

# What can be learned from white matter alterations in antisocial girls

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## Article Info

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## ABSTRACT

Antisocial behavior in youths constitutes a major public health problem worldwide. Conduct disorder is a severe variant of antisocial behavior with higher prevalence rates for boys (12%) as opposed to girls (7%). A better understanding of the underlying neurobiological mechanisms of conduct disorder is warranted to improve identification, diagnosis, or treatment. Functional and structural neuroimaging studies have indicated several key brain regions within the limbic system and prefrontal cortex that are altered in youths with conduct disorder. Examining the structural connectivity, i.e. white matter fiber tracts connecting these brain areas, may further inform about the underlying neural mechanisms. Diffusion tensor imaging (DTI) is a non-invasive technique that can evaluate the white matter integrity of fiber tracts throughout the brain. To date, DTI studies have found several white matter tracts that are altered in youths with conduct disorder. However, a majority of these studies have focused on male or mixed-gender groups, and only a few studies have specifically investigated white matter alterations in girls with conduct disorder. Ultimately, studies that directly compare boys and girls with conduct disorder are necessary to identify possible sexual dimorphic neural alterations and developmental trajectories of conduct disorder in youths.

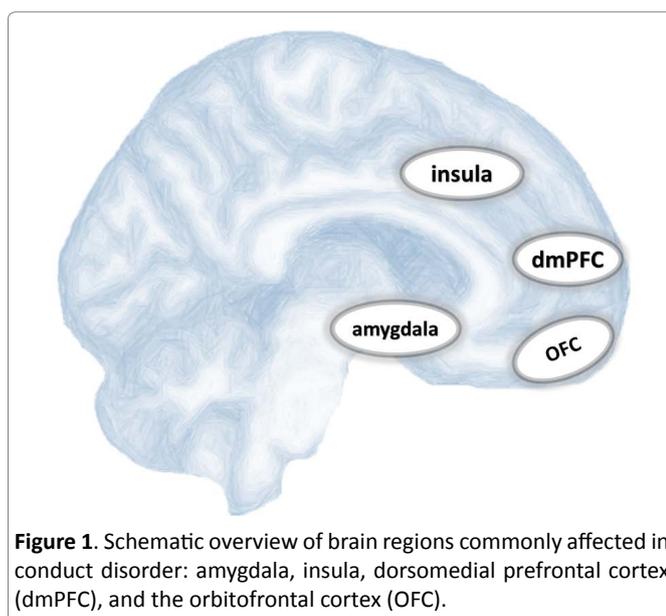
## Introduction

Antisocial behavior in children and adolescents is associated with significant societal, clinical, and economic consequences and is therefore considered a major public health burden worldwide. Youths with severe aggressive and antisocial behavior outside of the age-appropriate norm qualify for a diagnosis of conduct disorder. Conduct disorder is characterized by a repetitive and persistent pattern of behavior in which the basic rights of others or societal norms or rules are violated<sup>1</sup>. The life time prevalence of conduct disorder is estimated to be around 7% and 12%, for girls and boys respectively<sup>2</sup>. Furthermore, conduct disorder is thought to be very heterogeneous and several subtypes have been suggested (e.g. with or without callous-unemotional traits<sup>3</sup>). Particularly youths with severe subtypes of conduct disorder are at higher risk for persistent antisocial behavior and criminality in adulthood, and thus at great risk for developing antisocial personality disorder later in life<sup>1,4</sup>. Previous studies have suggested that an increased understanding of the neurobiological basis of conduct disorder and its subtypes in youths may increase the modest treatment success of current intervention methods<sup>5</sup>. So far, research studies using functional and structural neuroimaging techniques have identified dysfunctions and structural alterations within a set of cortical and subcortical brain regions. Cortical brain regions that are often identified as being altered in conduct disorder by voxel-based approaches include gray matter structures of the limbic system (e.g. amygdala, insula, and cingulate cortex) and

prefrontal cortex<sup>6-12</sup>. The limbic system is important for various processes in human social behavior that are often impaired in youths with conduct disorder, such as emotion processing and regulation<sup>9</sup>. The prefrontal cortex (PFC) plays a significant role in cognitive control by means of attention and decision-making over the simple and more automatic behaviors<sup>13</sup>. The amygdala and prefrontal cortex are bi-directionally interconnected through white matter tracts of the prefrontal-limbic circuitry<sup>14</sup>. Investigating the functional and structural connectivity of this circuitry could give more insight in the etiology of conduct disorder<sup>15-17</sup>.

### Brain connectivity in conduct disorder

In line with individual reports, meta-analyses have summarized that brain regions commonly affected in conduct disorder are part of specific neural networks, specifically the emotion processing and regulation network (see figure 1)<sup>18,19</sup>. Brain areas within those networks are functionally and structurally interconnected with one another by anatomical white matter tracts consisting of abundant thin myelinated axons. Thus far, studies investigating functional brain connectivity in youths with severe antisocial behavior have found a reduced functional connectivity between the amygdala and two regions of the prefrontal cortex, namely the ventromedial prefrontal cortex<sup>7</sup> and the orbitofrontal cortex<sup>17,20</sup>. Consequently, researchers have hypothesized that the observed reduced amygdala-PFC connectivity is correlated with abnormal white matter structures in these youths<sup>15,21</sup>. Although functional networks help to identify the neural dynamics between brain areas, it cannot inform about the actual structural architecture. Hence, investigating white matter tracts will be an important step toward understanding the dysfunctional neural interplay and connectivity that contribute to conduct disorder.



**Figure 1.** Schematic overview of brain regions commonly affected in conduct disorder: amygdala, insula, dorsomedial prefrontal cortex (dmPFC), and the orbitofrontal cortex (OFC).

### Diffusion Tensor Imaging

A commonly used neuroimaging technique allowing the investigation of the microstructural properties of white-matter is diffusion tensor imaging (DTI). DTI is based on the three-dimensional diffusion of water molecules that is measured through multiple-directional diffusion-weighting gradient pulses. Hereby, specific features of this diffusivity are translated into tensors using mathematical equations based on the eigenvectors and eigenvalues within each voxel<sup>22</sup>. The most commonly used tensors to inform about microstructural integrity of white matter tracts are the fractional anisotropy (FA) and mean diffusivity (MD), which measure the anisotropic fraction of diffusivity and the diffusion magnitude respectively<sup>23</sup>. Other tensors occasionally used in DTI studies are axial diffusivity (magnitude of fastest diffusion direction) and radial diffusivity (diffusion magnitude of transverse direction)<sup>24</sup>. In order to analyze group differences, researchers either employ tract-based spatial statistics (TBSS)<sup>25</sup>, voxel-based analysis, or fiber tractography.

### Altered white matter structures in conduct disorder

DTI has aided studies investigating white matter structures in children and adolescents with conduct disorder, however, many discrepancies exist between the results of these studies. For example, DTI studies have identified increased fractional anisotropy in the uncinate fasciculus<sup>21,26-28</sup> and corpus callosum<sup>29,30</sup> of children and adolescents with conduct problems, while others observed decreased white matter integrity in the same white matter tracts<sup>26,31</sup>, as well as in the corona radiata, superior longitudinal fasciculus, fronto-occipital fasciculus, stria terminalis, and cerebellar peduncle<sup>31,32</sup>. Most studies vary in regard to the precise tract or set of tracts identified, and some do not detect white matter alterations at all<sup>20,33,34</sup>. Thus far, there is no clear picture about the underlying tract-based phenotype of antisocial behavior to date. Similar discrepancies exist when following-up on the relationship of specific DTI tensors in relation to behavioral severity of conduct disorder, such as psychopathic traits, callous unemotional traits, and amount of conduct disorder symptoms<sup>31,32,35-37</sup>. Some identify positive correlations<sup>35,37</sup>, while others reported negative<sup>31,32</sup> or no correlations at all<sup>29</sup>. These inconsistent findings regarding the direction and location of white matter alterations may result from differences in the analysis approaches used (e.g. TBSS, voxel-based analysis, or fiber tractography), small sample sizes, or group heterogeneity. Especially group heterogeneity is of importance when investigating antisocial behavior. The inclusion of youths can be defined based on different diagnostic criteria; some studies investigated only oppositional defiant disorder, while others focused on conduct disorder or a mixture of both. These heterogeneities were previously mentioned in

a recent review<sup>38</sup>, however, we suggest another important factor in antisocial behavior, namely sex. So far, most DTI studies have included only male or mixed-gender groups of youths with antisocial behavior. These factors could explain why study results differ in regard to the observed neural alterations.

### Sex differences and conduct disorder

Since most DTI studies have focused solely on male or mix-gender groups, it is unclear whether girls with conduct disorder also show similar white matter alterations as observed in boys<sup>21,30-32</sup>. So far only one study has directly investigated white matter alterations between adolescent boys and girls with conduct disorder and found sex differences for fractional anisotropy, i.e. higher in males within the bilateral uncinate fasciculus<sup>28</sup>. Another study investigating pre-adolescents with conduct problems indicated no sex differences for fractional anisotropy, but did observe a stronger relationship between conduct disorder symptoms and altered white matter integrity (i.e. axial diffusivity) in several tracts, for example the uncinate fasciculus in girls in comparison to boys<sup>35</sup>. Since the uncinate fasciculus interconnects the orbitofrontal cortex and amygdala, this major white matter tract has often been associated with antisocial behavior<sup>9,16,17</sup>. A recent DTI study indicated white matter alterations on a whole-brain level within a homogenous group of girls with conduct disorder<sup>29</sup>. Compared to typically developing girls, girls with conduct disorder had increased FA bilaterally within the body of the corpus callosum expanding towards the right cingulum and left corona radiata, independent of age, intelligence, and attention deficit hyperactivity disorder<sup>29</sup>. These findings align with the study of Zhang and colleagues (2014) who demonstrated FA increases within the body and genu of the corpus callosum of male adolescents with conduct disorder using a TBSS-approach. The corpus callosum has abundant projections to and from the hemispherical cortices, and thus is crucial for interhemispheric communication. The genu and body are subsections of this white matter tract and interconnect parts of the frontal, temporal, and parietal lobes that play an important role in motoric processes, executive functioning, and emotion processing<sup>39</sup>. Alterations of the corpus callosum are also linked to several other neuropsychiatric disorders, such as attention deficit hyperactivity disorder<sup>40,41</sup>, autism<sup>42,43</sup>, Tourette syndrome<sup>44</sup>, or developmental dyslexia<sup>45</sup>. Sex differences in psychiatric disorders<sup>46,47</sup>, e.g. prevalence rates, symptoms, chronicity, and recurrence, are not uncommon and are mostly based on genetic differences. Likewise, there are known sex differences in the behavioral phenotype and developmental trajectories of conduct disorder as revealed by previous epidemiological studies<sup>48,49</sup>. Consequently, this heightens the possibility of observing similar sex-dependent characteristics in the brain. So far, only few neuroimaging

studies have directly and indirectly investigated sex differences in youths with conduct disorder on a neural level<sup>28,29,50</sup>, which is likely caused by the lower prevalence-rate of conduct disorder in girls<sup>2</sup>. Therefore, an increase in large-site or multicenter studies is needed in order to increase the direct comparison between boys and girls with conduct disorder on a whole-brain level and identify possible sexual dysmorphic neural alterations. Secondly, longitudinal studies allow researchers to investigate the developmental trajectories of conduct disorder in children and adolescents. An increased understanding about sex-differences may lead to the development of future customized intervention programs.

### Methodological challenges and gaps in knowledge

Tensor measurements such as FA or MD inform researchers about the white matter integrity of the fiber tracts. However, it remains difficult to interpret the meaning of these measures on a neuronal or behavioral level. For example, reduced MD may indicate increased myelination or more compact white matter tracts, however, various other factors (e.g. fiber crossings) may play a role as well<sup>22</sup>. Moreover, it remains difficult for even the most advanced programs to determine which brain regions each fiber tract connects to, and even then an altered FA or MD does not automatically indicate an enhanced or diminished activation within that brain region, but merely indicates alterations within the connectivity between brain areas. Therefore, to understand the impact of white matter alterations in conduct disorder, the relationship between fiber tracts and behavior needs further investigation using advanced neuroimaging techniques in both humans and animal models. Also, indirect correlations with healthy participants can inform the scientific field more about factors influencing the development of conduct disorder.

### Summary

Neuroimaging studies have indicated several key brain regions within the limbic system (e.g. amygdala and insula) and prefrontal cortex (e.g. orbitofrontal cortex and ventromedial prefrontal cortex) that display alterations of gray matter volume and brain activity in youths with severe antisocial behavior. These brain regions are interconnected through white matter fiber tracts. Examining these tracts enhances the understanding how altered neural connectivity is linked to conduct disorder. DTI is a useful neuroimaging technique for researchers to non-invasively investigate the white matter integrity of fiber tracts throughout the brain. Nevertheless, to date DTI findings are inconsistent regarding the direction and location of white matter alterations in youths with severe antisocial behavior. These discrepancies are likely caused by the heterogeneity of the samples included in each study. The inclusion of homogeneous or separate samples regarding

sex and clinical diagnosis is therefore recommended for DTI studies that investigate the relationship between white matter alterations and conduct disorder. Furthermore, an increase in large-scale or multicenter studies using longitudinal approaches enhances the possibility to inform about gender specific developmental characteristics. In this manner, DTI studies can further our knowledge of the underlying neurobiological mechanism of antisocial behavior which can aid the development of effective prevention and intervention programs.

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