-onset; 8 TD controls, aged 16–18 years	Empathy for pain task	None	CD > Controls: increased activation in anterior midcingulate cortex, amygdala, caudate, and temporal pole bilaterally for painful situations caused by accidents vs. non-painful situations.
Jones <i>et al.</i> (2009) <sup>26</sup>	Community	30 males: 17 CP/HCU traits; 13 TD controls (M age: 11.6)	Implicit processing of emotional facial expressions	APSD	CP/HCU < Controls: reduced right amygdala activation to fearful faces.
Crowley <i>et al.</i> (2010) <sup>42</sup>	Community	40 males: 20 youths in treatment for antisocial substance dependence; 20 TD controls aged 14–18 years (M: 16.5)	Risky decision making task	None	ASD < Controls: reduced activity during decision-making in OFC, DLPFC, ACC, basal ganglia, insula, amygdala, hippocampus, and cerebellum. Reduced activity whilst experiencing wins in ACC, temporal regions, and cerebellum. ASD > Controls: increased activity during losses in OFC, DLPFC, brain stem, and cerebellum.
Marsh <i>et al.</i> (2011) <sup>39</sup>	Community	28 adolescents: 14 CD/ODD/HCU (8 male); 14 TD controls (11 male), aged 10.9–16.9 years (M: 14)	Moral judgment implicit association task	YPI, APSD & PCL-YV	CD/ODD/HCU < Controls: reduced right amygdala activation when making judgments about legal actions. Significantly less functional connectivity between the amygdala and OFC, bilateral regions of temporal cortex and inferior parietal cortex during task performance.
Finger <i>et al.</i> (2011) <sup>44</sup>	Community	30 adolescents: 15 CD/ODD/HCU (9 male); 15 TD controls (9 male) (M age: 13.7)	Passive avoidance learning task	APSD & PCL-YV	CD/ODD/HCU > ADHD/Controls: Increased activity in bilateral medial frontal gyri during punished reversal error learning. Increased caudate activity during punished reversal errors. CU traits predicted variability in VMPFC response.
Viding <i>et al.</i> (2012) <sup>23</sup>	Community	46 males: 15 CP/HCU; 15 CP/LCU; 16 TD controls, aged 10–16 years (M age: 14.2)	Backward masking of fearful faces	ICU	CP/HCU < CP/LCU & Controls: Reduced right amygdala activation during preattentive processing of masked fearful faces.



TABLE 1. Continued

Study	Nature of sample	Participants	fMRI paradigm	Measure of CU traits	Main Results <sup>a</sup>
Finger <i>et al.</i> (2012) <sup>68</sup>	Community	31 adolescents: 15 CD/ODD/HCU (11 male); 16 TD controls (10 male) (M age: 14.3)	Passive avoidance learning task	YPI, APSD & PCL-YV	CD/ODD/HCU < Controls: abnormal (disrupted) functional connectivity between the anterior cingulate cortex and amygdala. Level of amygdala-cortical connectivity not predictive of CD/ODD symptom severity.
Sebastian <i>et al.</i> (2012) <sup>37</sup>	Community	47 males: 31 CP; 16 TD controls, aged 10–16 years (M: 13.9)	Cognitive/affective theory of mind task	ICU	CP < Controls: reduced right amygdala activation for affective vs. cognitive theory of mind judgments. Unique variance on CD symptoms was positively associated with amygdala activity within the CP group, whilst unique variance associated with CU traits was negatively associated with amygdala activity.
White <i>et al.</i> (2012) <sup>27</sup>	Community	36 children/adolescents: 17 DBD/HCU (13 male); 19 TD controls (9 male), aged 10–17 years (M: 15.4)	Spatial attention task with emotional faces	APSD	DBD/HCU < Controls: reduced activity within the dorsal endogenous orienting network (comprising of superior parietal lobule and inferior parietal sulcus) for fearful face congruent relative to incongruent trials. No significant relationship between CU traits and differential response to fearful congruent vs. incongruent trials.
White <i>et al.</i> (2012) <sup>29</sup>	Community	32 children/adolescents: 15 DBD/HCU (12 male); 17 TD controls (9 male), aged 10–17 years (M: 15.1)	Top-down attentional load task with emotional faces	APSD	DBD/HCU < Controls: reduced amygdala activation to fearful faces under low- relative to high-attentional load. Significant negative correlation between amygdala activation to fearful relative to neutral faces and CU trait scores.
White <i>et al.</i> (2013) <sup>45</sup>	Community	38 children/adolescents: 20 DBD (17 male); 18 TD controls (10 male), aged 10–18 years (M: 15.1)	Passive avoidance task	APSD	DBD > Controls: reduced sensitivity to expected value information in VMPCF (when choosing objects) and anterior insular cortex (when refusing objects). Reduced modulation of activity by prediction error following reward in the caudate, but increased modulation following punishment.
Cohn <i>et al.</i> (2013) <sup>28</sup>	Community	76 adolescents: 25 DBD + CD/ODD (desistent) (20 male); 25 DBD + CD/ODD (persistent) (18 male); 26 TD controls (23 male) (M age: 17.5) (DBD onset mean age: 6.6)	Fear conditioning task	YPI	DBD + CD/ODD (desistent & persistent) > Controls: increased activation within left anterior cingulate cortex, right insula and left amygdala. Unique variance on YPI CU traits was negatively associated with activation in the ACC whilst unique variance associated with the impulsive-irresponsible facets was positively correlated with activation in the amygdala, insula and ACC.
Lockwood <i>et al.</i> (2013) <sup>36</sup>	Community	55 males: 37 CP; 18 TD controls, aged 10–16 years (M: 13.9)	Empathy for pain task	ICU	CP < Controls: reduced neural activation to other's pain observed within bilateral anterior insula, ACC and inferior frontal gyrus. Unique variance on CU traits was negatively associated with response to pain in the anterior insula and ACC in the CP group.
Marsh <i>et al.</i> (2013) <sup>35</sup>	Community	35 adolescents: 14 ODD/CD/HCU (8 male); 21 TD controls (15 male), aged 10–17 years (M: 14.9)	Empathy for pain task	YPI, APSD & PCL-YV	CD/ODD/HCU < Controls: reduced activity in rostral ACC, putamen and amygdala. Activation observed in the amygdala and ACC negatively correlated with CU severity.

White <i>et al.</i> (2013) <sup>40</sup>	Community	38 children/adolescents: 20 DBD (17 male); 18 TD controls (10 male), aged 10–18 years (M: 15.1)	Passive avoidance probabilistic reward task	APSD	DBD < Controls: reduced modulation of activity as a function of expected value of avoidance within ventromedial PFC, anterior insula and caudate regions of interest. Significantly reduced modulation of caudate activity as a function of prediction error related to punishment. No association between activity within these regions and CU trait severity.
Lozier <i>et al.</i> (2014) <sup>32</sup>	Community	46 children/adolescents: 14 CP/HCU (7 male); 16 CP/LCU (9 males); 16 TD controls (10 males), aged 10–17 years (M: 13.8)	Implicit processing of emotional facial expressions	ICU	No significant group differences within right amygdala in response to fearful expressions. Across CP/HCU & CP/LCU groups, unique variance on CU traits was negatively associated with right amygdala response to fearful expressions, whilst unique variance on CP symptoms was positively correlated with amygdala response. Reduced amygdala activity mediated the association between CU traits and proactive aggression.
Fairchild <i>et al.</i> (2014) <sup>72</sup>	Community	40 females: 20 CD; 20 TD controls, aged 14–20 years (M: 17.3)	Implicit processing of emotional facial expressions	YPI & ICU	CD < Controls: Reduced medial OFC activation. CU traits negatively correlated with activation in the fusiform gyrus for sad vs. neutral faces. CD > Controls: Increased anterior insula activation.
Sebastian <i>et al.</i> (2014) <sup>24</sup>	Community	55 males: 17 CP/HCU; 17 CP/LCU; 17 TD controls, aged 10–16 years (M: 14.0)	Implicit processing of emotional facial expressions	ICU	CP/LCU > Controls: Increased amygdala and ACC/OFC activation to fearful eyes. Correlation between RTs and amygdala activation to fearful eyes.
O'Nions <i>et al.</i> (2014) <sup>38</sup>	Community	48 males: 16 CP/HCU; 16 ASD; 16 TD controls, aged 10–16 years (M: 13.9)	Cognitive theory of mind task	ICU	CD/HCU = Controls: No difference in neural response between groups. Children with ASD exhibited atypical neural processing within the context of the task.

Anatomical abbreviations: ACC – anterior cingulate cortex, DLPFC – dorsolateral prefrontal cortex, OFC – orbitofrontal cortex, PCC – posterior cingulate cortex, PFC – prefrontal cortex, VMPFC – ventromedial prefrontal cortex. Note: ADHD – Attention-deficit hyperactivity-disorder, APSD – Antisocial Process Screening Device, ASD – antisocial substance dependence, CD – conduct disorder, CP – conduct problems, DBD – disruptive behaviour disorder, HCU – high callous/unemotional traits, ICU – Inventory of Callous-Unemotional Traits, K-SADS – Kiddie Schedule for Affective Disorders and Schizophrenia, LCU – low callous/unemotional traits, ODD – oppositional defiant disorder, PCL-YV – Psychopathy Checklist: Youth Version, TD – typically developing, YPI – Youth Psychopathic Traits Inventory

<sup>a</sup> CU traits in the Main Results refer to lack of empathy and guilt, and shallow affect. Individual authors may have used a different label, i.e. psychopathic traits, in their paper, but for ease of reading we have used CU traits consistently. The Measures of CU traits column lists the specific measure used.

TABLE 2. Structural MRI studies of disruptive behaviour disorders in youths

Study	Nature of sample	Participants	Methods	Measures of CU-traits	Main Results <sup>a</sup>
Sterzer <i>et al.</i> (2007) <sup>55</sup>	Clinical	24 males (12 CD/childhood-onset; 12 TD controls) aged 12 years (M: 12.6)	VBM	None	CD < Controls: Significantly reduced grey matter in left amygdala and bilateral anterior insula. In the CD group, bilateral anterior insula grey matter volume correlated positively with empathy score.
Huebner <i>et al.</i> (2008) <sup>51</sup>	Clinical	46 males (23 CD/childhood-onset (17 co-morbid for ADHD); 23 TD controls) aged 12–17 years (M: 14.4)	VBM	None	CD < Controls: 6% reduction in average grey matter volume. Significantly reduced grey matter volume in bilateral temporal cortex, left amygdala, left hippocampus, orbitofrontal & ventromedial regions. CD symptom severity inversely correlated with grey matter volume within limbic structures. CD > Controls: Significant increase in grey matter volume within cerebellum bilaterally.
De Brito <i>et al.</i> (2009) <sup>64</sup>	Community	48 males (23 CP/HCU traits; 25 TD controls) aged 10–13.3 years (M: 11.7)	VBM	APSD	CP > Controls: Boys with elevated CU traits showed increased grey matter concentration within medial OFC and ACC. Increased grey matter volume and concentration observed in bilateral temporal regions.
De Brito <i>et al.</i> (2011) <sup>66</sup>	Community	48 males (23 CP/HCU traits; 25 TD controls) aged 10–13.3 years (M: 11.7)	VBM	APSD	CP < Controls: Significantly decreased white matter concentration in right superior frontal lobe, right dorsal ACC, right superior temporal gyrus and left precuneus. CP > Controls: Increased white matter concentration within bilateral middle frontal gyrus.
Dalwani <i>et al.</i> (2011) <sup>75</sup>	Clinical	44 males (25 antisocial substance dependence; 19 TD controls) aged 14–18 years (M: 16.6)	VBM	None	Patients < Controls: Whole-brain analysis revealed significantly reduced grey matter volume in left DLPFC, right lingual gyrus and bilateral cerebellum. Grey matter volume in left DLPFC negatively associated with severity of substance dependence. Patients > Controls: Significantly increased grey matter volume in right precuneus.
Fahim <i>et al.</i> (2011) <sup>52</sup>	Community	47 males (22 DBD; 25 TD controls) aged 8 years (M: 8.4)	VBM & SBM	None	DBD < Controls: Significantly decreased grey matter density in left medial PFC, cingulate, and bilateral insula cortices. Increased DBD score associated with decreased grey matter density in left medial middle and superior frontal cortex, precuneus, and right superior temporal and occipital/cuneus regions.
Fairchild <i>et al.</i> (2011) <sup>54</sup>	Community	90 males (36 CD/childhood-onset; 27 CD/adolescent-onset; 27 TD controls) aged 16–21 years (M: 18.0)	VBM	YPI & ICU	CD < Controls: Reduced grey matter volume in amygdala bilaterally (including the insula). CD (adolescent-onset) < Controls: Reduced amygdala and right insula grey matter volume. CD (childhood-onset) < Controls: Reduced amygdala grey matter volume. Right insula volume was negatively correlated with CD-symptom severity in both sub-groups.
Hyatt <i>et al.</i> (2012) <sup>56</sup>	Community	43 male/female adolescents (19 CD (10 male); 24 TD control (14 male) aged 12–18 years (M: 16.2)	SBM	None	CD < Controls: Reduced cortical thickness mainly in several posterior brain regions across the temporal and parietal lobes. Reduced gyrfication primarily located in anterior brain regions (insula, inferior and dorsal frontal regions including lateral OFC, VMPFC and ACC), but also in the temporal and parietal lobes.
Stevens <i>et al.</i> (2012) <sup>53</sup>	Community	72 male/female adolescents (24 CD; 24 ADHD; 24 TD controls; 51Male) aged 15–16 years (M: 15.9)	VBM	None	CD < Controls: 13% reduction in grey matter volume reflecting deficits in frontal, temporal, parietal and subcortical regions. Increased grey matter in right OFC, bilateral amygdala and bilateral temporal cortices associated with increased symptom severity in CD adolescents.
White <i>et al.</i> (2013) <sup>76</sup>	Community	59 adolescents (32 DBD (25 male); 27 TD controls (19 male) (M age: 14.9)	Manual Tracing	ASPD & ICU	Large cavum septum pellucidum observed in 7/32 DBD adolescents but not for any of the controls. No correlation between size of cavum septum pellucidum and CU traits.
Ermer <i>et al.</i> (2013) <sup>69</sup>	Prison	191 male prisoners (M age: 17.3)	VBM	PCL-YV	Psychopathic trait scores negatively associated with grey matter volume in regions of interest: PCC and OFC (extending into parahippocampal cortex and temporal poles). Increased grey matter volume in pre-frontal cortex positively associated with psychopathic traits.



Fairchild <i>et al.</i> (2013) <sup>49</sup>	Community	42 females (22 CD, 17 adolescent-onset; 20 TD controls) aged 14–20 years (M: 17.3)	VBM	YPI	CD < Controls: Significantly reduced bilateral anterior insula and right striatal grey matter volumes. Right DLPFC volume was negatively correlated with CD symptom severity whilst CU traits were positively correlated with bilateral OFC volume.
Olvera <i>et al.</i> (2014) <sup>50</sup>	Prison	72 male/female adolescents (24 CD with bipolar disorder (16 male); 24 CD (21 male); 24 TD controls (16 male) (M age: 15.8)	VBM	None	CD + bipolar disorder < Controls: Decreased grey matter volume of the right medial PFC, superior and inferior frontal gyrus, ACC and temporal gyrus. CD only = Controls: No differences in brain volume.
Cope <i>et al.</i> (2014) <sup>70</sup>	Prison	39 female prisoners (M age: 17.6)	VBM	PCL-YV	Negative correlations between CU traits and grey matter volume in limbic and paralimbic regions, including OFC, parahippocampal cortex, temporal poles and hippocampus.
Wallace <i>et al.</i> (2014) <sup>57</sup>	Community	49 male/female adolescents (22 CD; 27 TD controls) aged 10–18 years (M: 14.9)	SBM	ICU	CD < Controls: Reduced cortical thickness in superior temporal cortex and reduced gyrification in the VMPFC. Amygdala and striatum (pallidum and putamen) cortical volumes also reduced. Right temporal cortical thickness was inversely correlated with CU trait severity.
Li <i>et al.</i> (2005) <sup>52</sup>	Community	76 adolescents (36 with DBD (25 male); 40 TD controls (21 male) (M age: 14.0)	DTI tractography	K-SADS	DBD < Controls: 13% reduction in FA in the arcuate fasciculus and FA deficits in PFC.
Finger <i>et al.</i> (2012) <sup>68</sup>	Community	31 adolescents (15 with psychopathic traits (ODD/CD; 11 male); 16 TD controls (10 male) (M age: 14.3)	DTI tractography & TBSS	YPI, APSD & PCL-YV	DTI analysis did not reveal any disruption in structural connections within the uncinate fasciculus or any other tracts.
Passamonti <i>et al.</i> (2012) <sup>73</sup>	Community	26 males (13 with childhood onset CD; 13 TD controls) (M age: 18.5)	Voxel-based DTI & DTI tractography	YPI	CD > Controls: Increased FA within the right ventral external capsule and uncinate fasciculus tract.
Sarkar <i>et al.</i> (2013) <sup>60</sup>	Community	43 male children/adolescents (27 CD; 16 TD controls) aged 12–19 years (M: 16.0)	DTI tractography	APSD	CD > Controls: Greater FA and reduced perpendicular radial diffusivity in the left uncinate fasciculus (trend for increased FA in right uncinate fasciculus). A positive correlation between left uncinate fasciculus integrity and severity of APSD scores across groups with a trend in the CD group alone ( $p = 0.09$ ).
Haney-Caron <i>et al.</i> (2014) <sup>58</sup>	Community	41 children/adolescents (17 CD (10 male); 24 TD controls (15 male) aged 12–18 years (M: 15.8)	TBSS	None	CD < Controls: Lower FA and axial diffusivity in frontal and temporal lobes. FA values were negatively correlated with number of CD symptoms in the CD group.
Zhang <i>et al.</i> (2014) <sup>61</sup>	Clinical	69 males (36 CD; 33 TD controls) (M age: 15.1)	TBSS and quantitative tractography	APSD	CD > Controls: Higher FA within the corpus callosum bilaterally (including body and genu). Impulsivity measures correlated positively with higher FA in fibers projecting from the corpus callosum.
Zhang <i>et al.</i> (2014) <sup>63</sup>	Clinical	56 adolescents (27 CD (14 males); 29 TD controls (16 males) aged 13–16 years (M: 14.0)	TBSS and quantitative tractography	APSD	Male CD > Female CD: Higher FA of the bilateral uncinate fasciculus and lower radial diffusivity in the left uncinate fasciculus. Male CD > Male Controls: Higher FA and lower radial diffusivity in bilateral uncinate fasciculus.

Anatomical abbreviations: ACC – anterior cingulate cortex, DLPFC – dorsolateral prefrontal cortex, OFC – orbitofrontal cortex, PCC – posterior cingulate cortex, PFC – prefrontal cortex, VMPFC – ventromedial prefrontal cortex. Note: ADHD – Attention-deficit hyperactivity-disorder, APSD – Antisocial Process Screening Device, CD – conduct disorder, CP – conduct problems, DBD – disruptive behaviour disorder, DTI – diffusion tensor imaging, FA – fractional anisotropy, HCU – high callous/unemotional traits, ICU – Inventory of Callous-Unemotional Traits, K-SADS – Kiddie Schedule for Affective Disorders and Schizophrenia, LCU – low callous/unemotional traits, ODD – oppositional defiant disorder, PCL-YV – Psychopathy Checklist: Youth Version, SBM – surface based morphometry, TBSS – tract based spatial statistics, TD – typically developing, VBM – voxel based morphometry, YPI – Youth Psychopathic Traits Inventory.

<sup>a</sup> CU traits in the Main Results refer to lack of empathy and guilt, and shallow affect. Individual authors may have used a different label, i.e. psychopathic traits, in their paper, but for ease of reading we have used CU traits consistently. The Measures of CU traits column lists the specific measure used.

that some of the GM differences observed by De Brito *et al*<sup>64</sup> might represent a potential endophenotype for DBD/HCU.<sup>67</sup> Despite evidence of group differences in functional connectivity, Finger *et al*<sup>68</sup> did not observe differences in structural connectivity within the uncinate fasciculus or other white matter tracts when comparing DBD/HCU youths and TD youths using DTI.

sMRI studies investigating the association between CU traits and VBM, SBM, and DTI metrics have revealed somewhat inconsistent findings. For example, a VBM study using a large sample of male adolescent prisoners with DBD (N = 191) revealed negative associations between GM volume and psychopathic traits in the posterior cingulate cortex and OFC, extending into temporal poles and parahippocampal cortex.<sup>69</sup> This pattern of results was recently replicated in females.<sup>70</sup> In contrast, Fairchild *et al*<sup>49</sup> found that, across DBD and TD females, CU traits were positively correlated with bilateral OFC GM volume, but negatively correlated with anterior insula and striatal GM volume. In a large sample of males with DBD (N = 63), Fairchild *et al*<sup>54</sup> found no relationship between GM volumes and CU traits. Using SBM, a negative association between CU traits and cortical thickness in the superior temporal cortex has also been reported in youths with DBD.<sup>57</sup> Whilst Finger *et al*<sup>68</sup> did not find an association between CU traits and DTI metrics, a recent study reported a positive trend between psychopathic traits and FA in the left uncinate fasciculus,<sup>60</sup> and yet another revealed a negative trend between CU traits and FA values in the left uncinate fasciculus in males with DBD.<sup>61</sup>

### Neuroimaging Evidence: Sex Matters

Sex differences in DBD are presently overlooked, with most samples in neuroimaging studies of DBD including males only. Thus, it is unclear whether the current evidence base also applies to females.<sup>14</sup> Given evidence of sex differences in brain development and brain functioning in TD youths,<sup>71</sup> it is conceivable that females with DBD might present different impairments from those observed in males with DBD. Yet, to date, only one fMRI study has compared females with DBD to TD females, reporting that those with DBD exhibited reduced medial OFC and increased anterior insula activity to sad, angry, and neutral faces, which is indicative of general face processing impairments.<sup>72</sup> These results contrast with those observed in males using the same task, whereby males with DBD, compared to TD youths, exhibited increased activity to neutral faces and reduced activity to angry faces, which is indicative of more specific impairments in emotion processing.<sup>73</sup>

In terms of sMRI studies, Fairchild *et al*<sup>49</sup> found that both males and females with CD showed similar reduction in GM volume in the amygdala compared to TD

youths, which is consistent with evidence that both males and females with DBD show impaired fear conditioning. Crucially, however, a sex by diagnosis interaction was observed in the bilateral anterior insula: DBD females showed reduced GM volume compared to TD females, with the opposite pattern observed among males. A recent DTI study also reported a sex by diagnosis interaction whereby males with DBD, compared to TD males, had higher FA and lower radial diffusivity of the bilateral uncinate fasciculus, but no group differences were observed between the females with DBD and the TD females. Interestingly, higher FA and lower radial diffusivity in the uncinate fasciculus were found in males with DBD compared to females with DBD.<sup>61</sup>

The above results suggest that both males and females with DBD are characterized by functional and structural abnormalities in key regions implicated in affective processing, empathy, and decision-making, but the nature of these deficits within a number of regions varies across sex. Our group is currently investigating the potential origins and implications of these differences within the context of the FemNAT-CD study (<http://www.femnat-cd.eu>), a large multisite European study examining environmental and neurobiological factors associated with the development of DBD in male and female youths.

### Implications for Treatment

The neuroimaging findings reviewed in this article add to the existing body of genetic, behavioral, and experimental evidence by highlighting that youths with DBD/HCU and DBD/LCU are characterized by different neurocognitive vulnerabilities, which are likely to influence intervention implementations and outcomes. Treatments for these subgroups should be tailored to their unique affective, neurocognitive, and motivational styles to maximize their effectiveness.<sup>11</sup> Despite evidence that youths with DBD/HCU are less responsive to treatment, and that their antisocial behavior is under strong genetic influence, these youths should not be considered “untreatable.”<sup>9,11</sup> An increasing body of evidence shows that intensive and tailored treatments can reduce antisocial behavior and levels of CU traits in these youths, particularly when their reward-oriented style is primed.<sup>11</sup> Neuroimaging evidence suggests that such interventions should seek to increase sensitivity to other’s distress cues, and improve prediction error and expected value signaling during decision-making, possibly through a two-pronged approach that combines behavioral and pharmacological interventions.<sup>8,74</sup> While youths with DBD/LCU might also benefit from behavioral and pharmacological interventions that target decision-making, in contrast to youths with DBD/HCU, they are more likely to respond to interventions that focus on increasing anger control/emotion regulation and reducing harsh and inconsistent

parenting, given that these children are more likely to come from dysfunctional families.<sup>11</sup> Clearly, any form of intervention should systematically account for the influence of the level of CU traits on treatment response.<sup>36,37</sup>

## Conclusions

There is increasing recognition among the research and clinical community that youths with DBD are characterized by different patterns of behavioral problems and affective profiles, reflecting different underlying causal mechanisms.<sup>11</sup> The evidence base accumulated over the last 20 years has shown that subtyping youths with DBD based on their level of CU traits identifies two subgroups of antisocial youths, who are characterized by different vulnerabilities and behavioral profiles.<sup>9,11</sup> Consistent with experimental data showing high emotional reactivity in DBD/LCU and low emotional reactivity in DBD/HCU, recent fMRI evidence has shown that high levels of CU traits in DBD are associated with hyporesponsivity to affective stimuli and others' distress in cortical and subcortical regions, such as the anterior insula, ACC, and amygdala. In contrast, low levels of CU traits are associated with heightened response in those regions. No sMRI study has directly compared these two subgroups, and those studies that have examined the associations between CU traits and sMRI indices have produced mixed findings. The paucity of neuroimaging investigations that have focused on females and on the role of sex differences is another important gap in this work. It is hoped that the mounting body of neuroimaging evidence investigating the role of CU traits on brain function and structure could inform the development of tailored treatments for both male and female youths with DBD.

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