

## Neuroimaging findings in disruptive behavior disorders

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DOI:

[10.1017/S1092852914000789](https://doi.org/10.1017/S1092852914000789)

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*Document Version*

Peer reviewed version

*Citation for published version (Harvard):*

Baker, RH, Clanton, RL, Rogers, JC & De Brito, SA 2015, 'Neuroimaging findings in disruptive behavior disorders', *CNS spectrums*, vol. 20, no. 4, pp. 369-381. <https://doi.org/10.1017/S1092852914000789>

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Final version of record available at: <http://dx.doi.org/10.1017/S1092852914000789>

Checked Jan 2016

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## **Neuroimaging findings in disruptive behaviour disorders**

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Word Count: 4041

**Acknowledgments:** Rosalind Baker, Jack Rogers and Stéphane De Brito are supported by the European Commission's Seventh Framework Programme (FP7/2007–2013) under Grant Agreement n° 602407 (FemNAT-CD) (<http://ec.europa.eu>). Roberta Clanton is supported by a PhD studentship from the College of Life and Environmental Sciences, University of Birmingham. We thank Dr Graeme Fairchild for his comments on a previous version of the manuscript.

## Abstract

Decades of research have shown that youths with disruptive behaviour 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 behaviour and aggression. Conduct problems in youths with HCU and LCU are thought to reflect distinct causal vulnerabilities, with antisocial behaviour in youths with DBD/HCU reflecting a predominantly genetic aetiology, whilst antisocial behaviour 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. Firstly, fMRI studies examining the neural correlates of affective stimuli, emotional face processing, empathy, theory of mind, morality, and **affective** 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.

Keywords: disruptive behaviour disorders, conduct disorder, conduct problems, **disruptive behaviour disorders**, callous-unemotional traits, antisocial behaviour, fMRI, voxel-based morphometry, surface-based morphometry, diffusion tensor imaging, **sex differences**.

## Introduction

Disruptive behaviour disorders (DBD), which include conduct disorder/conduct problems and oppositional defiant disorder, are characterised by aggressive and antisocial behaviour during childhood and adolescence<sup>1</sup>. These behaviours 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 ten times more than a child displaying no conduct problems<sup>2</sup>. Crucially, DBD in youths are not only predictive of antisocial and aggressive behaviours 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 incorporating 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 characterise adult psychopaths, a particularly severe group of antisocial individuals<sup>7</sup>. While youths cannot be labelled 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, behavioural, experimental and neuroimaging studies have shown that youths with DBD/HCU and those with DBD/LCU are characterised 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 Disorder* (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 behaviours 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, 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 behaviour in different ways, 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. Whilst 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 behaviour is different between the sexes; whilst 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 behaviours more often exhibited by males<sup>14</sup>. Whilst males are more likely to show overt behaviours, such as vandalism and aggressive stealing, females are more likely to show covert behaviours such as lying and sabotaging relationships<sup>17</sup>. With the aim of extending research on females with DBD, the Fem-NAT-CD consortium - a large multisite European study which our group is part of - 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 paper we selectively review recent functional (fMRI) and structural (sMRI) magnetic resonance imaging research on DBD, focusing particularly on the role of CU traits. Firstly, fMRI studies examining the neural correlates of affective stimuli, emotional face processing, empathy, theory of mind, morality, and **affective** decision-making in DBD will be discussed. This is followed by a review of the studies investigating brain structure and structural connectivity in DBD. 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, identifying 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 which 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 characterised by distinct emotional, cognitive and behavioural 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>. **Furthermore, compared to TD youths, youths with DBD and high anxiety levels (possibly reflecting LCU) have also been found to exhibit reduced activity within the dorsal ACC, a key region for emotion regulation, in response to negative affective stimuli.** These results might partly explain why youths with DBD/LCU have a propensity towards emotion regulation difficulties and reactive aggression when feeling 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<sup>27,28</sup>) and unconscious fearful faces<sup>23</sup>. These findings have been recently extended by White et al.<sup>29</sup>, showing that an atypical amygdala response to consciously processed fearful faces in youths with DBD/HCU is not secondary to an attentional deficit (i.e., increased top-down control) but 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 grey, which mediate the perceived somatosensory sensation of pain<sup>33</sup>. Surprisingly, Decety et al. 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<sup>34</sup>. 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 characterised 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. found that those with DBD/HCU, compared to TD youths, showed reduced response in the ACC and



ventral striatum to perceived pain in others<sup>35</sup>. 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 found that cartoons requiring understanding distress in others within the context of social situations produced reduced amygdala and anterior insula activity in youths with DBD relative to TD youths<sup>37</sup>. This reduced activation was negatively correlated with the unique variance associated with CU traits. Using the same task, O'Nions and colleagues 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<sup>38</sup>. These results dovetail with behavioural and experimental data<sup>13</sup> and highlight the fact that youths with DBD/HCU do not have a deficit in understanding the mental state 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>. **and are able to callously manipulate others for their own benefit<sup>13</sup>.**

The immoral judgment seen in youths with DBD/HCU may result from impairments in emotional empathy and **affective** decision-making (see below); deficits thought to reflect dysfunctions within the amygdala-VMPC 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 socialisation of youths with DBD/HCU, putting them at increased risk of

displaying severe antisocial behaviour and proactive aggression without feeling guilt or empathy for their victims.

### *Affective 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 *affective* 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 (i.e., 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 (i.e., the expected value associated with a stimulus/action) within the VMPFC and aberrant prediction error signalling within the caudate (i.e., 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 revealing that during a decision-making task with environmental (e.g.

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 <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 which is not influenced by levels of CU traits. These results fit with behavioural studies showing 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 behaviours despite the resulting adverse consequences such as exclusion from schools and imprisonment.

Insert Table 1 Here

### 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 firstly review sMRI studies on youths with DBD that were not subdivided using measures of CU traits. This is followed by a review of the small number of studies that have used structural MRI data to examine the correlates of CU traits using group comparisons and/or parametric analyses.

Structural MRI 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 grey 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 behaviour<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. Whilst no microstructural differences in this fibre 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 (TBSS vs tractography), different age ranges and, for some studies, a failure to account for levels of CU traits in the sample (e.g.<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 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 De Brito et al.<sup>65</sup> study, as well as left precuneus. Follow-up analyses on twins revealed that some of the GM differences observed by De Brito et al. might represent a potential endophenotype for DBD/HCU<sup>67</sup>. Despite evidence of group differences in functional connectivity, Finger et al. 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<sup>68</sup>.

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. 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<sup>49</sup>. In a large sample of males with DBD (N=63), Fairchild et al. found no relationship between GM volumes and CU traits<sup>54</sup>. 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. did not find an association between CU traits and DTI metrics<sup>68</sup>, 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>.

Insert Table 2 Here

### 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 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, indicative of more specific impairments in emotion processing<sup>73</sup>.

In terms of sMRI studies, Fairchild et al. found that both males and females with CD showed similar reduction in GM volume in the amygdala compared to TD youths, consistent with evidence that both males and females with DBD show impaired fear conditioning<sup>49</sup>. 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 characterised 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, 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 above add to the existing body of genetic, behavioural and experimental evidence by highlighting that youths with DBD/HCU and DBD/LCU are characterised 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 maximise their effectiveness<sup>11</sup>. Despite evidence that youths with DBD/HCU are less responsive to treatment, and that their antisocial behaviour 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 behaviour 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 signalling during decision-making, possibly through a two-pronged approach combining behavioural and pharmacological interventions<sup>8,74</sup>. While youths with DBD/LCU might also benefit from behavioural and pharmacological interventions targeting decision-making, in contrast to youths with DBD/HCU, they are more likely to respond to interventions focusing 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 characterised by different patterns of behavioural 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 characterised by different vulnerabilities and behavioural 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 is 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 focussing 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 functioning and structures could inform the development of tailored treatments for both male and female youths with DBD based on the levels of CU traits they exhibit.



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