Sex Differences in the Relationship Between Conduct Disorder and Cortical Structure in Adolescents

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Objective: Previous studies have reported reduced cortical thickness and surface area and altered gyrification in frontal and temporal regions in adolescents with conduct disorder (CD). Although there is evidence that the clinical phenotype of CD differs between males and females, no studies have examined whether such sex differences extend to cortical and subcortical structure.

Method: As part of a European multisite study (FemNAT-CD), structural magnetic resonance imaging (MRI) data were collected from 48 female and 48 male participants with CD and from 104 sex-, age-, and pubertal-status–matched controls (14–18 years of age). Data were analyzed using surface-based morphometry, testing for effects of sex, diagnosis, and sex-by-diagnosis interactions, while controlling for age, IQ, scan site, and total gray matter volume.

Results: CD was associated with cortical thinning and higher gyrification in ventromedial prefrontal cortex in both sexes. Males with CD showed lower, and females with CD showed higher, supramarginal gyrus cortical thickness compared with controls. Relative to controls, males with CD showed higher gyrification and surface area in superior frontal gyrus, whereas the opposite pattern was seen in females. There were no effects of diagnosis or sex-by-diagnosis interactions on subcortical volumes. Results are discussed with regard to attention-deficit/hyperactivity disorder, depression, and substance abuse comorbidity, medication use, handedness, and CD age of onset.

Conclusion: We found both similarities and differences between males and females in CD–cortical structure associations. This initial evidence that the pathophysiological basis of CD may be partly sex-specific highlights the need to consider sex in future neuroimaging studies and suggests that males and females may require different treatments.

Key words: conduct disorder, antisocial behavior, sex differences, brain structure, surface-based morphometry

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Conduct disorder (CD) is a psychiatric disorder that emerges in childhood or adolescence and is characterized by aggressive and antisocial behavior.[1] It incurs major costs for affected individuals, their families, and society in general.[2] Neurodevelopmental theories of CD propose that dysfunction in a set of cortical and subcortical brain regions causes increased vulnerability to antisocial behavior and aggression.[3] The regions that have received most attention are those implicated in emotion processing, empathy, decision making, and reinforcement learning, such as the amygdala, anterior insula, ventromedial prefrontal cortex (vmPFC), and striatum.[3] Amygdala dysfunction is argued to lead to impairments in stimulus-reinforcement learning, which may be particularly influential during socialization because the individual fails to learn the connection between their aggressive acts and the distress cues (e.g., sad expressions) displayed by others.[4] The anterior insula is implicated in processing aversive stimuli as well as awareness of one's own and others' affective and physiological states[5-6]; consequently, insula dysfunction may lead to empathy[7] and interoception deficits. Striatal dysfunction is thought to cause deficits in prediction error signaling, which would mean that the individual is less sensitive to discrepancies between the predicted and actual outcomes of their actions, thereby disrupting their ability to learn from reinforcement.[3] Finally, vmPFC dysfunction could lead to difficulties in representing the value of stimuli, which may impair effective decision making.[3,8]

In addition to these regions, there is increasing evidence that CD is associated with superior temporal and anterior and posterior cingulate cortex dysfunction, which may disrupt social cognitive and self-referential processing.[9,10]

Supplemental material cited in this article is available online.

Recent structural magnetic resonance imaging (MRI) meta-analyses have supported these neurodevelopmental models by confirming that individuals with CD have lower gray matter volume (GMV) in many of these regions, including the amygdala, anterior insula, vmPFC, and superior temporal cortex.[11]

Although the lifetime prevalence of CD is up to 10 times higher in males than in females,[12-14] it is nevertheless one of the most common disorders in adolescent females,[15] and one of the main reasons for referral to child and adolescent mental health services.[16,17] CD presents in different ways in males and females; males with CD display higher levels of aggression[18] but lower levels of comorbid disorders, such as depression,[19] and are more likely to develop antisocial personality disorder in adulthood.[13] Furthermore, there seem to be quantitative differences between males and females in vulnerability to risk factors.[20] It has been suggested that females may require a higher loading of genetic or environmental risk in order to develop CD.[21] Relating this differential threshold theory to the neuroimaging context, one prediction is that females who do surpass the threshold for a CD diagnosis may show more pronounced brain abnormalities than their male counterparts, which would be reflected in sex-by-diagnosis interactions.

Very few imaging studies have investigated sex differences in CD, and such studies have yielded inconsistent and inconclusive results. This is likely due to an underrepresentation of female participants in these studies[22] and hence insufficient power to detect sex-by-diagnosis interactions. There is preliminary evidence that CD is associated with reductions in amygdala[23] and orbitofrontal cortex (OFC)/vmPFC GMV[24] in both males and females. In contrast, one study found reduced anterior insula volume in females with CD relative to female controls, but the reverse effect in males.[23] Furthermore, a negative association between CD severity and superior temporal cortex GMV was reported in females but not in males.[25]

The current study addressed the lack of reliable evidence regarding possible sex differences in CD-related structural abnormalities by including a large, balanced sample of male ($n = 48$) and female ($n = 48$) adolescents with CD and similar-sized typically developing control groups. We used surface-based morphometry (SBM), which, in contrast to voxel-based morphometry (VBM), distinguishes among different cortical properties with distinct etiologies and developmental trajectories,[26] namely, cortical thickness (CT), surface area (SA), and gyrification (i.e., the amount of cortex folded within a sulcus compared to outside the sulcus). Although CT and SA display inverted-U trajectories across childhood and adolescence (peaking at 8.5 and 9 years, respectively), gyrification peaks in infancy and decreases over childhood.[27] Despite the fact that males and females show different brain developmental trajectories using these metrics,[27] previous SBM studies of CD have combined data from both sexes.

These studies have reported lower CT in the prefrontal cortex (PFC),[28-31] superior temporal cortex,[28-32] supramarginal/angular gyrus,[29,32,33] precuneus,[28,29,31,32] and fusiform gyrus,[29,32] and lower SA in PFC[29,33] in participants with CD compared to controls. Furthermore, lower gyrification in the OFC/vmPFC,[32] and higher gyrification in the superior frontal gyrus (SFG), insula, fusiform gyrus,[30] and precentral gyrus[32] have been reported in individuals with CD versus controls. Despite considerable overlap between the regions that have been identified using SBM and VBM methods, SBM studies have highlighted additional regions that have not yet been incorporated in neurodevelopmental models of CD. For example, the most robust finding from these studies—lower superior temporal gyrus CT—has not been incorporated into theories of CD, despite various functional magnetic resonance imaging (fMRI) and VBM studies also reporting abnormalities in this region.[11,34]

Accordingly, we predicted that CD would be associated with the following: lower CT in the OFC/vmPFC and superior temporal cortex; gyrification abnormalities in the insula and PFC; and lower SA in the PFC. We further hypothesized that cortical abnormalities would be most evident in the most severely disordered individuals, namely, those with more CD symptoms,[35] and potentially those with elevated callous-unemotional (CU) traits.[36] We also studied subcortical volumes to test for potential sex differences in the relationship between CD and the volume of subcortical structures such as the amygdala and striatum. Given the small number of females included in previous studies, it is not possible to make strong predictions regarding sex differences. Nevertheless, based on the hypothesis that the etiology and pathophysiology of CD is similar in males and females, but that females might require a higher loading of risk to surpass the threshold required to manifest the disorder,[21] we expected to observe CD-related structural alterations in similar regions in males and females, but to detect more pronounced or widespread deficits in females.

METHOD

Study Participants

The sample was selected from the Neurobiology and Treatment of Female Conduct Disorder (FemNAT-CD) study. It included 96 adolescents (48 females) with CD and 104 healthy adolescents (52 females; see Table S1, available online, for distribution of participants across sites). All participants were 14 to 18 years of age and classified as late- or postpubertal using the Pubertal Development Scale.[37] The study was approved by ethics committees at each site (Supplement 1, available online), and written informed consent was obtained for all participants.

Diagnoses of CD and comorbid disorders were made using the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime version (K-SADS-PL[38]), conducted separately with participants and parents by trained masters- and doctoral-level staff. The interrater reliability of CD was high (Cohen's $\kappa = 0.91$), and agreement across raters was 94.5%. Similarly high Cohen's κ values were obtained for attention-deficit/hyperactivity disorder (ADHD), major depressive disorder (MDD), and oppositional defiant disorder diagnoses (0.84–1.00). CD severity was defined as the number of CD symptoms endorsed across informants in the K-SADS-PL interviews. CU traits were assessed using the CU subscale of the self-report Youth Psychopathic traits Inventory (YPI).[39] Exclusion criteria included IQ < 70, neurological disorders, history of head trauma, autism spectrum disorders, and psychosis, as well as standard MRI exclusion criteria. Healthy